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DOLCE (FH-57)

Dolutegravir-Lamivudine naïve HIV-Infected Patients with ≤ 200 CD4.

Phase IV

Protocol version 3.0, December 13th, 2021

Principal Investigators:

Dr. María Inés Figueroa, MD, PhD

Fundación Huésped (Argentina)

Dr. Carlos Brites, MD, PhD

Universidade Federal de Bahia (Brazil)

Version Number: 3.0

Date: December 13th, 2021

Signature Page

Investigator Signature:

I have read this protocol and agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice.

Signed: _____ Date: _____

Signed: _____ Date: _____

Sponsor's signature:

I have read and approve this protocol. I assure that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Signed: _____ Date: _____

Sponsor Information Page

This study is sponsored by Fundación Huésped and funded by an Investigator grant from ViiV.

Sponsor:

Fundación Huésped

Carlos Gianantonio, (Ex Angel Peluffo) 3932 (C1202ABB)

Buenos Aires, Argentina

Sponsor contact:

UEM-Gardel Multicentric Studies Unit

Fundación Huésped

Carlos Gianantonio, (Ex Angel Peluffo) 3932 (C1202ABB)

Buenos Aires, Argentina

Telephone +54 11 4981-1855/7777

Fax +54 11 4982 4024

E-mail: UEMgardel@huesped.org.ar

Clinical Study Protocol

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Protocol Number:	FH-57
Investigational Product:	Dolutegravir-Lamivudine
Development Phase:	Phase IV .
Study Design:	Randomized, non-comparative, open, multicenter study
Authors	Omar Sued, MD, PhD Carlos Brites, MD, PhD
Sponsor	Fundación Huésped The study will be supported by an Investigator-Initiated Research Grant from ViiV.
Clinicaltrials.gov: (Registry number)	NCT04880395

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the US and Argentinean regulations.

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1. Introduction

1.1. Background Information

Dolutegravir (DTG), a second generation integrase inhibitor (INI) is one of the most potent antiviral drugs: - with IC50 values in the nanomolar rage (2.7 to 12.6nM) *in vitro* and *in vivo* 10-day monotherapy, with 50 mg of DTG, resulting in 2.48 log_{10} copies/mL decline in HIV viral load. Large clinical trials showed non-inferior efficacy and a safety profile of DTG similar to raltegravir (RAL) with 88% of participants virologically suppressed at 48 weeks[1], and superiority when compared with efavirenz[2]. DTG has been shown to have a high genetic barrier as in randomized clinical trials the emergence of INI resistant mutation among failing patient is extremely rare.[3]

Lamivudine is cheap, well tolerated and with a very low potential of drug interactions, it allows also a once daily dosing.[4]

Dual therapy based on dolutegravir + lamivudine (DTG+3TC) has been developed for initial treatment or as simplification of treatment-experienced, virologically suppressed individuals. The PADDLE study[5] and the ACTG5353 study[6] demonstrated that DTG+3TC resulted in potent antiviral activity. GEMINI 1&2 trials demonstrated non-inferiority compared to a dolutegravir based three-drug regimen at both week 48 (primary endpoint) and week 96. [7,8] The combination has also been shown to be effective and safe as a simplification strategy among suppressed patients, switching from TAF based regimens in the TANGO study.[9]

1.2. Rationale

Dolutegravir plus lamivudine has been included as a recommended regimen for antiretroviral treatment naïve patients in both the DHHS[10] and EACS[11], although EACS guideline still requires >200 CD4/mm^3 for this indication. The combination has the potential of becoming a first-line preferred therapy across multiple geographies globally and could represent a new global standard of care for ART expansion. In fact, WHO is proposing the transition of ART programs to DTG based combinations[12,13] that contain tenofovir. Avoiding tenofovir might reduce costs, pill size and need for renal monitoring. DTG+3TC can be proposed as a preferred combination for several reasons. DTG is an extremely potent antiviral compound

with proven clinical efficacy in both treatment- naïve and treatment-experienced HIV-infected patients. The genetic barrier of DTG resistance is higher than other first generation INIs. Metabolism primarily by uridine diphosphate glucuronosyltransferase (UGT)1A1 anticipates no significant drug–drug interactions and the pharmacokinetic profiles support once day dosing. 3TC is a safe and well tolerated drug and the presence of the M184V resistance mutation might not preclude anti-viral activity. DTG+3TC allows a once a day dosing schedule. In addition, this combination does not require preliminary testing (with the exception of testing for hepatitis B infection in order to avoid lamivudine monotherapy in those with chronic infection), dose adjustment in moderated renal disease or special monitoring needs. DTG+3TC is an attractive combination from a safety perspective as it is not associated with many of the toxicities described for other drugs (lipid alterations in PIs; CNS toxicity, liver toxicity or rash in NNRTI; mitochondrial toxicity in NRTI; and renal and bone disease in tenofovir). However, the information about efficacy in patients with advanced HIV disease is limited.

One third of new HIV diagnosis is identified with advanced HIV disease: In Brazil, 30% of new diagnosed individuals have less than 200 CD4 cells/mm^3,[14] while in Argentina the figure is similar, with 32.6%.[15] Therefore, it is critical to demonstrate that this new intervention is effective in this sub-population. In previous studies, three-drug regimens based on Dolutegravir performed well and even better than the comparator arm among participants with less than 200 CD4 cells/mm^3: in SPRING2 the response in the DTG arm was 78% vs 68% in the RAL arm. In the SINGLE Study it was 79% in the DTG arm vs 77% in the EFV arm, and in the FLAMINGO it was 91% in the DTG arm vs 79% in the Darunavir arm.[16] However, the sub-samples for these studies were small (less than 60 participants in each one). For patients with CD4≤ 200 cells/mm^3 in the GEMINI study the dual therapy arm achieved a percentage of viral suppression at 48 weeks similar to previous studies with 79% of success, but the comparator (DTG-TDF-FTC) achieved 93% of viral suppression.[7] Whilst caution needs to be taken interpreting these results due to the small numbers (9% of the Gemini 1&2 populations) and the fact that majority of those patients with low CD4 cell counts considered snapshot failures were due to non-treatment related reasons, this finding makes it imperative to explore further the efficacy of DTG+3TC dual therapy in this sub-population.

2. Objectives

2.1. Primary objective:

To assess the antiviral activity at week 48 of DTG+3TC among ART-naïve HIV patients with a CD4 count ≤200 cells/mm3.

2.1.1. Primary endpoint:

Proportion of patients with viral load < 50 copies/mL at week 48 using the ITT-exposed analysis (FDA snapshot) for the intent-to-treat exposed (ITT-E) population.

2.2. Secondary objectives:

- To assess the antiviral activity of DTG+3TC and DTG+TDF/XTC (TDF/FTC or TDF/3TC) at week 24
- To evaluate the safety and tolerability of DTG+3TC and DTG+TDF/XTC over time
- To assess the antiviral activity of DTG+3TC and DTG+TDF/XTC at week 48 in patients with baseline viral load >100,000 c/mL
- To evaluate immunological activity (CD4+ lymphocyte [CD4 counts]) at Week 24 and Week 48
- To assess the development of HIV-1 resistance in patients with virologic failure or viral rebound whilst being treated with DTG+3TC or DTG+TDF/XTC
- To evaluate the incidence of disease progression (HIV-associated conditions, AIDS and death) with DTG+3TC and DTG + TDF/XTC treatment over time

2.2.1. Secondary endpoints:

- Proportion of patients treated with DTG+3TC and DTG+TDF/XTC with HIV-1 levels of less than 50 copies/mL at week 24
- Frequency, type and severity of adverse events and laboratory abnormalities and proportion of patients who discontinue DTG+3TC or DTG+TDF/XTC due to adverse events or death
- Proportion of patients with baseline HIV-1 RNA >100,000 c/mL that achieve virological suppression at week 48

- Changes in CD4 count, CD8 count and CD4/CD8 ratio between baseline and 48 weeks
- Number and type of resistance mutations in case of virologic failure (defined as a confirmed viral above 200 copies/mL on or after week 24 or confirmed viral rebound at any time-point)
- Incidence of IRIS or disease progression (HIV associated conditions, AIDS and death)

2.3. Tertiary objectives:

- To explore change in health-related quality-of-life and depression, for subjects treated with DTG+3TC and DTG+TDF/XTC.

2.3.1. Tertiary endpoints:

- Change from Baseline in health-related quality of life using EQ-5D-5L and PHQ9 at Weeks 24, and 48.

3. Investigational Plan

3.1. Overall Study Design and Plan: Description

This is a phase IV randomized, open-label study describing the antiviral efficacy, safety and tolerability of dual therapy with DTG+3TC as initial therapy among naïve HIV-1 subjects with CD4 ≤200 cells/mm^3.

3.2. Treatment arms and duration

The study will include 230 HIV-1-infected subjects, meeting all inclusion criteria and not meeting any exclusion criteria for this study. They will be randomly assigned in a 2:1 ratio to receive DTG plus 3TC or DTG plus TDF/XTC. Randomization will be stratified by country and by screening plasma HIV-1 RNA (> or ≤ 100.000 copies/mL).

This study will consist of a screening period of up to 10 days, a 48-week treatment period, followed by a 4-week post-treatment follow-up (FU) period to document late adverse events.

At the screening visit, subjects must be willing and able to give written informed consent (signed and dated) prior to any study-specific procedure. Participants will receive a unique screening number and will undergo all the study procedures corresponding to the screening visit.

The investigator will document in the clinical record the informed consent process, provide a signed copy to the participant, and evaluate and document whether the subject meets all eligibility criteria. All the laboratory results should be evaluated and signed by the investigator or a sub-investigator. Women of child bearing potential should be fully informed about the potential risk of using dolutegravir during conceptional period (refer to Section 4.2).

At the Baseline Visit, subjects will undergo the study procedures identified in **Table 1** and will initiate DTG+3TC for 48 weeks, or DTG+3TC/TDF depending on the assigned arm. Subjects will receive instructions about the study medications and the dosing schedule. The participants should begin taking their study medication within 24 hours of the Baseline Visit. Subjects will return to the investigator's site for the study visits and procedures. Subjects who prematurely discontinue from the study must return for a Final /Discontinuation Visit.

After finishing or discontinuing the protocol, the investigator will make all efforts to ensure continuity of treatment through her/his regular care provider in order to avoid unnecessary interruptions. For patients that discontinue due to virological failure or toxicity, efforts will be made to ensure a proper switch to an effective treatment, or a safe regimen, as appropriate, and as early as possible.

A DSMB will be instituted to ensure external review of efficacy and safety in order to protect the scientific and ethical interest and wellbeing of subjects.

4. Subjects selection and withdrawal criteria

4.1. Study population

Subjects will be HIV-1-infected patients without ARV experience (naïve), who are willing to start ARV therapy, with ≥ 18 years of age, and who meet all inclusion criteria and do not meet any of the exclusion criteria.

4.2. Management of Women of Child Bearing Potential and pregnancy

Study participants should be informed that an observational study identified a potential risk of neural tube defects in infants born to women who were taking DTG when they became pregnant. These defects happen early in pregnancy, before many women even know they are pregnant.

Women who are pregnant or breastfeeding, or women who plan to become pregnant in the next year are excluded from this study. Women of reproductive potential should be counselled on the importance of avoiding pregnancy, safer sexual practices and the proper use of their chosen contraceptive methods in accordance with the applicable contraceptive product label, or, for non-product methods, as determined by the investigator, and reminded about this at every study visit.

The subject's chosen contraceptive method must be used for an adequate time period (at least 10 days) before dosing with the DTG-containing study medication is initiated and continued throughout the treatment- and post-treatment- periods until it is predicted that a clinically insignificant amount of study medication(s) is present in the subject (i.e., 30 days or one month after stopping DTG).

4.3. Sample Size

This study is designed to assess the antiviral effect of DTG+3TC in naïve HIV individuals with CD4 ≤200 cells/mm^3. No formal comparative statistical hypothesis testing will be performed. The study will include 230 HIV-1-infected subjects, meeting all inclusion criteria and not meeting any exclusion criteria for this study. Assuming an 80% response rate for DTG+3TC, a sample size of 153 subjects would have > 85% power to detect a response rate of greater than 70%.

In this study, though comparing DTG+3TC to DTG+TDF/XTC is not the primary objective, it will still be randomized to include a group of patients on DTG + TDF/XTC using a 2:1 allocation ratio (DTG+3TC: DTG+ TDF/XTC).

A total sample size of 230 (153+77) would be recommended for the study.

Although the objective of the study is not to test a statistical hypothesis between the two treatment groups, the sample size has been chosen to provide an adequate

number of subjects for assessing the antiretroviral activity of DTG+3TC in this patient group.

Figure A: relationship between study power and sample size required assuming a response rate of 80% against a pre-specified target response rate of 70%.

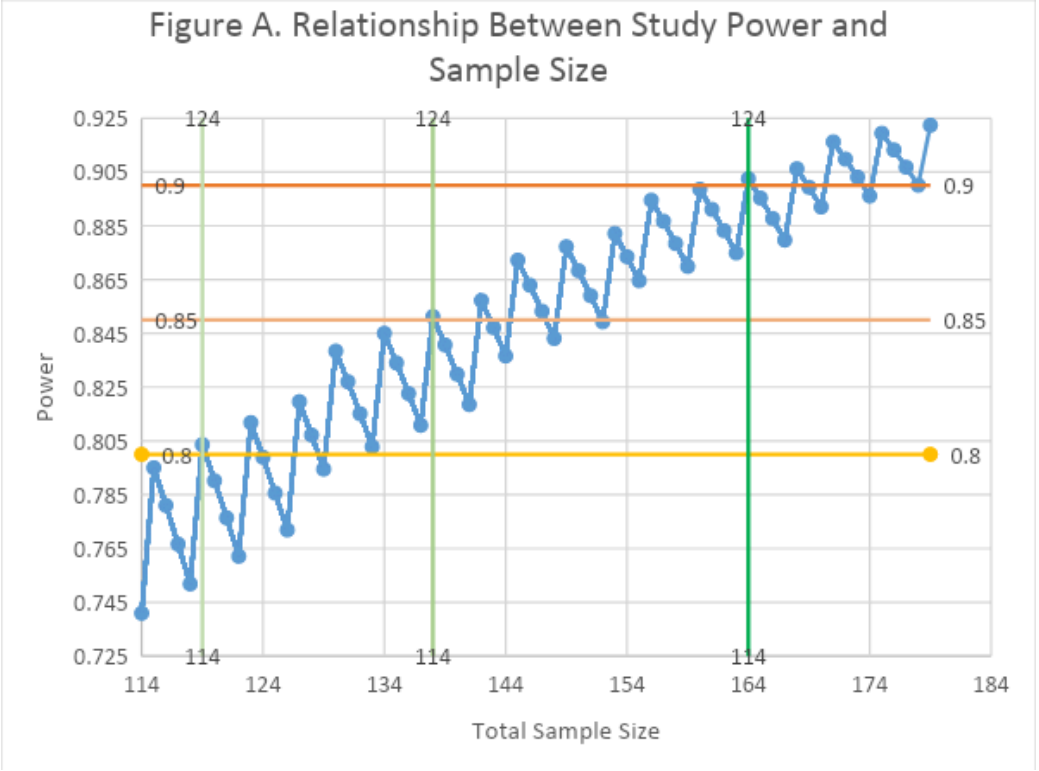
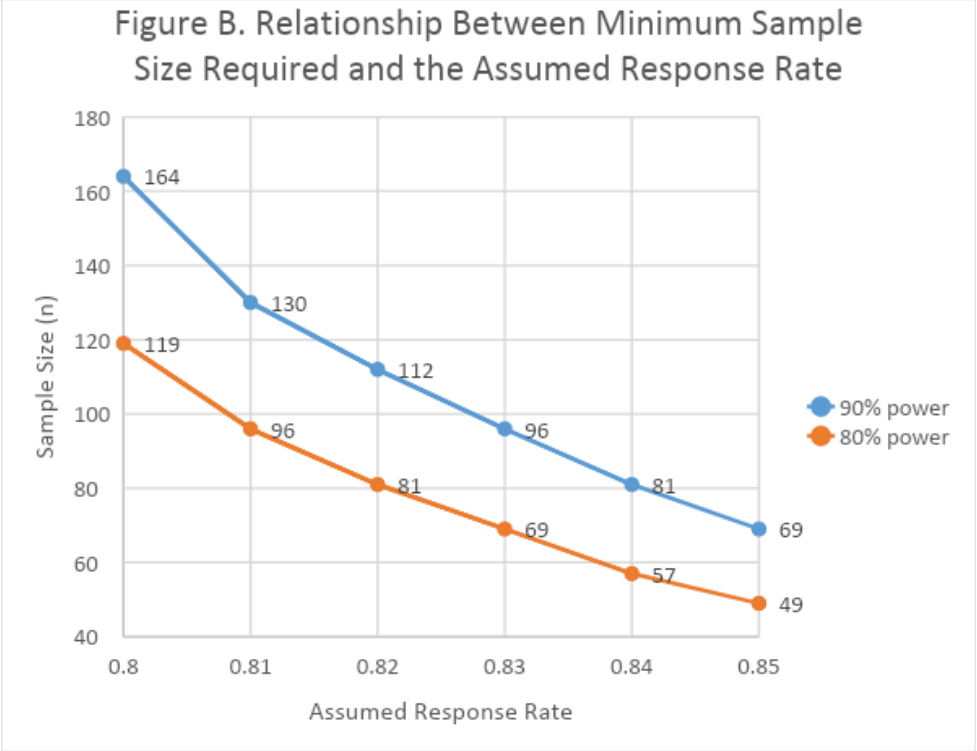


Figure B: relationship between minimum sample size required and the assumed response rate against the pre-specified response rate of 70%; different targets for power (80% and 90%) are considered.



Deviations from inclusion and exclusion criteria will not be allowed. Subjects will be allowed to re-screen for this study one time except where exclusionary HIV-1 resistance was present. A single repeat test (re-test) per analyte or assessment is allowed during the screening period to determine eligibility

4.4. Inclusion Criteria

A subject will be eligible for study participation if he/she meets ALL of the following criteria:

1. Subject has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB) / Independent Ethics Committee (IEC), after the nature of the study has been explained and the subject has had the opportunity to ask questions.
2. Documented HIV-1 infection defined as a positive rapid test or ELISA plus a plasma HIV-1 RNA (>1,000 copies/mL) or a positive western blot. A previous result performed on the last 30 days can be used.
3. ≥18 years of age.
4. Naïve to ARV therapies (defined as ≤ 10 days of prior therapy with any antiretroviral therapy following an HIV diagnosis). Previous use of PrEP or

PEP is allowed if there is documented HIV seronegativity between the last prophylactic dose and the date of HIV diagnosis.

5. HIV RNA at screening visit > or = 1,000 copies/mL. A previous result performed on the last 30 days can be used.
6. CD4 at screening < or = 200 cells/mL. A previous result performed on the last 30 days can be used.
7. Subjects can comply with protocol requirements.
8. Subject agrees not to take any medication during the study, including over-the-counter medicines or herbal preparations, without the approval of the trial physician.
9. Subject's general medical condition, in the investigator's opinion, does not interfere with assessments and completion of the study.
10. A female may be eligible to enter and participate in the study if she is not pregnant (as confirmed by serum pregnancy test negative at screening, and a urine negative test at baseline), not lactating and at least one of the following condition applies:

a) Women with non-reproductive potential, defined as pre-menopausal females with documented tubal ligation or hysterectomy, or bilateral oophorectomy; or as post-menopausal women defined as 12 months of spontaneous amenorrhea, and ≥45 years of age in women without hormonal replacement therapy.

b) Women with reproductive potential and agrees to follow one of the contraceptive options listed in the Appendix 3 from at least 15 days prior to the first dose of medication and until at least 30 days after the last dose of study medication and completion of the follow-up visit.

Any contraception method must be used consistently, in accordance with the approved product label. All subjects participating in the study should be counselled on safer sexual practices including the use of effective barrier methods and the choice of effective contraceptive method should be documented in the eCRF.

4.5. Exclusion Criteria

Patients will NOT be selected to be part of this study if they meet ANY of the following criteria:

1. Women who are pregnant or breastfeeding, or women who plan to become pregnant in the next year.
2. Subjects testing positive for Hepatitis B surface antigen (+HBsAg) at screening, or anticipated need for Hepatitis C virus (HCV) therapy with drugs with potential drug-drug interaction during the study.
3. Subjects with severe hepatic impairment (Child-Pugh class C), or unstable liver disease (ascites, encephalopathy, coagulopathy, or oesophageal or gastric varices) or cirrhosis.
4. Opportunistic infections that impede to start ART immediately (specifically tuberculosis, meningeal tuberculosis or cryptococcosis within the first month of specific treatment). Subjects with other suspected or confirmed active opportunistic infections and subjects with cryptococcal disease after the initial period can be included if she/he can follow the protocol and if her/his participation could benefit the subject. A clear documentation of these aspects must to be done in the clinical chart of the participant.
5. Subjects who in the investigator's judgment, pose a significant suicidality risk.
6. History or presence of allergy to the study drugs or their components or drugs of their class.
7. Treatment with any of the following agents within 28 days of screening: radiation therapy; cytotoxic chemotherapeutic agents; any immunomodulators that alter immune responses; or treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening; or exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of investigational product.
8. Any previous evidence of resistance to dolutegravir (defined as the presence of G118R, Q148 H/K/R or R263K), to lamivudine (presence of the mutation M184V) or resistance to tenofovir (mutation K65R or more than 3 TAMs) with a Sanger sequence method or using next-generation sequencing (NGS) at a frequency >15%. If the subject does not have a previous resistance test, samples will be taken at the screening visit and the subject can be randomized and start the study. while awaiting the results (**see section 4.8**).
9. Any verified Grade 4 abnormality.

10. Alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal (ULN), or ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (with >35% direct bilirubin).
11. Creatinine clearance of <50mL/min via Cockroft-Gault method

4.6. Withdrawal Criteria

Subjects discontinuing study treatments before week 48 are considered withdrawn from the study. A subject may withdraw from study treatment at any time at his/her request or may be withdrawn at any time at the discretion of the investigator for safety, or other reasons. Those subjects will not be replaced. The study might allow temporary interruptions for management of toxicities or other reasons. Consultation with the medical monitor is required.

Subjects **may** be withdrawn from the study if:

1. Subject non compliance, as evaluated by the investigator;
2. At the request of the subject, the investigator, the IRB, or the sponsor;
3. The subject requires concurrent prohibited medication;
4. The investigator considers that, for safety reasons, it is in the best interest of the subject that he or she is withdrawn;
5. The resistance test shows evidence of resistance to dolutegravir (defined as the presence of G118R, Q148 H/K/R or R263K), to lamivudine (presence of the M184V mutation) or to tenofovir (K65R mutation or more than three TAMs), should be discussed with the study medical monitor. In this case, the researcher will evaluate the risk of keeping the patients in the study depending on the type of mutations and the virological evolution. The opinion of the study medical monitor should be sought for any resistance test with mutations to any study drugs.

Subjects **must** be withdrawn from the study if:

1. The subject meets virological failure criteria
2. Subject requires dose modification of DTG, 3TC, TDF or FTC
3. Individual meets liver toxicity stopping rules
4. Subjects with an adverse event Grade ≥4 that is considered causally related to the investigational product(s)

5. Pregnancy
6. For certain other toxicities (see Section 9)

If a subject is prematurely withdrawn from the study, all procedures specified for the withdrawal visit should be performed. The date and the reason for discontinuation must be noted on the case report form (CRF). If possible, perform the follow up visit after 4 weeks after the last dose of study.

4.7. Management of individuals who fails to attend the clinic for a planned clinical visit:

The site should attempt to contact the subject and re-schedule the missed visit as soon as possible.

Counselling should be provided at each visit to identify individuals experiencing challenges to continue in the study.

In cases where the subject is considered lost to follow up, the investigator team should document in the medical chart that they had performed at least 3 telephone calls, had sent 1 certified letter, and had tried to contact them through social networks.

4.8. Virologic Withdrawal Criteria for Subject Management and Viral Resistance Testing

Patients will have a HIV resistance test at the time of inclusion in the study. They may be randomized without having the results of resistance tests, due to the urgency of initiating treatment and the low risk of primary resistance. The situation will be re-evaluated upon receiving the results. Those participants whose resistance test shows evidence of resistance to dolutegravir (defined as the presence of G118R, Q148 H / K / R, or R263K), lamivudine (presence of the M184V mutation), or resistance to tenofovir (K65R mutation or more than three TAMs) should be discussed with the study medical monitor and followed according instructions. For mutations that do not predict decreased efficacy of dolutegravir, the investigator may consider performing a viral load to assess response before making the decision to exclude the participant.

Subjects with confirmed virological rebound or virological non-response will be considered to have met virological withdrawal criteria. For clinical management virological rebound is defined as a confirmed (repeated within 4 weeks of the first measurement) rebound in plasma HIV-1 RNA levels ≥ 200 c/mL after prior virological suppression to ≤ 200 c/mL. Non response is defined as a decrease in plasma HIV-1 RNA of less than 1 $\log^{10}$ c/mL by week 12, with subsequent confirmation, unless plasma HIV-1RNA is ≤ 200 c/mL; or by a confirmed plasma HIV-RNA levels ≥ 200 c/mL on, or after week 24.

For confirmation, investigators should not schedule re-assessment blood draws in the presence of factors that could be associated with virologic blips, such as intercurrent infection, treatment interruption due to toxicity management or non-compliance, or vaccinations. Subjects should have received full doses of investigational product for at least 2 weeks at the time of HIV-1 RNA re-assessment.

In all participants meeting virological withdrawal criteria a genotypic test and plasma storage should be requested. Sites should discuss cases with Medical Monitor before withdrawing individuals.

4.9. Screening Failures

A subject is considered a screening failure if after providing informed consent, the subject's circumstances or conditions change or the outcome of a test or assessment becomes available which results in the subject's failure to meet one or more of the entry criteria, or results in the investigator deciding that the subject is no longer an appropriate study candidate. Subjects are allowed to re-screen for this study one time; this will require a new subject number. There is no timeline restriction for re-screening. A single repeat test (re-test) per analyte or assessment is allowed during the screening period to determine eligibility (with the exception of a disqualified screening genotype, which may not be retested).

5. Study Treatment

The term investigational product (IP) is used to describe any combination of products received by the subject as per the protocol design.

5.1. Dosage and Administration of study drugs

Arm	Dual therapy arm	Triple therapy arm	
Product name	Dolutegravir/lamivudine DTG+3TC FDC	Tenofovir disoproxil fumarate/ emtricitabine TDF/FTC, or Tenofovir disoproxil fumarate/ lamivudine TDF/3TC	Dolutegravir DTG
Unit Dose	50 mg DTG/300 mg 3TC	300 mg TDF/200 mg FTC or 300 mg TDF/300 mg 3TC,	50 mg DTG
Route	Oral	Oral	Oral
Frequency	QD	QD	QD
Dosing instructions	With or without food	With or without food in combination with DTG	With or without food in combination with TDF/FTC or TDF/3TC

5.2. Treatment assignment

Informed consent must be obtained prior to any study procedures. Subjects will be assigned to study treatment in accordance with the computer-generated randomization schedule. Randomization schedule will be generated by Fundación Huésped using REDCap. Subjects will be randomized in a 2:1 ratio to DTG+3TC or DTG plus TDF/XTC. After confirmation of fulfilment of study entry criteria, study site personnel will be required to randomize the participant using the REDCap randomization feature. Once randomized, and if subsequently the participant is withdrawn from the study, she/he cannot be rescreened. Randomization will be stratified on > or ≤ 100.000 copies/mL.

Participant will maintain the assigned treatment group throughout the study. Efforts to avoid errors should be implemented in the clinic including but not limited to maintain a randomization list at the pharmacy, double verification of the treatment prescription and dispensation and internal audits.

5.3. Drug provision

For Argentina:

DTG 50mg will be provided for Argentina in local commercial bottles with fill count of 30 tablets. DTG+3TC (as a single pill fixed dose combination) will be provided for Argentina in local commercial bottles with fill count of 30 tablets. For storage conditions, refer to the package insert leaflet provided with the local commercial packs.

For Brazil:

DTG+3TC (as a single pill fixed dose combination) will be provided for Brazil in local commercial bottles with fill count of 30 tablets. For storage conditions, refer to the package insert leaflet provided with the local commercial packs. The comparator should be requested locally through the regular HIV provider.

DTG/3TC.

Product details can be found below:

Dosage formulation:	White, oval, film-coated tablets
Unit dose strength(s)/Dosage level(s):	50mg/300mg
Route of Administration:	Oral
Dosing instructions:	Take one tablet once a day
Bottle specification from GSK/ViiV Healthcare	The tablets are packed in high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each 60 mL bottle contains 30 tablets and a 2-gram silica gel desiccant. The bottle will only have a batch number.
Storage Conditions	Store up to 30° C (86°F), protect from moisture.
Manufacturer	GSK

DTG 50mg (single entity) product details can be found below:

Dosage formulation:	yellow, biconvex, round, film-coated
Unit dose strength(s)/Dosage level(s):	50mg
Route of Administration:	Oral
Dosing instructions:	Take one tablet once a day

Bottle specification from GSK/ViiV Healthcare	The tablets are packed in high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each 60mL bottle contains 30 tablets. The bottle will only have a date of manufacturer and batch number.
Storage Conditions	Between 15^{O}C -30^{O}C (59° to 86°F)
Manufacturer	GSK

5.4. Preparation/Handling/Storage:

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from ViiV/GSK.

5.5. Packaging and Labeling

DTG+3TC (fixed dose combination) and DTG 50mg provided as single entity will be labeled as Investigational product by the Sponsor. The contents of the label will be in accordance with all applicable regulatory requirements and study protocol.

5.6. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution must document the amount of investigational product dispensed and/or administered to study subjects and the amount returned by study subjects. Product accountability records must be maintained throughout the

course of the study. Returned tablets may (optionally) be re-dispensed to the same patient only once per container, indicating that he/she must first complete the intake of the container in use and then continue with the new container used during the visit.

5.7. Treatment Compliance

Treatment compliance will be evaluated using ACTG adherence forms. This assessment will be conducted at each visit after baseline visit through the withdrawal visit or study completion. These data will be recorded in the subject's CRF.

Good adherence to treatment will be considered when at least 80% of daily intakes are completed (equivalent to ≥ 24 tablets per month).

5.8. Treatment overdose

For the purposes of this study, an overdose is not an AE or SAE, unless it is accompanied by a clinical manifestation meeting AE or SAE criteria.

5.9. Treatment after the end of study

At week 48 doctors will arrange the provision of antiretroviral treatment through the regular HIV provider of the participant. Investigators should do all needed for avoiding unnecessary discontinuation of treatments. Subjects randomized to receive DTG+3TC once daily and who successfully completed 48 weeks of treatment will be given the opportunity to continue receiving this regimen either as single entities or as the FDC (fixed dose combination), depending on which is available via the local HIV provider, unless the subject no longer derives clinical benefit.

5.10. Concomitant Medications and Non-Drug Therapies

Subjects should be advised to notify their Investigator of any current or proposed concomitant medication, whether prescribed or over the counter, because of the potential for interactions between such treatments and the study medications. Potential drug-drug interaction should be investigated for any concomitant therapy and act accordingly.

Investigator should evaluate all concomitant medications that the participant took or is taken since the previous visit and all this information should be recorded in the

CRF. The minimum requirement is that the drug name and the dates of administration are to be recorded.

5.11. Permitted and prohibited Medications and Non-Drug Therapies

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described below).

Investigators are encouraged to prescribe all indicated chemoprophylaxis for HIV associated conditions, following local and international guidance, at discretion of the subject and their physician. All concomitant medications, including blood products, and vaccines taken during the study should be recorded in the CRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn. This approach will minimize the risk of non-specific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

DTG should be administered 2 hours before or 6 hours after taking antacid products or sucralfate containing divalent cations (e.g. aluminum and magnesium). Proton pump inhibitors and H_2-antagonists may be used in place of antacids with no scheduling restrictions.

Concurrent administration of multivitamins is acceptable. DTG can be co-administered with calcium or iron supplements if taken with a meal. Under fasted conditions, DTG should be given 2 hours prior to or 6 hours after calcium or iron supplements.

Metformin concentrations may be increased by DTG. Subjects should be monitored during therapy and a metformin dose adjustment may be required.

5.12. Prohibited Medications and Non-Drug Therapies

The following therapies are not permitted at any time during the study. Contact medical monitor for discussing the need of specific therapies present in this list, or alternative therapies:

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Any experimental agents, others antiretroviral drugs, cytotoxic chemotherapy, or radiation therapy without authorization from the Medical Monitor.
- Systemically administered immunomodulators that directly affect immune responses such as Interleukin or interferon.
- HCV therapy that includes interferon, ribavirin or drugs with potential drug-drug interactions.
- Acetaminophen is not to be used in patients with acute viral hepatitis.
- Chronic use of glucocorticoids administered per oral or parenteral route. Short courses (less than 14 days) of oral prednisone, prednisolone, methylprednisolone are allowed.
- Drugs that may cause decreased concentrations of DTG including:
    - Carbamazepine
    - Oxcarbazepine
    - Phenobarbital
    - Phenytoin
    - St. John’s wort
    - Rifampicin or rifapentine
- Drugs that can cause toxicity in presence of DTG that include dofetilide, dalfampridine and pilsicainide as DTG may inhibit their renal tubular secretion resulting in increased concentrations and potential for toxicity.

6. Study Assessments and Procedures

Adherence to the study design requirements, including those specified in the **Table 1**, is essential and required during the study conduction.

6.1. Study procedures

Written informed consent must be obtained from each potentially eligible subject (or his/her legal representative) by study site personnel prior to the initiation of any screening procedures as outlined in this protocol. The consent form must have been approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

After signing an informed consent, subjects will complete screening assessments to determine subject eligibility. Each subject being screened for study enrolment evaluation will be assigned a subject number. This number will be given sequentially in chronological order of subject presentation.

Table 1 Assessments and Procedures.

Procedures	SCR	BSL Day 1	Week 4	Week 12	Week 24	Week 36	Week 48	Final visit or Discont. Visit
Window visits	**-10 days**	**0**	**+/-3days**	**+/-7days**	**+/-7days**	**+/-7days**	**+/-7days**	**+/-7days**
Written informed consent	X							
Demography, ART history, medical history, current medical conditions, vital signs, HIV risk factors and mode of transmission	X							
ECG	X							
Inclusion/exclusion criteria review and documentation in the chart[1]. Randomization[2]	X	X						
CDC Classification	X							
HIV associated conditions	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Physical Examination #	X	X	X	X	X	X	X	X
Waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), Body Mass Index (BMI)		X			X		X	
Vital Signs/ Weight measurement	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X
Dispense medication		X	X	X	X	X	X	
Adherence (Baseline ACTG questionnaire)		X						
Adherence (analogue scale and ACTG follow-up questionnaire)			X	X	X	X	X	
EQ-5D-5L and PHQ9[3]		X			X		X	
Plasma and serum storage	X	X	X	X	X	X	X	X
PBMC storage[4]		X			X		X	
Serum pregnancy test and contraception options counseling	X	X	X	X	X	X	X	X
Urinalysis and dipstick for proteins[5]	X	X			X		X	
HIV Genotype (PI, NRTI, NNRT) & INI genotype	X							
Syphilis testing[10]	X				X		X	

HCV antibodies	X							
HBV serology[6]	X							
HIV-1 RNA[10]	X	X	X	X	X	X	X	
CD4 and CD8 cell count[10]	X	X		X	X	X	X	
Hematology[7]	X	X	X	X	X	X	X	
Clinical Chemistry[8]	X	X	X	X	X	X	X	
Fasting lipids[9]		X			X		X	

1) Inclusion/exclusion criteria will be initially collected at screening and fully assessed at the Day 1 previous to randomization. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility, including review of additional assessments performed at Day 1.
2) Randomization may occur as soon as possible after having the required screening laboratories.
3) The questionnaires are recommended to be administered at the beginning of the visit before any other assessments are conducted
4) Whole blood/PBMC collection samples may be used for virologic analyses and for future research.
5) A morning specimen is preferred.
6) HBV: at screening HBsAg+HBs core, if negative participants should be vaccinated. If core is positive and HBsAg negative, a viral load should be requested.
7) CBC, formula and platelets and eritrosedimentation rate
8) Glucemia, urea, creatinine, creatinine clearence (Cockroft-Gault), AST, ALT, Alc Phost, Amylasemia, total bil, indirect bil, totel Chol, total protenin, uric acid.
9) An overnight fast is preferred; however, a minimum of a 8-hour fast is acceptable. HDL, LDL, Total Cholesterol, TG.
10) A laboratory result obtained within 30 days prior to the screening visit may be used, only for SCR visit.
Physical Examination: Completed on screening visit and then directed on subsequent visits.

6.2. Screening Assessments

- Informed consent: No procedure can be performed until an informed consent form is signed and a copy provided to the participant.
- Medical History. A complete medical history, including demography, ART history, current medical conditions, HIV risk factors, mode of transmission, history of tobacco, drug and alcohol use, opportunistic infections and previous allergies or drug adverse events will be obtained.
- Concomitant medication review
- Complete Physical Examination.
- Height: This examination will serve as the baseline examination for the entire study.
- Weight: Using a standard operating procedure, and calibrated weight scale.
- Vital signs: Blood pressure, pulse and body temperature.
- CDC category based on the 1993 classification, which should be documented in the medical record.
- Laboratory determinations:
  - HIV-1 genotype (a genotype performed in the last 90 days does not requires to be repeated).
  - Plasma HIV-1 RNA (*Abbott RT PCR*). Previous results of this determination may be used if it is not more than 30 days old at the date of the screening visit.
  - CD4 and CD8 cell counts. Previous results of these determinations may be used if they are not more than 30 days old at the date of the screening visit.
  - Hematology, clinical chemistry panel and urinalysis.
  - Serologies including syphilis screening (VDRL or RPR, and FTA Abs if reactive), HCV antibodies, HBV surface antigen and anti-core antibodies. If core antibodies are positive and HBV surface is negative, a viral load for HBV should be requested. Anti-Hbs should be requested for those with negative markers and, if needed vaccination should be offered. Previous results of

syphilis screening may be used if they are not more than 30 days old at the date of the screening visit.

- Serum pregnancy test (for women with fertile potential).
- Plasma and serum storage.

- ECG: a 12-lead resting ECG will be obtained at the screening visit and as clinically indicated during the study. A qualified physician from the site will interpret, sign, and date all ECG tracings. The site physician will also provide his/her global interpretation as a written comment on the tracing using the following categories:
    - Normal ECG
    - Abnormal ECG - not clinically significant
    - Abnormal ECG - clinically significant

The results of all clinical evaluations during screening must be within clinically acceptable limits as defined by the test laboratory and reviewed by the investigator.

6.3. Baseline Visit procedures

- Eligibility criteria review: all inclusion and exclusion criteria must be reviewed and documented in the clinical chart and verified by a second physician before proceeding to randomize a participant.
- Medical History: will be updated prior to study drug administration and as necessary during the study. Pregnancy risk and contraceptive options counseling.
- Concomitant medications: All new medications or changes in the medications recorded at screening visit should be recorded.
- Any adverse event that could occur since the participant signed the Inform Consent.
- Adherence (Baseline self-report ACTG questionnaire).
- Changes in the Physical Examination.
- Weight and vital signs (blood pressure, pulse and body temperature). Anthropometric parameters such as Body mass index (BMI) Waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) will be measured at baseline, 24 and 48 weeks.
- Quality of life EQ-5D-5L questionnaire.

- Laboratory determinations:
    - Plasma HIV-1 RNA (*Abbott RT PCR*).
    - CD4+ and CD8 + cell counts.
    - Hematology, clinical chemistry panel and urinalysis.
    - Serum pregnancy test (for women with fertile potential).
    - PBMC storage.
    - Plasma y serum storage.
    - Fasting lipids and metabolic markers. Eight hours fasting blood samples (water is permitted) will be required for baseline visit and visits on week 24 and 48.

7. Efficacy outcomes

7.1. Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected using the Abbott RealTime HIV-1 Assay with a lower limit of quantitation of 40 c/mL.

7.2. Lymphocyte Subsets

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage, and absolute CD4 and CD8 cell counts).

7.3. Fat distribution

Changes in body composition will be measured using weight, BMI, and anthropometry.

7.4. Quality of life and depression

The EQ-5D-5L and PHQ9 assessment should be administered at the beginning of the visit at baseline, week 24 and week 48, prior to collection of blood for analysis and other scheduled assessments. These questionnaires include the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L), developed by EuroQol group, and the PHQ9, patient health questionnaire 9 items, developed by Columbia University.

8. Safety

Safety will be assessed from adverse events, physical examination, vital signs and clinical laboratory data.

8.1. Adverse Events

Throughout the course of the study (which begins when the Informed Consent is signed), the investigator will monitor each subject for the development of any clinical and/or laboratory evidence of an adverse event (AE). An adverse event is defined as any undesirable medical occurrence in a subject who participates in a study and includes those events/experiences which do not necessarily have a causal relationship to the study drug regimen.

An adverse event may be a symptom, sign, or abnormal laboratory finding. Any worsening of a pre-existing condition or intercurrent illness should be reported as an adverse event/experience. A laboratory abnormality should be reported as an adverse event if action is required (e.g. study drug interruption, discontinuation, or treatment is required). The nature of the adverse sign or symptom, its date and time of onset, duration and severity, therapy employed (if any) and the investigator's opinion of causality to study drug with an alternate etiology, if appropriate, must be documented. For adverse events/experiences to be considered as intermittent or continuous, the events should be of similar nature and severity.

The investigator will follow all adverse events to satisfactory clinical resolution or the establishment of a stable chronic stage upon study completion.

For this study, the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, Corrected version July 2017 will be used for grading events. The table can be found in the following link:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

If the event is not present in this table, the investigator will rate the severity of the adverse event according to the following definition:

Mild:	The adverse event is transient and easily tolerated by the subject.
Moderate:	The adverse event causes the subject discomfort and interrupts the subject's normal activities.
Severe:	The adverse event causes considerable interference with the subject's normal activities and may be incapacitating or life-threatening.

The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. When assessing causality, the investigator should determine if there is a **"reasonable possibility"** of being related to the study product, based on facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship and alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.

The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

For each AE/SAE the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The investigator may change his/her opinion of causality in light of follow-up information.

8.2. Serious Adverse Events

The investigator will inform the Sponsor, the local IRBs, ViiV Healthcare and the appropriate Regulatory Agency within 24 hours of any serious adverse event reported in this study (see Table 4). A Serious Adverse Event (SAE) is an adverse drug experience that results in any of the following outcomes:

- **Death.**
- **Life-threatening situation** — the subject was at risk of death at the time of the adverse event/experience. It does not refer to the hypothetical risk of death if the AE were more severe or were to progress.
- **Inpatient hospitalization or prolongation of existing hospitalization**.
- **Persistent or significant disability/incapacity** — Any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life functions, including the ability to work. This is not intended to include transient interruption of daily activities.
- **Congenital anomaly/birth defects —** Any structural abnormality in subject's offspring that occurs after intrauterine exposure to treatment.

Important medical events/experiences that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event/experience when, based on appropriate medical judgment, **they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above**. Examples of such medical events/experiences include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependence or drug abuse.

Please note that a severe adverse event/experience is not necessarily serious, as the term severe is a measure of intensity while a serious adverse event is determined based on the aforementioned regulatory criteria.

In addition to the above, any event meeting liver stopping criteria (as described in Table 2) should be reported as an SAE.

Reporting of Suspected, Unexpected Serious Adverse Reactions (SUSARS)

In addition, an SAE with onset after exposure to study drugs must be reported if the SAE meets the definition of unexpected given below:

- Expected AEs are AEs that have been previously observed with use of the study drugs and are listed in the package insert. Expectedness is not based

on what might be anticipated from the pharmacological properties of the study agent.

- Unexpected AEs are AEs for which the nature or severity (intensity) is not consistent with the applicable agent information (package insert).

Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

8.3. Other Events that should be reported

8.3.1. Cardiovascular events

Any cardiovascular event will be required to be reported in the Cardiovascular section of the CRF within one week of acknowledging the event. This will include Myocardial infarction/unstable angina, congestive heart failure, arrhythmias, new valvulopathy, pulmonary hypertension, cerebrovascular events/stroke and transient ischemic attack, peripheral arterial thromboembolism, deep venous thrombosis/pulmonary embolism and revascularization.

8.3.2. New AIDS event and AIDS related deaths

Any new AIDS defined condition (based on the CDC classification 1993) should be reported within one week of acknowledging the event. This will include information about laboratory tests, previous use of prophylaxis and diagnosis. Physicians are encouraged to use the best updated local guidelines to offer primary prophylaxis to these participants. In addition, chest X ray and cryptococcus antigen should be considered in the initial evaluation for patients with CD4 count below 100 cells/mm^3.

8.3.3. Suicidal Ideation or Behaviors

Subjects with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some

reports of depression, suicidal ideation and behaviour (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with integrase inhibitors, including DTG. Therefore, it is appropriate to monitor subjects for suicidality before and during treatment.

Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour, or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour.

The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related (PSRAE) and if it meets the SAE criteria in order to meet the timing for reporting (PSRAE within 1 week and SAE within 24 hrs of becoming aware of the event). PSRAE may include, but is not limited to an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. PSRAE forms should be completed and reported to Sponsor within one week of the investigator diagnosing and reporting a possible suicidality-related serious adverse event.

8.3.4. Immune Reconstitution Inflammatory Syndrome (IRIS)

Investigators need to carefully document and manage signs and symptoms that could be related to IRIS. In addition, the Medical Monitor will review the AE terms and HIV conditions in order to identify IRIS cases and might require additional information to characterize these events.

To define IRIS, French criteria (2004) will be used, which requires 2 major criteria or 1 major criterion plus 2 minor criteria

Major criteria:

A: atypical presentation of opportunistic infections or tumor´s in patients responding to ART, manifested by any of the following:

- Localized disease
- Exaggerated inflammatory reaction

- Atypical inflammatory response in affected tissues
- Progression of organ dysfunction or enlargement of preexisting lesions after definitive clinical improvement with pathogen specific therapy prior to ART and exclusion of treatment toxicity and new diagnoses

B: Decrease in plasma HIV RNA >1 log^{10} copies/mL

Minor criteria

- Increase in CD4 count after ART
- Increase in an immune response specific to the relevant pathogen
- Spontaneous resolution of disease with continuation of ART

The diagnosis of this syndrome is a diagnosis of exclusion, after ruling out other diagnoses such as non-response to opportunistic infections treatments, poor adherence, recurrence of opportunistic infections, toxicity or drug reaction, neoplasia, or other causes of fever. In biological terms, the IRIS could be associated with a burst of specific Th1 CD4+ T cells to tuberculin purified protein derivative, detectable by ELISPOT for IFN-γ.

9. Toxicity management

Adverse events that occur during the study should be evaluated by the Investigator.

IP may be interrupted at the discretion of the Investigator and according to the severity of the AE, but permanent discontinuation of the IP will require withdrawal of the participant from the study. IP should be restarted as soon as medically appropriate; in general, this should be no longer than 4 weeks after interruption (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of IP or temporary interruption of one or more but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus and can be discussed with the Medical Monitor. Guidance is provided below on general subject

management and IP interruptions based on the severity of the AE. All changes in the IP must be accurately recorded in the subject's eCRF. No IP dose reductions will be allowed.

In the event of a discontinuation of a DTG-containing product for suspected drug induced liver injury, other clinically significant liver chemistry elevations, severe skin reaction or hypersensitivity reaction, subjects should not be rechallenged with a DTG-containing product due to the risk of a recurrent reaction. These subjects should be withdrawn from study and seek/be reviewed for alternative antiretroviral therapy (but may continue on study, only for AE surveillance, but off study drug).

Secondary syphilis should be ruled out in all participants presenting allergic reaction or rash during the study.

9.1. Allergic Reaction

Subjects may continue investigational products for Grade 1 or 2 allergic reactions at the discretion of the 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.

Subjects with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the investigational product(s) should permanently discontinue the investigational product regimen and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the adverse event.

9.2. Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing antiretroviral therapy. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. The index case of a hypersensitivity reaction with DTG involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well

as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme have been reported for DTG in clinical trials.

Subjects with an isolated Grade 1 rash may continue investigational product 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.

Subjects may continue investigational product for an isolated Grade 2 rash. However, investigational product (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently 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.

Subjects should permanently discontinue investigational product (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the adverse event.

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 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, corrected version July 2017).

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

9.3. Toxicity Grade 1-2:

Subjects who develop a study drug-related Grade 1 or 2 adverse event or laboratory abnormalities may continue study medications.

9.4. Toxicity grade 3-4:

For bilirubin, ALT, AST elevation see **Section 9.5.**

If the Investigator has compelling evidence that the Grade 3 or 4 AE or toxicity has not been caused by IP, dosing may continue (such as high glucose in someone who had not performed adequate fasting, or elevated CPK in some participant that performed exercises).

Subjects who develop a Grade 3 AE or toxicity, which the Investigator considers related or possibly related to the IP, should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤ 2, IP may be re-started. If the same Grade 3 AE recur within 28 days in the same subject, the IP should be permanently discontinued, and the subject withdrawn from study. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to have withdrawal study evaluations completed. A Follow-Up visit should be performed 4 weeks after the last dose of IP.

Subjects with lipid abnormalities or other Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and if this is the case, may continue IP if the Investigator has compelling evidence that the toxicity is not related to IP.

Subjects who develop a Grade 4 AE or toxicity related to the study drug should have IP permanently discontinued. However, if there is compelling evidence that the AE is not causally related to the IP, dosing may continue. Subjects should be rechecked each week until the AE returns to Grade 2. Subjects experiencing Grade 4 AEs requiring permanent discontinuation of IP should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study

evaluations as noted above. Subjects with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and may continue therapy if the Investigator has compelling evidence that the toxicity is not related to IP (including lipid abnormalities) A follow-up visit should be performed 4 weeks after the last dose of study medication if AEs or laboratory abnormalities are ongoing.

9.5. Liver Chemistry Stopping and Follow up Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study drug and the follow-up period. For any participant meeting one of the criteria outlined in Table 2 or Table 3, or if the Investigator believes that it is in the best interest of the patients, the Investigator must follow the required actions and follow up assessments also outlined in these tables.

o Table 2 Liver Chemistry Stopping Criteria - Liver Stopping Event

ALT absolute	*ALT ≥ 8xULN*
ALT increase	*ALT ≥ 5xULN but <8xULN persists for ≥ 2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)*
Bilirubin[1, 2]	*ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)*
INR[2]	*ALT ≥ 3xULN **and** International normalized ratio (INR)>1.5, if INR measured*
Cannot Monitor	*ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for >2 weeks*
Symptomatic[3]	*ALT ≥ 3xULN (if baseline ALT is ≤ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity* *ALT ≥ 3x baseline (if baseline ALT>ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity*
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	***Follow Up Assessments***
● **Immediately hold study drugs.** ● **If a causal relationship between the liver event and study drugs cannot be ruled out, then study drugs must be permanently**	● Viral hepatitis serology, including: ● Hepatitis A immunoglobulin M (IgM) antibody;

discontinued and the Subject not rechallenged due to the risk of a recurrent reaction. ● Report the event to FH within **24 hours**. ● Events of possible drug-induced liver injury with hyperbilirubinemia[2] will be reported to FH as serious adverse events using the serious adverse event case report form. ● Complete the liver event case report form for all events meeting liver stopping criteria, and submit to FH within one week of first becoming aware of the event ● Perform liver event follow up assessments. ● Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING**). ● Permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments. **MONITORING:** ● Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries (include ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) and perform liver event follow up assessments at the central laboratory as described to the right. ● A specialist or hepatology consultation is recommended. ● Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline.	● HBsAg and hepatitis B core antibody; ● 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. Record alcohol use on the liver event case report form ● Serum creatinine kinase and lactate dehydrogenase. ● Obtain complete blood count with differential to assess eosinophilia. ● Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (or gamma globulins). ● Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease. Complete Liver Imaging and/or Liver Biopsy case report form. ● Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) **or** ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury **must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia). Record the appearance or worsening of any such clinical symptoms on the adverse event report form.

o Table 3 Liver Chemistry Increased Monitoring Criteria

Criteria	Actions
ALT ≥ 5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for >2 weeks.	● Notify the medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. ● Subject can continue study treatment ● Subject must return weekly for repeat liver chemistries (ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) until resolution, stabilization (ALT <5×ULN on 2 consecutive evaluations) or return to within baseline ● If at any time subject meets the liver chemistry stopping criteria, proceed as described above

9.6. Hyperglycemia

Subjects who experience study drug-related glucose elevations of Grade 3 or 4 may continue study medications, provided that appropriate management of hyperglycemia is instituted in a timely manner. A confirmatory fasting glucose level should be obtained within two weeks after the first Grade 3 or 4 glucose elevation. Hyperglycemia may be managed with oral hypoglycemic agents or insulin as deemed clinically appropriate by the investigator.

9.7. CPK Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2-4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained. Grade 4 elevations in CPK should have a repeat assessment after the subject has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the IP, IP should be discontinued, and the subject withdrawn from the study.

9.8. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state. Subjects who experience asymptomatic triglyceride or cholesterol elevations may continue to receive IP.

9.9. Decline in Renal Function

Treatment with a DTG fixed dose combination containing 3TC or TDF/XTC must be discontinued in any Subject developing moderate to severe renal impairment during the study, as indicated by creatinine clearance measuring <30 mL/min via calculated with Cockroft-Gault method.

10. Reporting

10.1. Observation period for Adverse Event reporting:

The observation period for adverse events (AE) and serious adverse events (SAE) reporting in an individual patient will start at the time of patient screening (after Inform Consent is signed) and continue through the Final Visit (4-week post-treatment follow-up visit) or up to 4-weeks after the last dose of treatment, whichever is later, to document late adverse events or SAE resolution.

10.2. Pregnancy reporting

Any pregnancy that occurs during study participation must be reported using the Pregnancy Report Form to ensure subject safety and the patient must be discontinued immediately from study drug.

Each pregnancy must be reported to the sponsor within one week of learning of its occurrence. 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 sponsor using the Pregnancy Report Form. Fundación Huésped Medical Monitor will fill the Antiretroviral Pregnancy Registry. Pregnancy complications and elective terminations for any reason must be reported as an AE or SAE. Spontaneous abortions must be always reported as an SAE. Reporting would continue until 6-8 weeks after the estimated delivery date.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

10.3. Events reporting Time Periods for SAEs and pregnancy report

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation and will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators in accordance with all applicable timelines

Table 4: Timing for reporting by investigator to sponsor, local regulatory agencies and ViiV Healthcare

	Initial reports		**Follow up information**	
Type of event	**Time frame**	**Documents**	**Time frame**	**Documents**
All SAEs	24 hours	SAE data collection form	24 hours	Follow up SAE data collection form
Pregnancy	1 week	Pregnancy form	2 weeks	Pregnancy Follow up form
All events meeting liver chemestry stopping criteria (see Section 9.5)	24 hours	SAE data collection form	24 hours	Follow up SAE data collection form

For subjects receiving DTG/3TC or DTG liver issues registered on the eCRFs should be reported to ViiV Healthcare within 1 week. See section 9.5.

11. Data Management

For this study, subject data will be entered in a REDCap CRF database and transmitted electronically to Fundación Huésped. Data will be managed following internal FH standard procedures, in order to ensure confidentiality, data protection, data integrity and data consistency.

11.1. Data Analysis and Statistical Considerations

11.1.1. Hypotheses

This study is designed to assess the antiviral effect of treatment with a DTG+3TC regimen at Week 48 among naïve individuals with CD4 ≤200 cells/mm^3. No formal statistical hypothesis testing will be performed.

11.1.2. Analysis populations

- Intent-to-Treat Exposed (ITT-E) Population: This population will consist of all randomized subjects who receive at least one dose of study medication. Subjects will be assessed according to their randomized treatment, regardless of the treatment they receive. Unless stated otherwise, the ITT-E Population will be used for efficacy analyses.
- Per Protocol (PP) Population: This population will consist of subjects in the ITT-E Population with the exception of major protocol violators, e.g. violations which could affect the assessment of antiviral activity. The PP population will be used for sensitivity analyses of the primary efficacy measure.
- The Safety Population is defined as all subjects who receive at least one dose of study medication. Subjects will be analyzed according to the actual treatments received. Unless otherwise stated, the Safety Population will be used for safety analyses.

11.1.3. Analysis data sets

Responses at < 50 c/mL will be calculated according to a snapshot algorithm, as established by the FDA. After week 36 any VL > 50 c/mL needs to be confirmed with a new VL performed within 4 months of the previous one.

For assessing virological outcome the windows will be defined as recommended by FDA snapshot analysis:

- Week 24, weeks 18-30 (days 127-210)
- Week 48, weeks 42-54 (days 295-378)

11.1.4. Treatment comparisons

No formal comparisons will be performed in this study

11.2. Interim Analysis

The first analysis will be conducted when all subjects complete their week 24 visit. The primary analysis will be conducted with all subjects complete their Week 52 visit.

Blind DSMB analysis will be performed regularly through the study and will inform changes in the protocol implementation. First meeting will be scheduled when enrolling 50% of the planned participants, and every 4 months thereafter.

11.3. Statistical Plan

Descriptive statistics will be used to evaluate the primary and secondary outcomes. The results will be given as median and interquartile ranges (IQR) or frequencies (%) and 95% CI, as appropriate. At each timepoint, longitudinal differences from baseline will be assessed using Student's t-test for paired samples in log10 transformed HIV-1 RNA. A two-tailed P value <0.05 will be considered to be statistically significant. Baseline and follow-up characteristics will be compared using the Wilcoxon rank-sum test or the chi square/Fisher’s exact test. Changes in CD4 will be measured as number of cells gained with treatment at 24 and 48 weeks. For resistance, descriptive statistics will be calculated for the presence of INI mutations at any point during follow up. All AEs will be evaluated, summarized and described as proportion of patients presenting events, and total number of events. AE and DAIDS grading will be also used for laboratory test.

11.3.1. Efficacy analyses

The primary efficacy outcome variable is the proportion of virologic response defined as the proportion of patients with viral load count less than 50 copies/mL at week 48 in an ITT-E analysis using the FDA´s Snapshot algorithm and its 95% confidence interval (CI).

The following secondary efficacy endpoints will be summarized using descriptive statistics:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm in the triple arm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related AE, safety stopping criteria, or lack of efficacy);
- Changes from baseline in CD4+ counts at Week 24 and Week 48.

The following tertiary efficacy endpoint will be summarized by event type and treatment arm using descriptive statistics:

- Change from Baseline in health-related quality of life using EQ-5D-5L at Weeks 4, 24, and 48 (or at study Withdrawal)

11.3.2. Safety

All AEs, SAEs and laboratory abnormalities will be evaluated, summarized and described as proportion of patients presenting events, and total number of events. AE and DAIDS grading will be also used for laboratory tests.

Safety will be assessed by the incidence and severity of all adverse events, incidence and severity of related AEs, incidence and severity of AEs leading to withdrawal and incidence of SAEs.

In addition, proportion of subjects who permanently discontinued IP due to AEs or death, proportion of IRIS, proportion of a new AIDS diagnosis or AIDS related death will be summarized.

All adverse events will be described using the MedDRA classification system.

11.4. Procedure for Handling Missing, Unused, and Spurious Data

No imputations or replacement of missing data will be performed. Observations will be censored at the time of last follow up.

11.5. Procedures for Reporting Deviations from the Original Statistical Plan

Any deviations will be reported as amendments to the statistical analysis plan.

12. Study Conduct Considerations

12.1. Posting of Information and Results

The study information from this protocol was published prior to the start of subject enrollment in the clinical trial registry clinicaltrial.gov under the publicly available ID number NCT04880395. The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer-reviewed journal for publication no later than 18 months after the last subject's last visit. When manuscript publication in a peer-reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing

12.2. Regulatory and Ethical Considerations, including the Informed Consent Process

A regulatory approval from the IRB is required before initiating the study according the ICH GCP and local regulations.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.

- Investigator reporting requirements.

It is investigator's responsibility to ensure that each subject is given adequate explanation of the aims, methods, anticipated benefits and potential risks of this study and voluntarily signs and dates the IRB/IEC-approved informed consent form prior to study participation. The investigator must also explain that subjects have the right to refuse to participate in the study or to withdraw at any time for any reason, without prejudice with respect to future treatment.

The investigator will document in the subject's medical record that informed consent was obtained prior to the performance of any study related procedure and will retain the original consent form with the study records. A copy of the signed and dated consent form should be given to the subject.

12.3. Data Handling and Record Keeping

Electronic Case Report Forms (eCRFs) will be used to store information collected during this study. The system will allow to audit of any entry or correction made. CRFs will be completed for each subject enrolled in this study with the data extracted from source documents. Any necessary corrections in source document will be made by drawing a single line through the incorrect entry and the correction will be written with the date and signature of the investigator or his/her designee. Data will not be obliterated by blacking out, use of correction fluid, or by erasing the original entry. If the reason for the correction is not obvious, a brief explanation (e.g., transcription error) will accompany the change.

12.4. Quality Control

In accordance with applicable regulations, GCP, and local procedures, internal monitoring unit will train the staff on the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and clinical requirements. An initiation site visit will be performed before start.

Sponsor monitors will ensure that the:

- Data are authentic, accurate and complete.

- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements.

12.5. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Monitoring Unit will conduct frequent quality assurance assessments of the site records. Information collected on CRFs and laboratory results will be verified by the quality monitor. More information on this can be found in the monitoring plan. Errors and deviations will be documented, summarized and discussed with investigators. Trainings will be provided as needed.

Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) agrees to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

12.6. Study and Site Closure

This study will be considered completed after the last subject completes the last study-related clinic visit or assessment. Upon completion or termination of the study, the monitor will conduct site closure activities with site staff, in accordance with applicable regulations, GCP and local Standard Operating Procedures.

13. References

1 Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382(9893):700-708. doi:10.1016/S0140-6736(13)61221-0

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3. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2013;13(11):927-935. doi:10.1016/S1473-3099(13)70257-3

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antiretrovirals in low- and middle-income countries – what are the issues? *AIDS*. May 2018:1. doi:10.1097/QAD.0000000000001845

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Appendices

14. Appendix 1. Protocol Synopsis

Protocol Title:	DOLCE: Dolutegravir-Lamivudine naïve HIV-Infected Patients with ≤ 200 CD4/mm^3
Protocol Number:	FH-57
Study Objectives:	To assess the antiviral activity at week 48 of DTG+3TC among naïve HIV patients with a CD4 count ≤ 200 cells /mm^3.
Primary endpoint:	Proportion of patients with viral load < 50 copies/mL at week 48 using the ITT-exposed analysis (FDA snapshot) for the intent-to-treat exposed (ITT-E) population
Secondary Objectives:	● To assess the antiviral activity of DTG+3TC and DTG+TDF/XTC at week 24 ● To evaluate the safety and tolerability of DTG+3TC and DTG+TDF/XTC over time ● To assess the antiviral activity of DTG+3TC and DTG+TDF/XTC at week 48 in patients with baseline viral load >100,000 c/mL ● To evaluate immunological activity (CD4+ lymphocyte [CD4 counts]) at Week 24 and Week 48 ● To assess the development of HIV-1 resistance in patients with virologic failure or viral rebound treated with DTG+3TC or DTG+TDF/XTC ● To evaluate the incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG + 3TC and DTG + TDF/XTC over time
Secondary endpoints:	● Proportion of patients treated with DTG+3TC and DTG+TDF/XTC with HIV-1 levels of less than 50 copies/mL at week 24 ● Frequency, type and severity of adverse events and laboratory abnormalities and proportion of patients who discontinue DTG+3TC or DTG+TDF/XTC due to adverse events or death ● Proportion of patients with baseline HIV-1 RNA >100,000 c/mL that achieve virological suppression at week 48 weeks, ● Changes in CD4 count, CD8 count and CD4/CD8 ratio between baseline and 48 weeks ● Number and type of resistance mutations in case of virologic failure (defined as a confirmed viral above 200 copies/mL after week 24 copies/mL or viral rebound at any timepoint) ● Incidence of IRIS and disease progression (HIV associated conditions, AIDS and death).
Tertiary objectives:	● TDF/XTCTo explore change in health-related quality-of-life for subjects treated with DTG plus 3TC and DTG + TDF/XTC
Tertiary endpoints:	● Change from Baseline in health-related quality of life using EQ-5D-5L and PHQ9 at Weeks 24, and 48
Patient Population:	HIV-1-infected subjects aged >18 years who are naïve to antiretroviral therapy with ≤200 CD4 cell/mm^3
Study Design:	Prospective, Phase IV, randomized, multicenter, parallel group study design

Regimens:	Dolutegravir 50 mg /lamivudine 300 mg QD FDC Dolutegravir 50 mg QD plus tenofovir 300 mg/emtricitabine 200mg or plus tenofovir 300 mg/ lamivudine 300 mg.
Duration:	48 weeks
Sample size:	230 subjects

15. Appendix 2. CDC Classification System for HIV-1 Infections (1993)

Reference - 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41 (No. RR-17):1-19.

Clinical Categories

The clinical categories of HIV infection are defined as follows:

Category A

Category A consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV

Category B (Symptomatic non-AIDS conditions)

Category B consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of conditions in clinical Category B include, but are not limited to:

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)

- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5℃) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

For classification purposes, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in clinical Category B.

Category C (AIDS indicator conditions as defined by diagnostic or presumptive measures).

Category C includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

Conditions in Category C include:

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive

- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration);or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or Extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent

- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV
- Non-CDC, HIV-associated conditions

16. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant

2. Intrauterine device or intrauterine system

3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])

4. Injectable progestogen [Hatcher, 2011]

5. Contraceptive vaginal ring [Hatcher, 2011]

6. Percutaneous contraceptive patches [Hatcher, 2011]

7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel’s review of subject’s medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Reference

Hatcher RA, Trussell J, Nelson AL, et al, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

17. Appendix 4: Essential Elements of Informed Consent

A signed consent must be obtained prior to any study-specific activities, the process needs to be documented in the medical chart, and a signed copy needs to be provided to the participant. The investigators should contact their local IRB regarding specific requirements. The ICF must include at least the following items:

- Explanation of the research, purpose, expected duration of participation, and description of procedures.
- A description of any reasonably foreseeable risks, inconveniences or discomforts to the patients and, if applicable, to an embryo, fetus or nursing infant.
- A description of any benefits to the patient or to others which may reasonably be expected from the research. According to Argentinean Regulation, no compensation is to be provided, but description of the reimbursement of transport and foods should be stated.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient, and where to obtain them.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.
- That the investigator and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly

available. If the results of the study are published, the subject's identity will remain confidential.

- To whom answers to pertinent questions about the research and research patients' rights, should be directed.
- A statement of the agreement to participate (e.g., "I agree to participate ...") with signature and date for the participant (or legally authorized representative) and for the person who explained the nature of the study to the patient (investigator or investigator's representative).
- A statement of anticipated circumstances or reasons under which the patient's participation may be terminated by the investigator without regard to patient's consent.
- A statement that significant new findings developed during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient (or the patient's legally acceptable representative) in a timely manner.

18. Appendix 5: Adherence questionnaires

ACTG Adherence Baseline Questionnaire

Date: _____ Self Interviewer Both

Patient ID: _____ How Administered? ☐ 1 ☐ 2 ☐ 3

The answers you give on this form will be used to plan ways to help other people who must take pills on a difficul schedule. Please do the best you can to answer all the questions. If you do not wish to answer a question, please draw a line through it. If you do not know how to answer a question, ask your study nurse to help. Thank you for helping in this important study.

INSTRUCTIONS: Please answer the following questions by placing a circle around the appropriate number response.

A. How sure are you that:

Please circle one response for each question.

		Not at All Sure	Somewhat Sure	Very Sure	Extremely Sure
1.	You will be able to take all or most of the study medication as directed?	0	1	2	3
2.	The medication will have a positive effect on your health?	0	1	2	3
3.	If you do not take this medication exactly as instructed, the HIV in your body will become resistant to HIV medications?	0	1	2	3

B. The following questions ask about your social support.

Please circle one response for each question.

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
1.	In general, how satisfied are you with the overall support you get from your friends and family members?	0	1	2	3

		Not At All	A Little	Somewhat	A Lot	Not Applicable
2.	To what extent do your friends or family members help you remember to take your medication?	0	1	2	3	4

Follow-up ACTG adherence Questionnaire

Subject # __ __ __ __ __ __ __ **Visit Date __ __ / __ __ __ / __ __**

Subject Initials __ __ __ **Week # __ __**

This questionnaire asks about study medications that you took recently. Many people find it hard to always remember their pills. For example,

- *Some people get busy and forget to carry their pills with them.*
- *Some people find it hard to take their pills according to special instructions, such as to increase the amount of medication you are taking if you have a herpes flare.*
- *Some people decide to skip pills to avoid side effects or to just not be taking pills that day.*

*We need to understand how people with HIV are really doing with their pills. Please tell us what you are **actually** doing. Don't worry about telling us if you don't take all your pills.*
We need to know what is really happening, not what you think we "want to hear."

---

1. How many doses of your study medication did you miss…

Yesterday? _____ dose(s)

The day before yesterday (2 days ago)? _____ dose(s)

3 days ago? _____ dose(s)

4 days ago? _____ dose(s)

If you did not miss any doses, write a zero (0) in the space provided.

2. This study medication needs to be taken 2 times a day. How closely did you follow this specific schedule over the last four days?

Never	Some of the time	About half of the time	Most of the time	All of the time
☐	☐	☐	☐	☐
0	1	2	3	4

3. Did study staff give you special instructions to take extra medication because of a herpes flare in the last four days?

Yes	No
☐	☐
1	2

If Yes, how often did you follow those special instructions over the last four days?

Never	Some of the time	About half of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

0	1	2	3	4

4. Some people find that they forget to take their pills on the weekend days. Did you miss any of your study medications last weekend - last Saturday or Sunday?

Yes	No
☐	☐
1	2

5. Some people find that they forget to take their pills on the weekend days. How often did you miss any of your study medications on a weekend during the past 3 months?

Never	Some of the time	About half of the time	Most of the time	All of the time
☐	☐	☐	☐	☐
0	1	2	3	4

6. When was the last time you missed any of your medications? *(Check one box)*

Within the past week	1-2 weeks ago	2-4 weeks ago	1-3 months ago	More than 3 months ago	Never
☐	☐	☐	☐	☐	☐
5	4	3			

19. Appendix 6: Quality of Life questionnaires

The form can be accessed at

http://www.med.umich.edu/pdf/weight-management/EQ-5D-HealthQ.pdf

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐

Self-Care

I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐

Pain/Discomfort

I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐

Anxiety/Depression

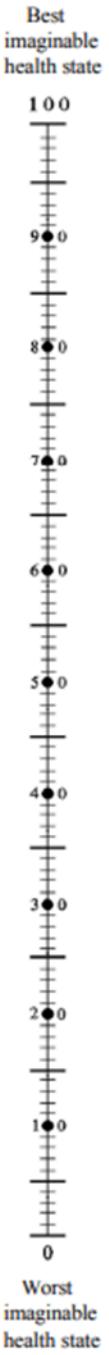
I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

2

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Because all replies are anonymous, it will help us to understand your answers better if we have a little background data from everyone, as covered in the following questions.

	Yes	No	
1. Have you experienced serious illness?			
in you yourself	☐	☐	PLEASE CHECK APPROPRIATE BOXES
in your family	☐	☐	
in caring for others	☐	☐	

2. What is your age in years? ☐

	Male	Female	
3. Are you:	☐	☐	PLEASE CHECK APPROPRIATE BOX

4. Are you: PLEASE CHECK APPROPRIATE BOX

- *a current smoker* ☐
- *an ex-smoker* ☐
- *a never smoker* ☐

	Yes	No	
5. Do you now, or did you ever, work in health care or social services?	☐	☐	PLEASE CHECK APPROPRIATE BOX

If so, in what capacity? .....

6. Which of the following best describes your main activity? PLEASE CHECK APPROPRIATE BOX

- *employed (including self employment)* ☐
- *retired* ☐
- *keeping house* ☐
- *student* ☐
- *seeking work* ☐
- *other (please specify)* ☐ .....

7. What is the highest level of education you have completed? PLEASE CHECK APPROPRIATE BOX

- some high school or less ☐
- high school graduate or GED ☐
- vocational college or some college ☐
- college degree ☐
- professional or graduate degree ☐

8. If you know your zip code, please write it here ☐

4

20. Appendix 7: Mental Health Questionnaire

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ **DATE:**_____

Over the last *2 weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).		TOTAL:		

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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21. Appendix 8: DTG+3TC Risk Assessment

Dolutegravir/Lamivudine

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigational Product: dolutegravir/Lamivudine Refer to Investigator Brochure and/or approved Local Prescribing Information for additional information		
Hypersensitivity and rash	Hypersensitivity reactions have been observed uncommonly with DTG. Rash, generally mild to moderate in intensity, was commonly reported in DTG Phase IIb/III clinical trials. No episodes of severe rash, such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme, were reported in these clinical trials.	Subjects with history or presence of allergy/sensitivity to any of the study drugs or their components are excluded Specific toxicity management guidance is provided for hypersensitivity reactions and rash The subject informed consent form includes information on this risk and the actions subjects should take in the event of a hypersensitivity reaction or associated signs and symptoms.
Drug induced liver injury and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for antiretroviral therapy containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus and/or hepatitis C virus co-infection, improvements in immunosuppression because of human immunodeficiency virus (HIV) virologic and immunologic responses to DTG-containing antiretroviral therapy, along with inadequate therapy for hepatitis B virus co-infected subjects, likely contributed to significant elevations in liver chemistries. There have been rare post-marketing reports of acute hepatic failure in association with DTG-containing regimens.	Subjects meeting any of the following criteria during the screening period are excluded from participating ● Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) ● Unstable liver disease, cirrhosis and/or known biliary abnormalities (except for hyperbilirubinemia or jaundice due to Gilbert's syndrome or asymptomatic gallstones) ● Subjects with hepatitis B infection or an anticipated need for hepatitis C virus therapy are excluded Specific/detailed liver stopping criteria and toxicity management

	Current treatment guidelines do not recommend monotherapy with 3TC for patients with HBV infection, which is what subjects randomized to DTG plus 3TC, would effectively be receiving. Emergence of HBV variants associated with resistance to 3TC has been reported in HIV-1-infected patients who have received 3TC-containing antiretroviral regimens in the presence of concurrent infection with HBV. Additionally, discontinuation of 3TC in HBV co-infected subjects can result in severe exacerbations of hepatitis B. For subjects co-infected with hepatitis C virus and HIV, treatment guidelines recommend that the hepatitis C virus infection is treated first before starting treatment for the HIV. Additionally, interferon and/or ribavirin toxicity maybe frequent and difficult to differentiate from adverse reactions to investigational product.	guidance are provided for suspected drug induced liver injury or other clinically significant liver chemistry elevations
Neural Tube Defects	In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was identified with exposure to dolutegravir compared to non-dolutegravir-containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking dolutegravir-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-dolutegravir-containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.03, 0.30) [Zash 2020]. Reproductive toxicology studies have not shown any relevant findings. DTG has been shown to cross the placenta.	Pregnancy testing should be performed before initiation of DTG therapy in all women of child bearing potential (negative pregnancy test at screening and randomization). Women who are pregnant or who plan to become pregnant, are excluded. All women of reproductive potential should use effective contraception (Appendix 3). The subject informed consent form provides information about this potential risk.

	Data available from other sources including the Antiretroviral Pregnancy Registry (APR), other cohorts and clinical trials are insufficient to confirm or refute this potential risk.	