A5375

An Open-Label, Phase II Pharmacokinetic Study to Evaluate Double-Dose Levonorgestrel Emergency Contraception in Combination with Efavirenz-Based Antiretroviral Therapy or Rifampicin-Containing Anti-Tuberculosis Therapy

NIAID CRMS # 38493

This file contains the current ACTG A5375 protocol:

- Protocol Version 2.0, dated 30 October 2020

A5375

An Open-Label, Phase II Pharmacokinetic Study to Evaluate Double-Dose Levonorgestrel Emergency Contraception in Combination with Efavirenz-Based Antiretroviral Therapy or Rifampicin-Containing Anti-Tuberculosis Therapy

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

National Institute of Allergy and Infectious Diseases

Non-IND Protocol

The Antiretroviral Therapy Strategies Transformative Science Group:	**Raphael Landovitz, MD, Chair**
The ACTG/IMPAACT Women's Health Inter-Network Scientific Committee*:*	**Elizabeth Connick, MD, Chair**
Protocol Chair:	**Kimberly Scarsi, PharmD, MS**
Protocol Vice Chair:	**Rosie Mngqibisa, MB, ChB, MPH**
DAIDS Clinical Representative:	**Pablo Belaunzaran Zamudio, MD, DTM&H, MSc**
Clinical Trials Specialist:	**Elizabeth Woolley, MPH**

FINAL Version 2.0
October 30, 2020

ACTG
AIDS CLINICAL TRIALS GROUP

A5375
FINAL Version 2.0
10/30/20

An Open-Label, Phase II Pharmacokinetic Study to Evaluate Double-Dose Levonorgestrel Emergency Contraception in Combination with Efavirenz-Based Antiretroviral Therapy or Rifampicin-Containing Anti-Tuberculosis Therapy

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

TABLE OF CONTENTS

Page

SIGNATURE PAGE 2

SITES PARTICIPATING IN THE STUDY 5

PROTOCOL TEAM ROSTER 6

STUDY MANAGEMENT 9

GLOSSARY OF PROTOCOL-SPECIFIC TERMS 11

SCHEMA 12

1.0 HYPOTHESES AND STUDY OBJECTIVES 14
- 1.1 Hypotheses 14
- 1.2 Primary Objectives 14
- 1.3 Secondary Objectives 14
- 1.4 Exploratory Objectives 15

2.0 INTRODUCTION 15
- 2.1 Background 15
- 2.2 Rationale 21

3.0 STUDY DESIGN 26

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS 27
- 4.1 Inclusion Criteria 27
- 4.2 Exclusion Criteria 29
- 4.3 Study Enrollment Procedures 30
- 4.4 Co-enrollment Guidelines 31

5.0 STUDY TREATMENT 32
- 5.1 Regimens, Administration, and Duration 32
- 5.2 Study Product Formulation and Preparation 32
- 5.3 Pharmacy: Product Supply, Distribution, and Accountability 33
- 5.4 Concomitant Medications 34

6.0 CLINICAL AND LABORATORY EVALUATIONS 35
- 6.1 Schedule of Evaluations (SOE) 35
- 6.2 Timing of Evaluations 36
- 6.3 Instructions for Evaluations 37

7.0 ADVERSE EVENTS AND STUDY MONITORING 44
- 7.1 Definition of Adverse Events 44
- 7.2 Adverse Event Collection Requirements for this Protocol 44
- 7.3 Expedited Adverse Event (EAE) Reporting to DAIDS 45
- 7.4 Study Monitoring 46

8.0 CLINICAL MANAGEMENT 47
- 8.1 Toxicity 47
- 8.2 Pregnancy 47
- 8.3 Breastfeeding 48

CONTENTS (Cont'd) Page

9.0 CRITERIA FOR DISCONTINUATION....48
9.1 Premature Treatment Discontinuation....48
9.2 Premature Study Discontinuation....48

10.0 STATISTICAL CONSIDERATIONS....48
10.1 General Design Issues....48
10.2 Outcome Measures....49
10.3 Randomization and Stratification....50
10.4 Sample Size and Accrual [53, 78-80]....50
10.5 Data and Safety Monitoring....53
10.6 Analyses....54

11.0 PHARMACOLOGY PLAN....57
11.1 Pharmacology Objectives....57
11.2 Pharmacology Study Design....57
11.3 Primary and Secondary Data, Modeling, and Data Analysis....57
11.4 Anticipated Outcomes....58

12.0 DATA COLLECTION AND MONITORING....58
12.1 Records to Be Kept....58
12.2 Role of Data Management....58
12.3 Clinical Site Monitoring and Record Availability....59

13.0 PARTICIPANTS....59
13.1 Institutional Review Board (IRB) Review and Informed Consent....59
13.2 Participant Confidentiality....59
13.3 Study Discontinuation....59

14.0 PUBLICATION OF RESEARCH FINDINGS....60

15.0 BIOHAZARD CONTAINMENT....60

16.0 REFERENCES....61

APPENDIX I: SAMPLE INFORMED CONSENT....67

ATTACHMENT I-A: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES....81

APPENDIX II: SAMPLE PARENTAL INFORMED CONSENT....83

ATTACHMENT II-A: PARENTAL CONSENT FOR USE OF SAMPLES IN OTHER STUDIES....97

APPENDIX III: SAMPLE ASSENT FORM....99

APPENDIX IV: PROHIBITED AND PRECAUTIONARY MEDICATIONS....106

SITES PARTICIPATING IN THE STUDY

A5375 is a multicenter study open to all US and non-US ACTG clinical research sites (CRSs).

PROTOCOL TEAM ROSTER

Chair/Pharmacologist
Kimberly Scarsi, PharmD, MS
Northwestern University CRS
University of Nebraska Medical Center
Antiviral Pharmacology Laboratory
College of Pharmacy
Room 3021
986145 Nebraska Medical Center
Omaha, NE 68198-6145
Phone: 402-559-9916
E-mail: kim.scarsi@unmc.edu

Vice Chair
Rosie Mngqibisa, MBChB, MPH
Durban International CRS
Enhancing Care Foundation
16 Charles Strachan
Westridge
Durban, KwaZulu Natal 4091
SOUTH AFRICA
Phone: 27-31-2611093
E-mail: mngqibisa@ecarefoundation.com

DAIDS Clinical Representative
Pablo Belaunzaran Zamudio, MD, DTM&H, MSc
HIV Research Branch,
TRP, DAIDS, NIAID, NIH
5601 Fishers Lane, Room 9E40B
Rockville, MD 20852
Phone: 240-292-4423
E-mail: pablo.zamudio@nih.gov

Clinical Trials Specialist
Elizabeth Woolley, MPH
ACTG Network Coordinating Center
Social & Scientific Systems, a DLH Company
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3282
E-mail: **elizabeth.woolley@dlhcorp.com**

Statisticians
Maxine Olefsky, MS
ACTG Statistical & Data Analysis Center
Harvard School of Public Health
FXB 549
Boston, MA 02115
Phone: 617-432-3263
E-mail: molefsky@sdac.harvard.edu

Laura Smeaton, MS
Statistical and Data Analysis Center
Harvard TH Chan School of Public Health
FXB Building, Room 511
651 Huntington Avenue
Boston, MA 02115-6017
Phone: 617-432-2525
E-mail: smeaton@sdac.harvard.edu

Data Managers
Mia Byrd, BA
ACTG Data Management Center
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900
E-mail: byrd@frontierscience.org

Kristine Coughlin, BA
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. 7239
E-mail: coughlin@fstrf.org

Tydie Higgins, MHA
ACTG Data Management Center
Frontier Science & Technology Research Foundation, Inc., 4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900
E-mail: thiggins@frontierscience.org

DAIDS Pharmacists
Kelly Parsons, PharmD
Pharmaceutical Affairs Branch
DAIDS, OCSO, PAB
5601 Fishers Lane
Room **9E15**
Rockville, MD 20852
Phone: 240-669-5721
E-mail: kelly.parsons@nih.gov

Irene Rwakazina, PharmD
Pharmaceutical Affairs Branch
DAIDS, OCSO, PAB
5601 Fishers Lane
Room 9E14
Rockville, MD 208**5**2
Phone: 301-761-7269
E-mail: irene.rwakazina@nih.gov

Pharmacologist
Anthony Podany, PharmD
University of Nebraska Medical Center
Antiviral Pharmacology Laboratory
College of Pharmacy
986145 Nebraska Medical Center
Omaha, NE 68198-6145
Phone: 402-559-1939
E-mail: apodany@unmc.edu

Investigators
Sharlaa Badal-Faesen, MD
MBBCH/Diploma in HIV Mana
University of the Witwatersrand
Helen Joseph (WITS HJH) CRS
Perth Road, Westdene
Johannesburg, Gauteng 2041
SOUTH AFRICA
Phone: 27-11-278818
E-mail: sfaesen@witshealth.co.za

Investigators (Cont'd)
Sara Bares, MD
Specialty Care Center CRS
University of Nebraska Medical Center
988106 Nebraska Medical Center
Omaha, NE 68198-8106
Phone: 402-559-8218
E-mail: sara.bares@unmc.edu

Liz Barr, PhD, MS
AIDS Clinical Trials Unit
1830 E. Monument Street, Suite 8074
Baltimore, MD 21205
E-mail: barrlizbarr@gmail.com

Susan E. Cohn, MD, MPH
Northwestern University CRS
Feinberg School of Medicine
Infectious Diseases Division
645 North Michigan Avenue, Suite 900
Chicago, IL 60611
Phone: 312-926-3693
E-mail: susan-cohn@northwestern.edu

Monica Gandhi, MD, MPH
University of California, San Francisco
HIV/AIDS CRS
4th Floor, Building 80, Room 423D
995 Potrero Avenue
San Francisco, CA 94110
Phone: 415-476-4082 Ext. 127
E-mail: monica.gandhi@ucsf.edu

David Haas, MD
Vanderbilt Therapeutics CRS
One Hundred Oaks
719 Thompson Lane, Suite 47183
Nashville, TN 37204
Phone: 615-936-8594
E-mail: david.haas@vanderbilt.edu

Investigators (Cont'd)

Felix Muhlanga, MM, MBChB, MMed
ObGyn
UZCHS- CTU
15 Phillips Road Belgravia
Harare, 111
ZIMBABWE
Phone: 263-4704966
E-mail: fmhlanga@uzchs-ctu.org

Field Representative
Becky Straub, RN, BSN, MPH
Chapel Hill CRS
2nd Floor, Bioinformatics
130 Mason Farm Road
Chapel Hill, NC 27599
Phone: 919-843-9975
E-mail: bstraub@med.unc.edu

Laboratory Technologists
Robin DiFrancesco, MT, (ASCP), MBA
NYS Center of Excellence in Bioinformatics and Life Sciences
State University of New York at Buffalo PSL TPRC
701 Ellicott Street
Buffalo, NY 14203
Phone: 716-881-7465
E-mail: rda@buffalo.edu

Chiraphorn Kaewkosaba, BSc
Chiang Mai University HIV Treatment (CMU HIV Treatment) CRS
110 Intavaroros Road, Sriphum
Muang, Chiang Mai 50200
THAILAND
Phone: 66-53-945-055 Ext. 119
E-mail: chiraphorn@rihes-cmu.org

Community Scientific Subcommittee (CSS) Representative
Cebisile Nkosi
Durban International CRS
Gate 1 King Edwards Hospital
719 Umbilo Road
Durban, Kwazulu, 4001
SOUTH AFRICA
Phone: 27-312054421
E-mail: nkosic@mut.ac.za

ACTG International Site Specialist
Morgan Gapara, MPH
ACTG Network Coordinating Center
Social & Scientific Systems, a DLH Company
4505 Emperor Boulevard, Suite 400
Durham, NC 27703
Phone: 919-287-4503
E-mail: morgan.gapara@dlhcorp.com

Laboratory Data Manager
Mark Lojacono, MA, MSc
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. 7346
E-mail: lojacono@fstrf.org

ACTG Laboratory Specialist
Sara Zabih, MS
ACTG Laboratory Center at UCLA (ALC-UCLA)
11075 Santa Monica Blvd.
Suite #200
Los Angeles, CA 90025
Phone: 310-794-9052
E-mail: **szabih@milabcentral.org**

STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5375@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5375@fstrf.org. A response should generally be received within 24 hours (Monday through Friday).

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5375 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the core protocol team.

- Send an e-mail message to actg.coreA5375@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to pharmacologic laboratory tests, contact the Pharmacologists.

- Send an e-mail message to actg.teamA5375@fstrf.org (ATTENTION: Kimberly Scarsi and Anthony Podany).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the Data Manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact **Tydie Higgins, Mia Byrd, and Kristine Coughlin** directly.
- For other questions, send an e-mail message to actg.teamA5375@fstrf.org (ATTENTION: **Tydie Higgins, Mia Byrd, and Kristine Coughlin**).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/participant registration questions or problems and study identification number SID lists:

- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

- Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 Ext.7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist.
- Send an e-mail message to actg.teamA5375@fstrf.org (ATTENTION: Elizabeth Woolley).

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@s-3.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation at US sites contact the Clinical Trials Specialist.
- Send an e-mail message to actg.teamA5375@fstrf.org (ATTENTION: Elizabeth Woolley).

For questions related to protocol activation at non-US sites contact the ACTG Site Coordination Group.
- Send an email message to actgsitecoordination@**dlhcorp**.com.

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, contact Pharmacists Irene Rwakazina and Kelly Parsons (kelly.parsons@nih.gov, irene.rwakazina@nih.gov).

Study Drug Orders
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Telephone Calls
Sites are responsible for documenting telephone calls made to A5375 team members.
- Send an e-mail message to actg.teamA5375@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate transaminase
AUC	area under the curve
BMI	body mass index
CLIA	Clinical Laboratory Improvement Amendments
CYP	cytochrome
DDI	drug-drug interactions
DMC	Data Management Center
DTG	dolutegravir
EC	emergency contraception
eCRF	electronic case report form
EFV	efavirenz
EMA	European Medicines Authority
EQA	external quality assurance
FTC	emtricitabine
GCLP	Good Clinical Laboratory Practice
INH	isoniazid
IRB/EC	institutional review board/ethics committee
IUD	intrauterine device
LMIC	low- and middle-income countries
LNG	levonorgestrel
MOPS	manual of procedures
OHRP	Office for Human Research Protections
PK	pharmacokinetic
POC	point of care
PSWP	protocol-specific web page
RIF	rifampicin
RSC	Regulatory Support Center
SNPs	single nucleotide polymorphisms
TB	tuberculosis
TFV	tenofovir
ULN	upper limit of normal

SCHEMA

A5375

An Open-Label, Phase II Pharmacokinetic Study to Evaluate Double-Dose Levonorgestrel Emergency Contraception in Combination with Efavirenz-Based Antiretroviral Therapy or Rifampicin-Containing Anti-Tuberculosis Therapy

DESIGN

A5375 is a phase II, open-label, four parallel group, partially randomized, pharmacokinetic (PK) study to evaluate if a double dose of levonorgestrel (LNG) emergency contraception (EC) overcomes known drug-drug interactions (DDIs) with efavirenz (EFV)-based antiretroviral therapy (ART) or rifampicin (RIF)-containing tuberculosis (TB) therapy. The safety of double-dose LNG EC versus standard-dose will also be compared.

Participants will be volunteers who do not currently require EC for contraception. Eligible participants will receive a single dose (1.5 mg) or a double dose (3.0 mg) of LNG EC based on their group assignment, which will be determined by their infection (HIV or TB; participants cannot be coinfected), and, for those who are living with HIV, by their ART regimen at enrollment (see Schema Figure 1). Women living with HIV who are taking EFV-based ART will be randomized to Group A or B (1:2 ratio). Women taking dolutegravir (DTG)-based ART will be assigned to Group C. Women who are HIV-negative and in the continuation phase of TB treatment taking RIF and isoniazid (INH) will be assigned to Group D.

DURATION

All participants will be followed for 4 weeks.

SAMPLE SIZE

116 participants; 17 in Group A, 33 in each of Groups B, C, and D.

POPULATION

Women who are 16 years of age or older, and who are either HIV+ and on stable ART, or who are HIV- and in the continuation phase of anti-TB therapy on daily INH/RIF.

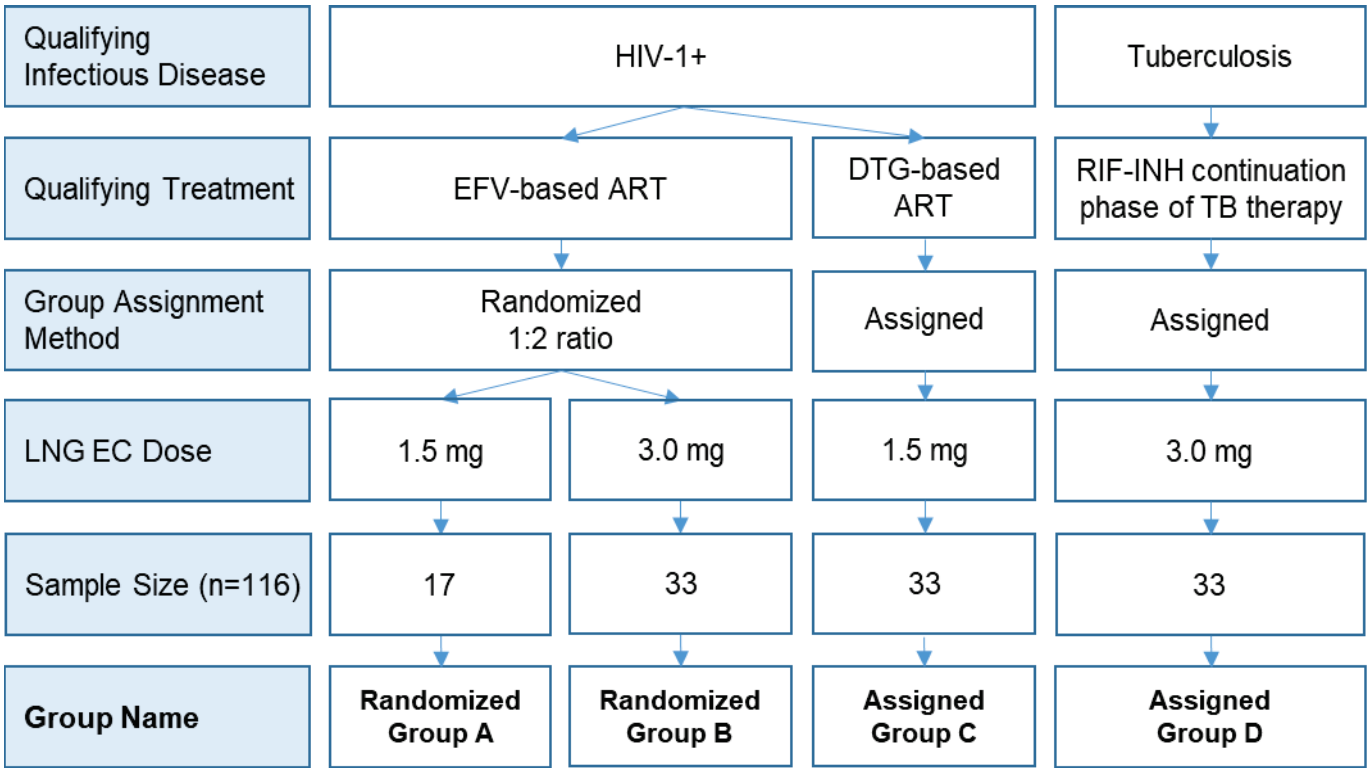
STRATIFICATION

At entry, women with body mass index (BMI) ≥30 kg/m^2 will be limited to no more than five within Groups B-D and no more than three within Group A.

REGIMEN

Women in Groups A and C will receive 1.5 mg LNG EC once at study entry.

Women in Groups B and D will receive 3.0 mg LNG EC once at study entry.



Schema Figure 1: Study Desig

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 Primary Hypotheses

1.1.1.1 Women receiving double-dose levonorgestrel (LNG) emergency contraception (EC) with efavirenz (EFV)-based antiretroviral therapy (ART) will achieve similar LNG concentrations compared to women receiving standard-dose LNG EC on dolutegravir (DTG)-based ART.

1.1.1.2 Women receiving double-dose LNG EC with rifampicin (RIF)-containing tuberculosis (TB) therapy will achieve similar LNG concentrations compared to women receiving standard-dose LNG EC on DTG-based ART.

1.1.2 Secondary Hypotheses

1.1.2.1 Among women receiving EFV-based ART, double-dose LNG EC will achieve significantly higher LNG concentrations than standard-dose LNG EC.

1.1.2.2 Women receiving standard-dose LNG EC with EFV-based ART will achieve significantly lower LNG concentrations than women receiving standard-dose LNG EC on DTG-based ART.

1.1.2.3 Double-dose and standard-dose LNG EC will have similar safety profiles.

1.2 Primary Objectives

1.2.1 To determine if doubling the dose of the LNG EC effectively overcomes the known drug-drug interaction (DDI) with EFV-based ART.

1.2.2 To determine if doubling the dose of the LNG EC effectively overcomes the expected DDI with RIF-containing TB therapy.

1.3 Secondary Objectives

1.3.1 To estimate the difference in LNG pharmacokinetic (PK) exposure with double-dose LNG EC compared to standard-dose LNG EC in women receiving EFV-based ART.

1.3.2 To estimate the difference in LNG PK exposure with standard-dose LNG EC in women receiving EFV-based ART compared to women receiving DTG-based ART.

1.3.3 To verify the absence of significant DDI between LNG EC and DTG-based ART.

1.3.4 To compare the safety of double-dose LNG EC compared to standard-dose LNG EC.

1.3.5 To evaluate the relationship between baseline measures of body weight (body fat percentage, total weight, and body mass index [BMI]) and LNG PK exposure.

1.4 Exploratory Objectives

1.4.1 To explore whether PK interactions between EFV, DTG, RIF, and LNG are affected by human genetic polymorphisms that have been reported to affect metabolism of these drugs.

1.4.2 To characterize the relationship between short- and long-term adherence to ART or TB therapy and LNG exposure using objective pharmacologic measures.

1.4.3 To assess the acceptability and practicality of EC as a contraceptive option in ACTG trials.

2.0 INTRODUCTION

2.1 Background

Despite progress in the global HIV response, adolescent girls and young women continue to be disproportionately affected by HIV, especially in sub-Saharan Africa. Globally, women constitute more than half of all people living with HIV, and 18.6 million girls and women were living with HIV in 2015 [1, 2]. In Sub-Saharan Africa, women account for approximately 56% of all new people living with HIV, and the incidence of HIV in women between the ages of 15 and 24 years accounts for 25% of all new infections [1].

Tuberculosis remains one of the greatest threats to public health, surpassing HIV as the leading cause of death from an infectious pathogen in 2015 [3]. Moreover, the HIV epidemic has fueled the resurgence of TB, leading to a dramatic increase in TB infections in low- and middle-income countries (LMIC) [4]. HIV infection increases the risk for TB (acquisition, reactivation, and reinfection), alters its clinical presentation, and reduces survival compared to patients with TB who are not living with HIV [5, 6]. For patients with latent TB, HIV is a significant risk factor for development of active TB [7, 8], and TB remains the most common cause of morbidity in patients living with HIV in resource-limited countries.

In 2014, women between 15-24 years old had a higher incidence of TB than men in areas of sub-Saharan Africa with high baseline TB prevalence [2]. In such settings of active TB treatment, preventing pregnancy becomes even more important in order for women to attain a level of health that will support future healthy pregnancies. Additionally, treatment options for TB may be limited during pregnancy because of concerns about teratogenicity. For instance, fetal exposure to RIF, although generally considered safe, is associated with bleeding disorders [9, 10]. Treatment of TB prior to pregnancy prevents TB exposure in the neonate, a condition associated with high infant mortality. Therefore, providing effective contraception and understanding potentially important DDIs between antimicrobials and contraceptives in populations of women living with either HIV or TB are both of paramount importance.

Emergency contraception (EC) use

Emergency contraception, also referred to as postcoital contraception, is a safe and effective form of birth control that prevents pregnancy when used on an episodic basis. Oral EC does not interfere with an established pregnancy but works by either preventing or delaying ovulation, or by inhibiting fertilization of an egg, depending on the stage of a woman's menstrual cycle and type of EC used.

The use of EC has expanded since becoming available without a prescription in pharmacies, both in the United States (US) and internationally. Types of EC include: LNG, ulipristal, combined oral contraceptives containing both estrogens and progestins (the Yuzpe method), mifepristone, and intrauterine devices that can be impregnated with progestins. The most commonly used oral EC is LNG [11], and it is the focus of this study. LNG EC tablets are registered in most countries and directly available to women in much of sub-Saharan Africa without a prescription [12].

The World Health Organization (WHO) recommends that all women and girls at risk of an unintended pregnancy have access to EC and that EC be routinely included within all national family planning programs [12]. Unintended pregnancy rates have been shown to be high worldwide, but especially in areas of limited resources where women may be disempowered to control their reproductive health. Provision of contraception and access to a variety of contraceptive methods are therefore critical to women in resource-limited settings. Given the prevalence of HIV and TB in these settings, investigations to expand our currently sparse knowledge base on DDIs between commonly used antiretroviral (ARV) therapies, TB treatment, and EC are urgently needed.

Populations who may benefit from EC

EC can be used after unprotected intercourse, contraceptive failure including the incorrect use of contraceptives, and sexual assault if it occurs without contraception coverage. EC is an essential birth control option for girls and women [12].

Unplanned and nonconsensual sexual activity has emerged as a critical issue for women living with HIV and at risk of HIV-infection. Incidence rates of sexual assault in women living with HIV are 1.6/100 person-years in the US [13]. In South Africa, intimate partner violence was reported in 20% of pregnant women with HIV attending an antenatal clinic [14]. Normative clinical and policy guidance was issued by the WHO [15], but these guidelines do not address issues specific to women living with HIV. For example, standard of care practice for sexual assault that could lead to pregnancy includes the provision of EC. However, the appropriate dosing of EC for the prevention of unintended pregnancies in combination with ART or anti-TB therapy is unknown.

Women participating in future clinical trials may also benefit from EC. Members of the HIV community frequently cite contraceptive requirements as a barrier to women's participation in clinical trials [16]. A 2016 survey of community members performed for this study found that 79% of women surveyed would be willing to use EC after unprotected sex that could lead to pregnancy (10% would need more information, including about side effects; 7% did not have sex that could lead to pregnancy). As one respondent noted, "I rarely have sex that could lead to pregnancy and would not be willing to go on any regular hormonal birth control

in order to participate in a clinical trial. I would be willing to use EC after instances of sex that could lead to pregnancy." Of women surveyed, 70% reported they would be more likely to participate in a study if EC and condoms were two of the contraceptive options available (18% reported no difference, and 11% said less likely). The overwhelming majority of survey respondents (96%) were in the US, so these results may not be generalizable to women in other countries. For women who are not sexually active at the time of enrollment, the need for continuous contraceptive methods can be onerous. For these women, EC, in combination with a barrier method, might be a reasonable contraceptive choice that would broaden women's participation in clinical trials evaluating HIV cure, new ART, and new anti-TB strategies. Data emerging from LMIC show increasing use, awareness, and willingness to use contraceptive agents, with one study describing that 85% of women were willing to use EC [17].

Antiretroviral therapy (ART) proposed in this study

Given that 95% of women living with HIV reside in LMIC [18], ART use for women in these regions primarily follows WHO guidelines. WHO guidelines for ART were recently updated to include either DTG- or EFV-based ART as preferred alternative first-line ART strategy [19]. DTG-based ART use is expanding in LMIC, and the US President's Emergency Plan for AIDS Relief (PEPFAR) programs are actively supporting the transition to DTG-containing regimens. Projections for ART drug procurement through 2025 in LMIC demonstrates that there will be an approximately even distribution of EFV- and DTG-based ART for first-line regimens (42% and 57% of all ART strategies, respectively) [20]. Therefore, this study will investigate these two important ART strategies in combination with EC to assess relevant DDIs.

2.1.1 Levonorgestrel (LNG)

Levonorgestrel is a progestational agent that inhibits ovulation by interrupting follicular development, and inhibits fertilization by altering the tubal transport of sperm and/or ova. In addition, it may inhibit implantation by altering the endometrium, but it is not effective once the process of implantation has begun [21]. LNG is commonly used in combination oral contraceptive pills, as EC, in progestin-releasing subdermal implants, and intrauterine devices. As EC, LNG should be taken within 72 hours after unprotected intercourse to prevent pregnancy. The absolute effectiveness of EC is difficult to determine because the rate varies with the timing of dosage with respect to unprotected intercourse, ovulation, and with the type of EC used. Estimates of LNG efficacy range from 59-94% [22]. In a multicenter randomized comparison of LNG versus ulipristal in nearly 1700 women presenting to family planning clinics for EC, there were 37 pregnancies with no statistical difference observed between the groups. To increase the power of the study, a meta-analysis was performed, and data from a total of 2221 women randomized to either ulipristal or LNG were compiled. This analysis confirmed that the pregnancy rate in both groups was lower than predicted, and that the pregnancy rate for LNG was 2.6% [23].

LNG for EC is typically given as a single 1.5 mg dose within 72 hours after intercourse. LNG reaches maximum concentration approximately 1.7 (range 1-4)

hours after administration and is 100% bioavailable after oral administration [21, 24, 25]. In 30 healthy, female volunteers, the mean (SD) LNG C_{max} was 19.1 (9.7) ng/mL, area under the curve $(AUC)_{inf}$ was 307.5 (218.5) ng*hr/mL, and half-life was 27.5 hours [21]. A clinical evaluation of another formulation of LNG (0.75 mg tablets, two tablets once) in five healthy volunteers found a geometric mean 44-hour (39-48-hours) half-life [26].

The effect of food on LNG absorption has not been evaluated. LNG is 97.5-99% protein-bound to sex hormone-binding globulin and albumin, only 2% of LNG is present as unbound drug. This, in addition to an inverse association between LNG concentrations and body weight [27-29], contributes to the high interpatient variability in drug levels. LNG is extensively metabolized to inactive metabolites via the cytochrome P450 (CYP) enzyme system, specifically the CYP3A4 isoenzyme, and co-administration of medications that induce or inhibit CYP3A4 are known to impact LNG concentrations. Approximately 45% of LNG and its metabolites are excreted in the urine and 32% in the feces, and the elimination half-life following a single oral dose LNG is approximately 17 to 24 hours. LNG is not known to influence exposure to ART or TB therapy [21].

LNG PKs are influenced by body weight as measured by BMI. Two studies have evaluated the effect of an overweight or obese BMI on LNG PKs. Edelman et al. found 49% lower $AUC_{0\text{-}2.5h}$ in women with BMI >35 compared to BMI <25 [30]. Pradipan et al. found 52% lower $AUC_{0\text{-}24h}$ in women with BMI >30 kg/m^{2}compared to BMI <25 kg/m^2 [31].

Studies have not been conducted to determine the PK parameter that is associated with LNG EC effectiveness. Variable doses of LNG EC have been evaluated, ranging from 0.4 to 1.5 mg, and the studies conducted were not designed to be dose-finding. Therefore, the concentration-response relationship is unknown [32]. Although there is a proposed threshold for LNG implant effectiveness, the mechanism of contraception is not the same between a long-acting contraceptive and EC so this concentration cannot be extrapolated to EC.

Safety Profile

The most common LNG EC side effects include heavier menstrual bleeding (30.9%), nausea (13.7%), lower abdominal pain (13.3%), fatigue (13.3%), headache (10.3%), dizziness (9.6%), breast tenderness (8.2%), and delay of menses >7 days (4.5%). These side effects are typically self-limiting during the treatment period. In contrast to other forms of contraception, EC does not have a contraindication with thromboembolic complications [21].

2.1.2 Rifampicin (RIF)

Rifampicin is a semi-synthetic rifamycin derivative that is highly active against mycobacteria, most gram-positive bacteria, and some gram-negative bacteria. It is bactericidal for both intracellular and extracellular microorganisms. By inhibiting prokaryotic DNA-dependent RNA polymerase, it suppresses the early elongation of

the nucleotide chain in RNA synthesis. It is a key component of TB treatment and RIF-containing regimens are associated with reduced mortality compared to non-RIF-containing regimens. Studies have demonstrated that addition of RIF to a TB regimen shortens the duration of treatment with higher cure rates [33]. Menzies et al. demonstrated that regimens that contain RIF for only 1 to 2 months of TB treatment instead of 6 months have higher failure rates with an increased chance of relapse and development of resistance [34]. WHO guidelines recommend that all individuals requiring TB therapy receive at least 6 months of RIF [35].

RIF is a potent inducer of multiple cytochrome P450 enzymes, such as CYP3A and CYP2B6. Drug transporters can accelerate clearance of drugs metabolized via the cytochrome p450 system, including ART [36, 37, 38], with potential loss of efficacy of these drugs. The effect of RIF on LNG PKs has not been evaluated, but several studies describe a 50% or greater reduction in exogenous oral progestin (e.g., norethindrone) exposure when combined with RIF [39-41]. Because exogenous progestins are believed to share the same metabolic pathway via CYP3A, the effect of one progestin is expected to be similar across other oral progestins.

Safety Profile

RIF is well-tolerated in the usual daily dose of 10 mg/kg (maximum 600 mg). It often causes harmless red-orange discoloration of tears, sweat, saliva, feces, and urine. Fewer than 4% of TB patients experience significant adverse reactions to RIF. Gastrointestinal adverse events (AEs) are the most common, and they include epigastric distress, anorexia, nausea, vomiting, cramps, and diarrhea. Hepatitis rarely occurs in persons who have normal baseline hepatic function. The incidence of hepatitis may be increased for older persons and those who have chronic liver disease or alcoholism, but remains substantially lower than that for pyrazinamide (PZA) or isoniazid (INH). RIF can cause a flu-like syndrome of fever, chills, and myalgia (felt to be related to the development of antirifampicin antibodies), although this is uncommon using the 600 mg dose given daily. In a very small proportion of patients the flu-like syndrome is associated with interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia, and shock. There may be changes in menstruation such as oligomenorrhea and amenorrhea [42].

2.1.3 Efavirenz (EFV)

EFV is a potent non-nucleoside reverse-transcriptase inhibitor (NNRTI) that is widely used in combination with other ARVs for the treatment of HIV-1 infection.

Steady-state plasma EFV clearance is known to be affected by relatively frequent genetic polymorphisms, primarily in CYP2B6 (especially rs3745274 and rs28399499) [36, 37, 43-45], and perhaps also in CYP2A6 [46]. Genotyping of CYP2B6 can be used to characterize individuals as belonging to slow, intermediate, and extensive EFV metabolizer groups.

EFV is known to decrease concentrations of many contraceptive hormones [47], presumably via CYP3A induction. EFV-based ART has been demonstrated to

decrease LNG exposure by approximately 50% after release from a contraceptive implant in women living with HIV [48]. EFV also decreased oral LNG by approximately 60% after a single dose in healthy volunteers (discussed further in section 2.2) [24].

Safety Profile

The most significant AEs observed in patients receiving EFV were central nervous system (CNS) symptoms, psychiatric symptoms, and rash [38]. CNS symptoms usually begin during the first one or two days of therapy and generally resolve after the first 2 to 4 weeks. Dosing at bedtime (and without food) improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in patients who continue to experience these symptoms.

Serious psychiatric adverse experiences have been reported, including severe depression, suicidal ideation or attempts, aggressive behavior, paranoid reactions, and manic reactions.

Rash is usually mild to moderate and occurs within the first 2 weeks of initiating therapy. In most persons, rash resolves with continuing EFV therapy within 1 month.

2.1.4 Dolutegravir (DTG)

Dolutegravir is a second-generation integrase strand transfer inhibitor (INSTI) that binds HIV integrase enzyme, inhibiting transfer of HIV DNA into the DNA of host cells. DTG has a rapid and durable virologic response with an optimized background treatment, low PK variability, few DDIs, and a high genetic barrier to resistance. DTG once daily dosing is recommended in treatment-naïve individuals or in individuals with no resistance to other INSTIs [19].

DTG is primarily a substrate of UDP-glycuronosyltransferase (UGT)1A1, with minor involvement of CYP3A4. Less than half the oral dose (31%) of DTG is eliminated in urine as metabolites, while the majority of the DTG is eliminated unchanged in feces (53%). Its elimination half-life is 14 hours. In vitro, DTG is also a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). DTG is not found to induce or inhibit these transporters or UGT and CYP isoenzymes at clinically relevant concentrations [49].

DTG has low DDI potential due to its lack of induction or inhibition of metabolizing enzymes and renal transporters. A study of DTG 50 mg twice daily with oral ethinyl estradiol and norgestimate found that the oral contraceptive PK profiles were not significantly impacted by coadministration with DTG [50]. In vitro, DTG inhibits the OCT2 transporter at clinically relevant concentrations, and a reversible increase in serum creatinine is has been observed clinically in the first 4 weeks of use (mean change: 0.11 mg/dL [-0.60 to 0.62 mg/dL]).

Safety Profile
DTG is generally well tolerated. In Phase III clinical trials, the most common AEs were nausea (14%), headache (13%), and diarrhea (17%). Other AEs included sleep disturbances (23%), fatigue (13%), as well as psychological effects like depression (6%), and anxiety (3%).

2.2 Rationale

Unintended pregnancies are associated with increased maternal and infant morbidity and mortality, risk of maternal to child transmission of HIV, and socioeconomic disparity in women living with HIV. Therefore, a range of available contraceptive choices are of critical importance to avoid unintended pregnancies.

Recently, the European Medicines Authority (EMA) and the United Kingdom (UK) guidelines on emergency contraception [51, 52] advised that women on CYP inducers, specifically EFV and RIF, should receive an adjusted dose of LNG EC (increased from 1.5 mg once to 3.0 mg once post-coital). Although dose adjustment is an accepted strategy to overcome DDIs, it is typically associated with a PK evaluation of the dose adjustment to ensure normal exposure is restored with the dose adjustment. In this instance, this recommendation was made in the absence of data to confirm this strategy corrects LNG exposure in the presence of this DDI.

The primary objective of this study is to provide evidence to support or refute this guideline recommendation: does doubling the dose of LNG EC overcome known DDIs with EFV or RIF by resulting in similar PK exposure between the dose-adjusted groups and the control group. PK is a well-established surrogate marker to evaluate the clinical impact of a DDI. In the absence of a known concentration-response relationship that can be used to inform a "no effect" relationship, the US Food and Drug Administration (FDA) recommends a bioequivalence range (see section 10.0) as an acceptable alternative to assess a DDI [53]. Given LNG EC does not have a known threshold for effectiveness that may be used to determine the "no effect" relationship (see section 2.1), we have designed this study utilizing standard FDA methods for determination of bioequivalence [54] to evaluate the impact of this DDI.

Emergency contraception drug-drug interactions (DDIs)
One of the challenges in using EC in clinical trials including HIV or TB therapy is the potential for DDI resulting in impaired EC effectiveness. There is a growing body of information documenting DDI between hormonal contraceptive agents and ARVs, as well as other drugs commonly used by women living with HIV [47]. LNG is metabolized by the CYP3A enzyme system to inactive metabolites. This results in a risk of DDI that may decrease LNG exposure, and possibly its effectiveness, with CYP3A inducers (such as EFV and/or RIF).

One PK study evaluated standard-dose LNG EC in combination with EFV. The combination resulted in a 57% reduction in overall LNG exposure area under the concentration time curve, likely related to CYP3A enzyme induction by EFV [24]. Notably, this study was conducted in 21 healthy-volunteer, HIV-negative women (10% reported Black race), with a

different dose of LNG for EC (0.75 mg q12h x 2 doses) than is currently recommended (1.5 mg x 1 dose). It was recently demonstrated that the magnitude of the DDI between EFV and LNG is influenced by CYP2B6 polymorphisms [55]; therefore, the extent of this DDI may be different in diverse ethnic and racial populations.

Supporting the relationship between pregnancy outcomes and low LNG PK exposure, one study identified unacceptably high pregnancy rates in Ugandan women using EFV and a continuous LNG contraceptive [48]. The relationship between LNG EC exposure and efficacy has also been established; obesity reduces LNG exposure and obese women have a 4-fold greater risk of contraceptive failure compared to women with normal weight [56]. Dose adjustment of LNG to 3.0 mg for EC in obese women results in normalized drug exposure without increasing LNG-related AEs [30]. Notably, no serious AEs were reported in the study group that received the increased dose of LNG EC [30].

DTG is not expected to alter LNG PKs. No studies examining LNG with DTG have been conducted. However, based on the routes of metabolism and elimination of LNG and DTG (sections 2.1.1 and 2.1.4), no clinically significant interaction is expected. A study of DTG plus a coformulated oral contraceptive containing a synthetic progestin, norgestimate, plus ethinyl estradiol found no clinically significant impact of DTG on norgestimate PKs among healthy women [50].

Considerations for enrollment of women and girls aged 16-17
This study includes a hormonal contraceptive method for use in women; therefore only women will be included. Because it is a hormonal contraceptive method intended to prevent pregnancy, pregnant women will not be included. LNG EC is not known to be associated with fetal or reproductive risk, but it is a contraceptive method intended to prevent pregnancy. Because the study is enrolling volunteers who do not require LNG EC to prevent pregnancy (i.e., within 72 hours after unprotected sex that could lead to pregnancy), an effective form of contraception (defined in section 4.1.5) is required during the study period for women of reproductive potential who engage in sex that could lead to pregnancy.

Adolescent girls aged 16-17 will be included as this age group is at greater risk for HIV infection, TB infection, unintended pregnancy, and gender-based violence. Both the American Academy of Pediatrics (AAP) and the Society for Adolescent Health and Medicine (SAHM) advocate for the use of LNG EC for girls requiring episodic contraception due to sex without contraception, contraceptive failure during sex, or gender-based violence [57, 58]. Further, both in the US and LMICs, both patient and provider knowledge regarding the use of EC is suboptimal, and family planning groups advocate for increased awareness and knowledge about the availability and use of EC [57-59]. Inclusion of this at-risk population of adolescent girls will achieve this increased awareness, while allowing the study population to appropriately represent the characteristics of girls and women for whom this therapy is needed. Girls under 16 years of age will not be included, as the PKs of LNG may be influenced by changing CYP metabolism during early adolescence. Sites may elect to only include adult (according to local age criteria) women if they lack access to enrollment of adolescent girls, or are unable to include this age group due to local regulations.

Breastfeeding Women

Breastfeeding women will be included only after their infants are 6 months old or older. Progestin-containing contraceptives are recommended during breastfeeding. During long-term contraception with progestins, steroid levels in infant plasma are only 1-6% of the levels in maternal plasma. Isolated cases of decreased milk production have been reported with the use of levonorgestrel; however, cohort evaluations indicate no adverse effects of progestin exposure have been found on breastfeeding (quality or quantity of milk) [21, 60, 61]. However, because this is a volunteer PK study **in** women who are not using the EC to prevent pregnancy, women breastfeeding an infant under 6 months of age will be excluded. After 6 months, weaning often starts and the infant will receive a smaller daily volume of breast milk.

Acceptability and practicality of EC as an exploratory objective

The ACTG has a demonstrated commitment to meaningful community engagement and increasing the diversity of trial participants. While at least one study of women in LMIC found that 85% of women were willing to use EC [17], the acceptability and practicality of administering EC in the context of an ACTG study has not yet been evaluated. An exploratory objective regarding acceptability and practicality of EC will provide valuable information about acceptability. This objective may also identify barriers to administration of EC at the site level regarding infrastructure, reimbursement, or education/outreach needs. Acceptability and practicality will be assessed via questionnaires for participants and site staff.

Postcoital contraception is generally reported to be an acceptable contraceptive option [62]. Allowing EC as a contraceptive option may be a viable strategy for increasing the enrollment of women of reproductive potential in ACTG trials. This exploratory objective will evaluate if postcoital contraception is acceptable in the context of an ACTG trial.

Inclusion of hair samples as an adherence metric in the study

Since this study will perform PK sampling to assess the impact of increased doses of LNG EC to overcome known DDIs between LNG and EFV or RIF, it is imperative to assure adequate long-term adherence to the ART or TB drug of interest at the time of study procedures. The demonstration of long-term adherence to the ART or TB drug in question will assure that these medications are at steady state at the time of PK sampling of the administered LNG EC in this protocol.

Self-reported adherence can overestimate drug-taking due to social desirability bias [63]. Medication electronic monitoring systems (MEMS) cannot measure actual drug ingestion. Plasma levels can be susceptible to “white coat effects,” where adherence improves transiently prior to study visits [64]. Moreover, marked day-to-day variation in plasma levels can limit their utility in representing typical patterns of adherence [65-69]. For medications phosphorylated intracellularly, such as the active moieties of tenofovir (TFV) or emtricitabine (FTC), concentrations of intracellular anabolites in dried blood spot (DBS) relay information on exposure over longer dosing periods [70]. Hair and DBS measures of TFV and FTC (and their anabolites tenofovir diphosphate [TFV-DP] and emtricitabine triphosphate [FTC-TP]) are strongly correlated [70]. However, because INSTIs (e.g., DTG) and NNRTIs (e.g., EFV) do not exhibit intracellular phosphorylation, measurement of intracellular concentrations in

DBS does not offer any additional advantage to plasma levels with these ARVs. The concentration of medications in hair reflects drug uptake from the systemic circulation over weeks to months and thereby provide a long-term measure of medication adherence [71].

Hair concentrations of ARVs are the strongest independent predictor of virologic success in large prospective cohorts of patients living with HIV [68, 69, 72-77], providing pharmacodynamic relevance for the longitudinal exposure data provided by hair samples. Hair levels of ARVs are stronger predictors of treatment outcomes than self-reported adherence [68, 72, 74-77] or single plasma ARV concentrations [68, 73].

Unlike phlebotomy, hair collection is noninvasive and does not require specific skills, sterile equipment, or specialized storage conditions. Hair sample collection merely requires a pair of scissors and storage and shipment at room temperature. The laboratory and its investigators have published data on high rates of acceptability and feasibility (>95%) of collecting hair samples for hair ARV monitoring in Africa [66, 67, 69]. Therefore, hair concentrations will provide long-term exposure information to EFV, DTG and INH (as a proxy for RIF adherence) in this study.

Pharmacogenetic evaluation

As described above, pharamacogenetic variation influences drug exposure, and single nucleotide polymorphisms (SNPs) in CYP2B6 that influence EFV metabolism were associated with the extent of the DDI between EFV and LNG in one report [**55**]. We plan to study the following SNPs in CYP2B6/CYP2A6 for EFV, UGT1A1 for DTG and SLCO1B1 for RIF. These SNPs occur in 25-50% of individuals regardless of ancestry allowing the identification of associations even with a small sample size.

In addition to these frequent SNPs, other SNPs that are known to be associated with ART or LNG will also be evaluated. For EFV, genotyping will include at least four CYP2B6 and CYP2A6 SNPs that predict increased plasma EFV exposure, including CYP2B6 516G→T (rs3745274), 983T→C (rs28399499), 15582C→T (rs4803419), and CYP2A6, -48T→G (rs28399433). These polymorphisms in combination explain approximately 35% of interindividual variability in plasma EFV exposure. For RIF, genotyping will include at least SLCO1B1 rs4149032 that has been associated with RIF bioavailability, and SLCO1B1 521T→C (rs4149056) that has been associated with decreased transporter activity. For DTG, genotyping will include at least UGT1A1 rs887829 that is associated with higher plasma DTG concentrations. For LNG, genotyping will include at least SNPs identified in genome-wide studies or PharmGKB for CYP3A4 *(*rs28371759, rs34670419, rs35599367), CYP3A5 (rs4646450, rs776746), CYP1A1 (rs2470893, rs2472297), CYP1A2 (rs1378942, rs2069514, rs2472299, rs2472304, rs28399424, rs56107638, rs56276455, rs72547516, rs762551) or estrogen phenotypes (rs1864729, rs2414095, rs2445762, rs117585797, rs727428).

Rationale Summary

EC represents a useful second method of contraception for women participating in clinical trials, as well as women who are unable or unwilling to receive continuous contraception. This study will evaluate the dose adjustment required of LNG EC in combination with EFV-based ART or RIF-containing TB treatment to provide evidence to support use of LNG EC

and its appropriate dosing during clinical care and clinical trial situations for women living with either HIV or TB. The following four groups of volunteers will be used to evaluate LNG EC in combination with important ART and TB strategies in LMIC.

- Randomized Group A: EFV-based ART with standard-dose LNG EC
  This group is important to describe the difference in LNG PKs with standard dose and double dose (Group B) of LNG EC in the context of EFV. Although one study reports the effect of EFV on LNG, this study was done in a predominately Caucasian group of healthy volunteers using an alternative dose of EC. The inclusion of Group A will inform the extent of this DDI in women living with HIV, and women of diverse genetic and ethnic backgrounds, given the US and non-US sites participating in A5375, particularly because of known pharmacogenetic differences across populations. In addition, it will inform whether doubling the dose of LNG EC from 1.5 mg to 3.0 mg in the presence of EFV results in higher LNG exposure. The dose-exposure relationship cannot be assessed without two different doses of LNG EC administered in the combination with EFV.

- Randomized Group B: EFV-based ART with double-dose LNG EC
  According to UK and EMA emergency contraception guidelines, this LNG EC dose is already recommended in the absence of data. EFV will remain clinically relevant in LMIC for the coming decades [20], so verifying that LNG PK exposure with a double dose of LNG EC in combination with EFV is safe and equivalent to LNG exposure in the absence of a DDI (Group C) will support women's contraceptive options.

- Assigned Group C: A control group receiving DTG-based ART with standard-dose LNG EC
  This group will act as an active control group, because a control group of women living with HIV who are not receiving ART is not ethically feasible. DTG was selected because it is not expected to have DDIs with LNG, and it is the regimen whose use is expanding in LMIC.

- Assigned Group D: RIF-containing TB therapy with double-dose LNG EC
  According to UK and EMA emergency contraception guidelines, this dose is already recommended in the absence of data. RIF is the cornerstone of TB therapy. Verifying that this double dose is safe and results in equivalent LNG exposure in the absence of a DDI (Group C) will support women's contraceptive options. The protocol team considered also including a group receiving RIF with standard-dose LNG EC; however, because RIF is a similar or more potent CYP inducer than EFV, the expected decrease in LNG exposure after standard-dose in combination with RIF is expected to be the same or even greater than that of Group A. The effect of dose escalation on LNG exposure in the presence of a DDI will already be addressed via comparison of Groups A and B. Therefore, to increase efficiency and conserve resources, the study is designed to only evaluate whether dose escalation of LNG EC overcomes the expected interaction with RIF.

3.0 STUDY DESIGN

A5375 is a Phase II, open-label, four parallel group, partially randomized, PK study to assess if a double dose of LNG EC overcomes known DDI with EFV-based ART and RIF-containing TB therapy. The safety of double-dose LNG EC versus standard-dose will also be compared.

Participants will be volunteers who do not currently require EC for contraception. This study will enroll a total of 116 women who are 16 years of age or older. Group assignment will be determined by infection status (HIV or TB; participants cannot be coinfected), and, for those who are living with HIV, by ART regimen at enrollment. Women living with HIV who are taking EFV-based ART will be randomized to Group A (17 participants) or B (33 participants) in a 1:2 ratio. Women taking DTG-based ART will be assigned to Group C (33 participants). Women who are HIV-negative and in the continuation phase of active TB treatment taking RIF and INH will be assigned to Group D (33 participants).

At study entry, participants in Groups A and C will receive a standard (1.5 mg) single dose of LNG EC. Participants in Groups B and D will receive a double (3.0 mg) dose of LNG EC. Intensive PK monitoring will be conducted pre-dose, and after the LNG EC dose. Women are expected to be at the clinical site while the initial 8 hour PK samples are collected and may return for the 24 and 48 hour samples.

Information about demographic factors that can affect drug concentrations such as age, ethnicity, disease state, and concomitant drug use will be collected on all participants. Whole blood will be collected and stored for pharmacogenetic analyses.

Body fat content will be estimated using weight, height, neck, hip, and waist measurements. Because LNG exposure is known to be inversely correlated with weight/BMI (i.e., women with an obese BMI have lower LNG exposure) [30, 31], women with a BMI ≥30 kg/m^2 will be limited to no more than five within each of Groups B-D, and no more than three within Group A. Therefore, the representation of obese women will be no more than 15% of the study sample, and stratification limits by group will help control for imbalance across groups for this potential confounder.

All participants will complete self-report questionnaires to assess adherence to TB therapy and ART, menstrual history and patterns after LNG EC administration, and to collect adverse effects commonly reported with LNG EC (i.e., irregular bleeding patterns). Adherence to ART and RIF will also be assessed by collecting hair samples and single plasma concentrations at entry.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Postmenarcheal female.

Note: Participant report and clinician's opinion are acceptable.

4.1.2 The following laboratory values obtained within 30 days prior to study entry by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance (EQA) programs.

- Absolute neutrophil count (ANC) ≥500 cells/mm^3
- Platelet count ≥50,000 platelets/mm^3
- Hemoglobin ≥8.0 g/dL
- Aspartate transaminase (AST) <5 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) <5 x ULN
- Creatinine ≤1.5 x ULN
- Total bilirubin ≤2.0 x ULN

4.1.3 Negative serum or urine pregnancy test within 30 days prior to study entry and within 48 hours prior to entry (if screening occurs more than 48 hours prior to entry) by any US clinic or US laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC)/CLIA-waived test, or at any network-approved non-US laboratory or non-US clinic that operates in accordance with GCLP and participates in appropriate EQA programs. The serum or urine pregnancy test must have a sensitivity of at least 25 mIU/mL.

4.1.4 Has not had sex that could lead to pregnancy without contraception within 14 days prior to study entry as defined in section 4.1.5, according to participant self-report.

4.1.5 Contraception requirements

All participants must agree not to participate in a conception process (e.g., active attempt to become pregnant or in vitro fertilization) for the duration of the study. Women of reproductive potential, who are participating in sexual activity that could lead to pregnancy, must agree to use at least one reliable method of contraception while in the study. Acceptable forms of contraceptives include:

- Male condom with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal IUD
- Bilateral tubal ligation
- Male partner vasectomy

4.1.6 Women and girls ≥16 years of age.

4.1.7 Ability and willingness of **the** participant to provide informed consent.

4.1.8 BMI (kg/m^2) available at entry. See section 6.3.5 for BMI calculation instructions.

Note: A maximum of **five** participants with BMI **≥**30 kg/m^2 will be allowed in each arm B-D and a maximum of **three** participants in Arm A.

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

Note: The term “licensed” refers to a US FDA-approved kit, which is required for all IND studies, or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally. Non-US sites are encouraged to use US FDA-approved methods for IND studies.

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

4.1.10 For women living with HIV: Receiving a stable qualifying concomitant ART regimen containing either once-daily DTG 50 mg or EFV 600 mg with no changes in the components of their ART for at least 30 days prior to study entry.

4.1.11 For women who are being treated for TB: HIV-negative at screening, documented within the prior 6 months by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, or plasma HIV-1 RNA viral load.

Note: The term “licensed” refers to a US FDA-approved kit, which is required for all IND studies, or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally. Non-US sites are encouraged to use US FDA-approved methods for IND studies.

WHO and CDC guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle

(e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.12 For women who are HIV-negative and being treated for TB: Receiving RIF and INH on a once daily dosing (7 days per week) schedule at study entry, after completion of the intensive phase of TB treatment.

Note: Inclusion of ethambutol as part of continuation phase of TB therapy is allowed.

4.1.13 Ability and willingness of participant to be contacted remotely for study visits.

4.2 Exclusion Criteria

4.2.1 Known allergy/sensitivity or any hypersensitivity to LNG or components of the formulation.

4.2.2 Bilateral oophorectomy, hysterectomy, or postmenopausal.

Note: Postmenopausal is defined as amenorrhea for at least 12 consecutive months prior to study entry (in the absence of medications known to induce amenorrhea), and have a documented follicle stimulated hormone-release factor (FSH) measurement >40 mIU/mL or a result in the testing laboratory's menopausal range. If an FSH level is not available, 24 consecutive months of amenorrhea prior to study entry (in the absence of medications known to induce amenorrhea).

Note: Clinical assessment and clinician's opinion are acceptable.

4.2.3 Currently pregnant, within 6 weeks of delivery, or currently breastfeeding an infant under 6 months of age.

Note: For recent pregnancy resolution during the first or second trimester, the participant is only eligible when the pregnancy test result is negative.

4.2.4 Receipt of LNG within 30 days prior to study entry.

4.2.5 Receipt of depo-medroxyprogesterone for 90 days prior to study entry, or norethisterone enanthate (NET-EN) within 60 days prior to study entry, or other hormonal contraceptives within 30 days prior to study entry.

4.2.6 Use of any drugs other than RIF and EFV known to: 1) induce CYP3A4 system within 30 days prior to study entry, and 2) inhibit the CYP3A4 system within 7 days prior to study entry. See Appendix IV for prohibited and precautionary medications.

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

4.2.8 Acute or serious illness requiring systemic treatment and/or hospitalization within 14 days prior to study entry.

4.2.9 Other medical, psychiatric, or psychological condition that, in the opinion of the site investigator, would interfere with completion of study procedures and or adherence to study drug.

4.2.10 For women living with HIV: Currently receiving medications for TB **disease**.

Note: Isoniazid alone given for TB prophylaxis is allowed.

4.2.11 For women living with HIV: Has missed one or more of the prescribed doses of HIV medications within 3 days prior to study entry.

Note: The entry visit may be rescheduled within the screening period once the participant has taken all prescribed doses within 3 days prior to study entry.

4.2.12 For women who are HIV-negative and being treated for TB: Has missed one or more of the prescribed doses of TB medication within 3 days prior to study entry.

Note: The entry visit may be rescheduled within the screening period once the participant has taken all prescribed doses within 3 days prior to study entry.

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. Protocol activation is required before each site can enroll any participants.

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICF(s) will not be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification from the DAIDS PRO that approves the site-specific ICFs and indicates successful completion of the amendment

protocol registration process. A copy of the final Amendment Registration Notification issued by the DAIDS PRO should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant (or, when necessary, the parent or legal representative if the participant is younger than 18 years of age or under guardianship) will be asked to read and sign the approved protocol consent form. For those under the age of consent, assent will also be obtained according to the local IRB requirements and regulations.

For participants from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Subject Enrollment System.

4.3.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.3.3 Randomization/Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the protocol, an ACTG Screening Failure Results form must be completed and keyed into the database.

Participants who meet the enrollment criteria will be randomized (if taking EFV-based HIV therapy) or registered (if taking DTG-based HIV therapy or RIF-containing TB therapy) to the study according to standard ACTG DMC procedures.

4.4 Co-enrollment Guidelines

- US sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Co-enrollment in A5128 does not require permission from the A5375 protocol chairs.
- Non-US sites are encouraged to co-enroll participants in A5243, “Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.” Co-enrollment in A5243 does not require permission from the A5375 protocol chairs.
- For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as levonorgestrel emergency contraception (LNG EC) 1.5 mg or 3 mg.

5.1 Regimens, Administration, and Duration

5.1.1 Regimen

At study entry, participants will be randomized or assigned in open-label fashion to Group A, B, C, or D, and will receive one standard (1.5 mg) or double (3 mg) dose of LNG EC depending on the randomized or assigned group as follows:

Table 5.1.1-1: LNG EC Dose by Group

Group	LNG EC Dose
Randomized Group A	1.5 mg once on Day 0
Randomized Group B	3 mg once on Day 0
Assigned Group C	1.5 mg once on Day 0
Assigned Group D	3 mg once on Day 0

5.1.2 Administration

LNG EC 1.5 mg: **A**dministered **orally** as one 1.5 mg tablet **or two 0.75 mg tablets**.
LNG EC 3 mg: **A**dministered **orally** as two 1.5 mg tablets **or four 0.75 mg tablets**.

The appropriate dose of LNG EC will be administered by mouth in a directly observed manner. LNG EC should be administered with food (or within 2 hours of food), but there is no calorie or other content requirements for that food intake.

5.1.3 Treatment Duration

Study participants will receive one dose of LNG EC on Day 0 and will be followed post-treatment for 4 weeks.

5.2 Study Product Formulation and Preparation

LNG EC **provided through the study will be supplied** as 1.5 mg round tablets. The tablets are pink and packaged in a blister pack in a carton. Do not use if carton is open or blister seal is broken or missing. The product should be stored at room temperature between 20-25°C (68-77°F).

LNG EC 1.5 mg or 0.75 mg tablets locally procured by the site and approved for use in A5375 by the protocol team must be stored in accordance with the manufacturer's instructions.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

LNG EC **1.5 mg (New Day™)** will be supplied by NorthStar Rx and will be made available to sites through the NIAID Clinical Research Products Management Center (CRPMC). Upon successful completion of protocol registration procedures, the product may be obtained by the site pharmacist by following the instructions provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

LNG EC 0.75 mg (Pregnon), supplied by Mylan, may be locally sourced by clinical research sites that are unable to import study-provided LNG EC. The A5375 Site Implementation Plan (SIP) must be completed by each site for protocol team notification and authorization of locally sourced LNG EC.

Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the United States in NIAID (DAIDS)-supported and/or -sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at https://www.niaid.nih.gov/sites/default/files/NonFDAapprovedProducts.pdf.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC **or other sources,** and subsequently dispensed. All study products must be stored in the investigational pharmacy.

5.3.3 Final Disposition of Study Product

All unused study products remaining at US clinical research sites after the study is completed or terminated must be returned to the NIAID CRPMC (unless otherwise directed by the sponsor). Study products may also be returned to the CRPMC for other reasons, as requested by the sponsor. Site pharmacists will follow the relevant instructions for return of unused study products provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

At non-US clinical research sites, the site pharmacist must follow the instructions provided in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for the destruction of unused study products.

5.4 Concomitant Medications

Whenever a concomitant medication or study product is initiated or a dose changed, investigators must review the concomitant medication's and study product's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Required Medications

Required ARV therapy (not provided through study) for participants living with HIV:

- Efavirenz (EFV) 600 mg in combination with two or more NRTIs

  OR

- Dolutegravir (DTG) 50 mg in combination with two or more NRTIs

Required TB treatment (not provided through study) for participants with TB:

- Rifampicin (RIF)

  AND

- Isoniazid (INH)

  Note: Pyridoxine (vitamin B_6), if recommended by local standard of care with INH, will not be supplied through the study and must be obtained locally by the site.

5.4.2 Prohibited Medications

Other hormone therapies, therapy for TB (except Group D), and significant CYP inducers or inhibitors other than study therapy. Prohibited medications are listed in Appendix IV.

5.4.3 Precautionary Medications

Precautionary medications are listed in Appendix IV.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations (SOE)

Table 6.1-1: Schedule of Participant Evaluations

Evaluation	Screening	Entry	Post-Dose	24 hours post-dose (±2 hours)	48 hours post-dose (±2 hours)	Post-dose (±3 days)			Clinically Indicated Visit	Premature Study Discontinuation
	-30 Days	Day 0		Day 1	Day 2	Day 7	Day 14	Day 28		
Documentation of HIV Status	X									
Medical History	X	X								
Gynecological History	X	X				X	X	X		X
Medication History	X	X								
Targeted Physical Exam	X	X							X	
BMI	X									
Body Fat Estimate Measurements		X								
Signs and Symptoms		X	X	X	X	X	X	X	X	X
Diagnoses		X		X	X	X	X	X	X	X
Concomitant Medications		X		X	X			X	X	X
LNG EC Administration		X								
Hematology	X									
Liver Function Tests	X									
Blood Chemistries	X									
Pregnancy Test	X	X							X	
CD4+/CD8+ for Groups A, B, & C		X								
HIV-1 RNA for Groups A, B, & C		X								
PK Sampling		X	X	X	X					
Whole Blood for Pharmacogenetic Assessment		X								
Hair Sampling			X							
Adherence Assessment (ART and TB Drugs)	X	X		X	X					
Acceptability and Practicality Questionnaire		X			X		X	X		X

Table 6.1-2: Schedule of Site Evaluations

Evaluation	Timepoint
Site Acceptability and Practicality Questionnaire	Once during site-participation in study

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur after the informed consent is signed and prior to the participant starting any study medications, treatments, or interventions.

Screening
Screening evaluations to determine eligibility must be completed within 30 days prior to study entry unless otherwise specified.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured for participants who do not enroll and entered into the ACTG database.

6.2.2 Entry Evaluations

Participants must complete all entry evaluations prior to administration of study treatment.

Participants must receive treatment under direct observation of study staff within 7 days of enrollment.

6.2.3 Post-Entry Evaluations

Post-entry evaluations occur after study treatment is administered.

The two final post-dose PK visits should occur 24 hours post-dose ±2 hours, and 48 hours post-dose ±2 hours. If the visit occurs outside of this window, but within 72 hours of the LNG EC dose, the sample should still be collected.

The 24 and 48 hours post-dose study visits may only be conducted remotely (e.g., telephone, telehealth) in the following situations during the COVID-19 outbreak:

- **A participant is unable to attend a visit because of personal illness, COVID illness among others in their home, or local conditions or guidelines restricting travel to the clinic; the site must inform the core team (actg.corea5375@fstrf.org).**
- **The site is temporarily unable to conduct non-essential visits in the clinic; the site must inform the core team (actg.corea5375@fstrf.org).**

Regardless of the situation, sites should document which visits were conducted remotely, attempt to obtain as much of the visit-specific required information as possible, based on the SOE, and record it on the relevant eCRF. The impacted visits and rationale must be reported and documented, following instructions provided by the team or network leadership.

Follow-up assessments at 7, 14, and 28 days post entry are conducted by remote contact interview and should occur within the ±3 days window.

If clinically indicated (refer to section 6.3.5), participants will be requested to return to the clinic for a visit.

Study Completion Evaluations
The week 4 evaluations will be performed as the final study visit. A study discontinuation eCRF must be keyed for all participants at the time of premature discontinuation, or at week 4 for participants who complete the study, including participants who miss the final visit.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized or Registered Participants Who Do Not Start Study Treatment
Participants who are enrolled but do not complete the study treatment will be taken off the study. No further evaluations are required. These participants will be replaced. All eCRFs must be keyed for the period up to and including the entry visit.

Premature Study Discontinuation
Women who do not complete the post-dose 8-hour PK study visit to assess LNG concentrations are not evaluable for the primary outcome and will be discontinued from the study and replaced. If the participant does not return for the 24- and 48-hour evaluations or is not reached for the follow-up evaluations on Days 7, 14, and 28, this will be considered a missed visit and the participant will remain on study.

Participants who prematurely discontinue from the study will have the premature discontinuation evaluations performed by remote contact interview or at the clinic prior to being taken off the study, as noted in the Schedule of Evaluations (SOE).

6.3 Instructions for Evaluations

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for Laboratories Performing Testing for DAIDS-Supported and/or Sponsored Clinical Trials, which is available at https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf.

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), and AE reporting of adverse events requirements.

6.3.1 Documentation of HIV-1

Sections 4.1.9 and 4.1.11 specify assay requirements for HIV-1 documentation.

6.3.2 Medical History

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

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B

Any pregnancy and/or pregnancy outcome within 1 year prior to study entry must be recorded.

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

6.3.3 Gynecological History

Baseline Gynecological History
Obstetric history, age of menarche, cycle length, and frequency will be obtained at the screening visit.

The menstrual history over the past 6 months will cover the participant's perception of her usual frequency of menstrual cycles, how long the menstrual bleeding usually lasts, and whether she usually has spotting between menstrual cycles.

Interval Gynecological History
The participant will be asked about spotting between menstrual cycles and the last menstrual period (date of first day of bleeding) will be collected at the clinic at the entry visit, and by remote contact interview post-entry, per the SOE. Questionnaires are posted on the DMC Portal in the Forms Management Utility.

Contraceptive History
At study entry, record all contraceptive methods currently utilized or utilized within the 120 days prior to study entry, including non-hormonal methods, as listed in section 4.1.5 (Contraception requirements) of the protocol.

6.3.4 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

The medication history evaluation will be assessed at the screening and entry pre-treatment visits and recorded on the eCRFs at the entry pre-treatment visit.

Table 6.3.4-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	1 year prior to study entry
Immune-based therapy	1 year prior to study entry
Tuberculosis therapy	1 year prior to study entry
Blinded study treatment	30 days prior to study entry
Prescription drugs for treatment of opportunistic infections	30 days prior to study entry
Prescription drugs for prophylaxis of opportunistic infections	30 days prior to study entry
Prescription drugs (other)	30 days prior to study entry
Alternative therapies	30 days prior to study entry
Dietary supplements	30 days prior to study entry
Sex-hormone medications or sex-hormone analogues or antagonists*	1 year prior to study entry except as noted below
Barrier methods for contraception	1 year prior to study entry
Other – in vitro fertilization (IVF)	30 days prior to study entry

*Includes: hormone-releasing IUDs (e.g., Mirena inserted in the last 5 years); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors or any other androgen, estrogen, spironolactone, emergency contraception, or progesterone analogue or antagonist therapy.

6.3.5 Clinical Assessments

Targeted Physical Examination
A targeted physical exam is to include vital signs (height [collected only at screening], weight, temperature, pulse, respiration rate, and blood pressure). A targeted physical exam will be conducted:

- As indicated in the SOE.
- If clinically indicated by any previously identified or new symptom possibly related to study treatment, study procedures, SAE, or pregnancy that the participant has experienced since the last visit or at this visit.

Post entry, see section 8.2 for collection requirements for pregnancy.

BMI
BMI calculated using height and weight collected at screening. Refer to the BMI Index calculator located on the FSTRF web site.

Body Fat Estimate Measurements
Collect as indicated in the SOE. Waist, hip, and neck measurements are required. Height will be recorded at screening. Please see the study-specific manual of procedures (MOPS) for body measurement instructions.

Signs and Symptoms
At entry, all grades of signs and symptoms that occurred within 30 days prior to study entry must be recorded.

Post-entry, information may be collected by remote contact interview or during a site visit via participant questionnaire (see section 6.3.13) including: nausea, stomach/abdominal pain, vomiting, tiredness, headache, dizziness, breast pain, vaginal bleeding (related to menstruation), and menstrual discomfort.

Refer to section 7.2 for AE collection requirements.

Diagnoses
Record all diagnoses identified by the ACTG criteria for clinical events and other diseases, as indicated in the SOE. Post-entry, information may be collected by remote contact interview or during a site visit.

Refer to section 7.2 for AE collection requirements.

Concomitant Medications
The following new and discontinued concomitant medications must be recorded as indicated in the SOE:

- Sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.4 for examples).

- ART medication modifications (Groups A-C only): Record all ARV medication modifications, including initial doses, participant-initiated modifications, physician modifications, and/or protocol-mandated modifications, inadvertent and deliberate interruptions of more than 7 days since last recorded per the SOE, and record any permanent discontinuation of ART treatment.
- TB medication modifications (Group D only): Record all TB medication modifications, including initial doses, participant-initiated modifications, physician modifications, and/or protocol-mandated modifications, inadvertent and deliberate interruptions of more than 7 days since last recorded per the SOE, and record any permanent discontinuation of TB treatment.

Post-entry, information may be collected by remote contact interview or during a site visit.

LNG EC Administration
Record the study treatment administration, including date and time of administration, and if the participant vomited the dose within 2 hours of administration. Refer to section 6.2.2 for the timing of dose administration.

6.3.6 Laboratory Evaluations

Record and key all laboratory values regardless of grade. Laboratory evaluations will be collected per the SOE.

Hematology
Hemoglobin, hematocrit, white blood cell (WBC) count, ANC, and platelet count.

Liver Function Tests
Total bilirubin, AST (SGOT), ALT (SGPT), and albumin.

Blood Chemistries
Electrolytes (sodium, potassium, chloride, and bicarbonate), creatinine, and blood urea nitrogen (BUN).

Pregnancy Test
Serum or urine β-HCG (urine test must have a sensitivity of ≤25 mIU/mL) by any US clinic or US laboratory that has a CLIA certification or its equivalent, or is using a POC/CLIA-waived test, or at any network-approved non-US laboratory or non-US clinic that operates in accordance with GCLP and participates in appropriate EQA programs.

There must be a negative pregnancy test within 30 days prior to study entry and within 48 hours prior to study entry, if screening occurs >48 hours prior to entry. If LNG EC is administered more than 24 hours after study entry, the pregnancy test must be repeated if the test was not done within 48 hours prior to LNG EC administration.

Note: The pregnancy test within 48 hours of study entry may be done on the day of entry, but must be performed before enrollment and before any enrollment procedures are completed.

Perform as clinically indicated, as specified in section 6.1. Record pregnancy and pregnancy outcome per section 8.2.

6.3.7 Immunologic Studies

CD4+/CD8+ for Groups A, B, & C
Obtain absolute CD4+/CD8+ count and percentages at entry from a laboratory that possesses a CLIA certification or equivalent **(US sites) or IQA certification (non-US sites).**

Note: If a CD4+/CD8+ count has been drawn for clinical care within the last 45 days, it may be used. This laboratory does not have to provide documentation of GCLP or EQA.

6.3.8 Virologic Studies

Plasma HIV-1 RNA for Groups A, B, & C
At entry, HIV-1 RNA must be performed by a laboratory that possesses a CLIA certification or equivalent **(US sites) or VQA certification (non-US sites)**.

Note: If plasma HIV-1 RNA has been drawn for clinical care within the last 45 days, it may be used. This laboratory does not have to provide documentation of GCLP or EQA.

6.3.9 Pharmacokinetic Sampling

Plasma will be obtained for LNG concentrations. Participants will have blood sampling within 30 minutes prior to LNG EC administration, and then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after administration of LNG EC. Participants may leave the clinical site after the 8 hour sample, and return for the 24- and 48-hour samples.

From the same samples collected for LNG analysis, measurement of EFV (Groups A and B), DTG (Group C), and RIF (Group D) concentrations will occur. EFV will be assessed from a sample collected 12-20 hours after the last dose of EFV. DTG or RIF will be assessed from a plasma sample collected 20-28 hours after the last dose of DTG or RIF. To accommodate this timing, EFV should be administered in the evening prior to the entry PK visit and if RIF or DTG are given in the morning, collect pre-dose LNG sample prior to administered DTG or RIF. See the MOPS for further instructions on timing.

The three doses of EFV, DTG, or RIF prior to the entry PK sampling period should be documented on the eCRF. Any EFV, DTG, or RIF dose administered

during the Day 0 PK visit should be documented. On Day 1 and Day 2, document any EFV, DTG, or RIF dose administered since the previous visit.

Additional details regarding LNG, ART, or RIF PK, please see section 11.3, the MOPS, and the laboratory processing chart (LPC) found on the A5375 PSWP.

6.3.10 Whole Blood for Pharmacogenetic Assessment

A single whole blood sample will be obtained from all study participants for human genotyping of polymorphisms that have been associated with metabolism and/or transport of the study drugs, including EFV (e.g., CYP2B6), RIF (e.g., SLCO1B1), and LNG. See the LPC on the A5375 PSWP for details regarding processing and shipping.

If the whole blood for drug metabolism genotype is not obtained at entry, this sample may be obtained at any later visit.

6.3.11 Hair Sampling

Hair samples will be collected per the SOE from participants to measure concentrations of EFV (Groups A and B), DTG (Group C), and INH (as a surrogate of adherence to RIF in Group D), to evaluate adherence to ART or anti-TB therapy at the time of LNG EC administration. Participants may opt-out of the hair collection procedure and remain enrolled in the study.

Please see section 11.3, the MOPS, and the LPC found on the A5375 PSWP for more details regarding hair sampling.

6.3.12 Adherence Assessment (ART and TB drugs)

Adherence to ART or TB drugs will be assessed per the SOE using the ACTG self-report questionnaires completed by the participant or completed with the help of site staff (counselor- or nurse-driven). Adherence to the relevant ART or TB drug at study entry will be further verified by collecting a plasma and hair specimen on that day for measuring ARV or INH/RIF concentrations. For sites with clinics located at a different location from the TB and ARV clinic, study staff will be encouraged to work closely with TB and ARV providers for monitoring of adherence to medication.

The adherence eCRF is posted on the DMC Portal in the Forms Management Utility.

6.3.13 Acceptability and Practicality Questionnaire

The acceptability and practicality questionnaire will collect information about the participant's experience of side effects known to be associated with LNG EC single dose, per the SOE. At entry, participants will also be asked about

relationship status, level of education, prior experience with EC, sex that could lead to pregnancy, and pregnancy intention.

At entry, the acceptability and practicality questionnaire will be collected via participant interview and entered on the questionnaire. **An entry, the Current Symptoms portion of this questionnaire should be collected prior to LNG dose receipt.**

NOTE: The discomfort/bothersome scale in the Current Symptoms questionnaire is NOT equivalent to the DAIDS grading table for reportable adverse events (please refer to protocol section 7.2), which has particular and more rigorous criteria the event must fulfill to be reported.

Post-entry, the acceptability and practicality questionnaire may be collected by remote contact interview or during a site visit.

Questionnaires are posted on the DMC Portal in the Forms Management Utility.

6.3.14 Site Acceptability and Practicality Questionnaire

Each participating site will complete a Site Acceptability and Practicality Questionnaire per the Schedule of Site Evaluations (Table 6.1-2).

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for this Protocol

AEs must be recorded on the eCRFs if any of the following criteria have been met:

- All Grade ≥3 AEs considered potentially or definitely related to LNG
- All Grade ≥2 nausea
- All Grade ≥2 diarrhea
- All Grade ≥2 menorrhagia or metrorrhagia
- Ectopic pregnancy (see EAE reporting requirements section 7.3.2)
- All AEs meeting Serious Adverse Event (SAE) definition or Expedited Adverse Event (EAE) reporting requirement

Note **A**: Normal menses are not a reportable event.

Note **B:** Events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017.

In addition, Addendum 1, Female Genital Grading Table for Use in Microbicide Studies, Version 1.0 – November 2007, will be used for vaginal symptoms and abnormal uterine bleeding unrelated to pregnancy.

Both grading tables are available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety

Office at DAIDSRSCSafetyOffice@tech-res.com.

7.3.2 Reporting Requirements for this Study

- The suspected, unexpected serious adverse reaction (SUSAR) Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agent for which expedited reporting is required is: levonorgestrel emergency contraception (LNG EC).
- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are*:*
  - Ectopic pregnancies*.*

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table corrected Version 2.1, July 2017, must be used.

In addition, Addendum 1, Female Genital Grading Table for Use in Microbicide Studies, Version 1.0 – November 2007, will be used for vaginal symptoms and abnormal uterine bleeding unrelated to pregnancy.

Note: normal menses are not a reportable event.

Both grading tables are available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the DAIDS EAE manual.
- After the protocol-defined EAE reporting period, unless otherwise noted, only SUSARs, as defined in Version 2.0 of the DAIDS EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

The protocol core team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation, data completeness, and AEs, as appropriate.

The DAIDS **C**linical **R**epresentatives will review and assess select EAE reports for potential impact on study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs, as applicable. Additionally, the DAIDS Clinical Representative will review aggregated adverse event summaries by open-label group **as distributed in the core team monitoring report described above, which will be distributed at least** every 6 months by SDAC.

The study will undergo interim review at least annually by an ACTG-appointed Study Monitoring Committee (SMC). The first interim review will occur no more than 1 year after the enrollment of the first study participant or 3 months after 25 women have completed the study, whichever occurs earlier. An interim review may also be convened if a concern is identified by the DAIDS Clinical Representative, the study chairs, or study statistician in consultation with the team. See section 10.0 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring will be outlined in a Study Monitoring Plan developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT

8.1 Toxicity

Toxicities will be evaluated and managed by the site staff in close consultation with the participants' primary care clinicians. Ongoing communication between the ACTG site staff and the participants' clinicians is encouraged. If a toxicity is identified, the ACTG site staff is encouraged to communicate with primary care providers as soon as possible.

If TB medication or ART is held for toxicity by the primary care physician, participants must inform the site staff. Information about these treatment modifications/interruptions must be recorded on the source document and eCRF.

Grades 1 and 2: Can be managed as per standard of care by the study doctor or local physician.

Grades 3 and 4: Participants must be stabilized and referred immediately to obtain treatment at local hospital, if required.

Vaginal Bleeding: Grade ≥2 must be closely monitored and managed as per standard of care.

Diarrhea: Grade 2 should be managed per standard of care by the study doctor or local physician. Participants with Grades 3 and 4 diarrhea must be stabilized and referred.

8.2 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: 800-258-4263; Fax: 800-800-1052. (For studies conducted at sites outside the United States, report to The Antiretroviral Pregnancy Registry—Telephone: 910-679-1598; Fax: 44-1628-789-666 or 910-256-0637.)

Pregnancy Outcomes and Reporting

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

8.3 Breastfeeding

Breastfeeding is discouraged at sites where alternative feeding options are feasible and available. Sites should follow local guidelines to prevent mother-to-child transmission during breastfeeding.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Premature Treatment Discontinuation

Because the study treatment is a single dose, this section does not apply. See section 9.2 for Study Discontinuation.

9.2 Premature Study Discontinuation

- Participant fails to complete PK specimen draws over the 8-hour period following study treatment
- Participant fails to initiate/take study treatment within 7 days of enrollment
- Participant has a positive pregnancy test prior to LNG EC administration
- Request by the participant to withdraw
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant
- At the discretion of the IRB/EC, FDA**,** NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, or investigator

Note: If the participant discontinues before evaluations for the primary outcome have been completed, the participant will be replaced.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5375 is a Phase II, prospective, partially randomized, open-label, multi-center controlled clinical trial designed to investigate the appropriate dosing of “single dose” levonorgestrel (LNG – intended to be used as EC), among women who are taking medications that might have PK interactions with LNG, such as particular anti-HIV ART regimens or an anti-TB regimen. This parallel group, DDI PK study has two directly assigned groups, and two randomized groups for a total of four distinct study groups:

women on DTG-containing ART regimens and women on RIF-containing TB regimens will be directly assigned to Groups C and D, respectively; and women on EFV-containing ART regimens will be randomized in a 1:2 ratio to Groups A and B, respectively.

Study treatment is LNG EC given once following entry evaluation completion in a directly observed manner: Groups A and C will receive standard dose of LNG 1.5 mg, and Groups B and D will receive double dose of LNG 3.0 mg. Absence of blinding does not affect study integrity via bias due to a number of study design factors including the following: directly observed administration of a study treatment that consists of only a single dose (i.e., one time versus longitudinal intervention), and the primary study outcome is an objectively assessed PK parameter (AUC). The key study evaluation is an intensive, 8-hour PK sampling around this one dose of study treatment. Length of study follow-up is 4 weeks for each participant, but follow-up subsequent to the 48-hour PK assessment will be performed remotely.

Women on the qualifying targeted concomitant medication regimens must not be pregnant, within 6 weeks postpartum, breastfeeding an infant under 6 months of age, or currently using other hormonally based contraception.

The primary completion date for each woman is one day after study treatment administration.

10.2 Outcome Measures

10.2.1 Primary Outcome Measure

10.2.1.1 Area under the Curve over 8 hours (AUC0-8h) for LNG.

10.2.2 Secondary Outcome Measures

10.2.2.1 Safety: Occurrence of any SAE potentially or definitely related to LNG, or occurrence of reportable AEs potentially or definitely associated with LNG EC use (see section 7.2 for list of targeted AEs) during study follow-up.

10.2.2.2 PK estimates of LNG including the following: maximum concentration (C_{max}), minimum concentration (C_{min}), oral clearance (CL/F), volume of distribution (Vd), half-life (T1/2), **time to minimum concentration (T_{min}),** and area under the Curve over 24 hours (AUC_{0-24h}), 48 hours (AUC_{0-48h}), and AUC_{inf} (infinity) of LNG.

10.2.3 Exploratory Outcome Measures

10.2.3.1 Concentration of targeted concomitant medication (e.g., DTG, EFV, and INH) in hair sample collected at entry as measure of long-term concomitant medication adherence.

10.2.3.2 Specific plasma concentration of targeted concomitant medication (e.g., trough of DTG or RIF, mid-dose concentration of EFV).

10.2.3.3 Human genetic variants/polymorphisms that are known to affect PK of EFV, DTG, RIF, or LNG (e.g., CYP2B6, SLCO1B1).

10.2.3.4 Acceptability and practicality of LNG based on participant self-report via study-specific questionnaires.

10.3 Randomization and Stratification

Enrollment to the study is deterministic (not-randomized) for participants who are currently taking either DTG based ART regimens, or RIF-containing anti-TB regimens; these women are directly assigned to Groups C and D, respectively. Participants on EFV-containing ART regimens will be randomized between Groups A (1.5 mg LNG) and B (3.0 mg LNG) in a 1:2 ratio using permuted block randomization that is dynamically balanced within each **institution**. To guard against potential confounding due to body weight or BMI of the participant, enrollment will be **limited** by BMI in the following manner. Women with BMI ≥30 kg/m^2 will be limited to no more than five within Groups B-D and no more than three within Group A. Therefore, the overall representation of obese women in the study sample will be limited to no more than 15%. The results of either randomization or enrollment to treatment group will be unblinded to participants, and clinical research site staff.

10.4 Sample Size and Accrual [53, 78-80]

Given that a therapeutic target for minimum exposure required or average exposure expected for single dose use of LNG as emergency contraception (EC) is unknown, this study is estimating whether adjusted dosing of LNG under a known DDI achieves similar exposure to LNG single dose as measured by the geometric mean ratio (GMR) of the AUC of LNG concentrations over the 8 hours post dose. The study design was developed under the constraints of requiring a parallel groups design (rather than a crossover design using healthy controls), practicalities of number of available participants to enroll and complete the study in a reasonable timeframe, and how the features of this highly variable drug (LNG) result in both power to test for bioequivalence as defined by a specified interval about equivalence, and precision of GMR estimates by the width of the 90% confidence interval.

The effective sample sizes of 30 women in Groups B-D and 15 women in Group A were chosen to provide adequate statistical precision about the estimated GMR, which compares arms in order to address the primary study objectives [54]. See below for the total sample size enrollment, which includes how these effective samples sizes are inflated slightly to accommodate missing primary outcome data.

Table 10.4-1: Sample size per arm (prior to inflation for replacements)

Assumptions: Sample size required to give 80% probability (power) to conclude bioequivalence defined as the 90% CI for the GMR being entirely within the No-effect Bounds (NEB). Various NEBs are provided for BE given that bounds of (80%, 125%) may be considered too conservative for highly variable drugs with a wide therapeutic ranges in PK exposure. [Note: Calculations use 5% significance level with two, one-sided tests (TOSTs) testing procedure.]

Sample Sizes per Arm in Table	Coefficient of Variation Estimates*								
	0.45			0.70			0.90		
Alternative Hypothesis (True GMR*):*	*100%*	*95%*	*90%*	*100%*	*95%*	*90%*	*100%*	*95%*	*90%*
NEB : (67%,150%)	20	22	27	43	45	57	63	67	84
NEB : (70%,143%)	26	28	37	55	59	79	81	87	117
NEB : (75%,133%)	40	45	72	85	97	154	126	144	228

*Note: CV for AUC(0-24hr) ranged from 0.45 to 0.90 in the individual arms of PK study of LNG-EC and St. John's Wort (Time period 1 when LNG-EC given alone, ref ct.gov NCT00131885). Package insert for LNG CV(AUC24hr)=0.7. Data not available for CV of AUC or LNG-EC under shorter time frames.

Summary of Table 10.4-1. Because primary outcome of current study is AUC(0-8hr), it is assumed that the CV for this study may be on the lower range of published AUCs(LNG) over 24 hours. Furthermore, the sample sizes for CV ≥ 0.7 result in study sizes beyond feasibility for execution. NEBs of (80%, 125%) are not given in the table as the required sample would be too large, even under assumed CV=0.45.

Table 10.4-2: Statistical Power assuming n=30 per arm (prior to inflation for replacements)

Assumptions: same as Table 10.4-1 above [NEB = No-effect bounds]

Statistical Power Estimates in Table	Coefficient of Variation								
	0.45			0.70			0.90		
Alternative Hypothesis (True GMR):	*100%*	*95%*	*90%*	*100%*	*95%*	*90%*	*100%*	*95%*	*90%*
NEB : (67%,150%)	95%	93%	85%	58%	56%	50%	29%	28%	25%
NEB : (70%,143%)	88%	84%	72%	40%	38%	33%	12%	12%	10%
NEB : (75%,133%)	63%	58%	45%	9%	9%	7%	0%	0%	0%

Summary of Table 10.4-2 Assuming CV(AUC0-8hr) = 0.45, and other design assumptions above, BE bounds of either (67%, 150%) or (70%, 143%) provide high statistical power, even under modest departures from equivalence alternative (e.g., true GMR of between 90% and 100%). The study design is not well powered for NEBs narrower than (70%, 143%), or for departures from equivalence much larger than 10%

(i.e., true GMRs of less than 90%). Please see references [53, 78-80] that show precedence for using NEBs of (70%, 143%) in similar situations.

Table 10.4-3: Some CI estimates under various alternatives (sample size 30 per arm before inflation for replacements and same assumptions above)—simulation results.

Because the study analysis plan is focused on estimation of the GMR of AUC(LNG) and 90% CI about the estimated (observed) GMR, the following table is provided to augment the sample size/power tables above.

Alternative Hypothesis (True GMR)	CV=0.45				CV = 0.75			
	Q1 Observed GMR	Q3 Observed GMR	Median Observed GMR	Typical 90% CI (median LCB and UCB)	Q1 Observed GMR	Q3 Observed GMR	Median Observed GMR	Typical 90% CI (median LCB and UCB)
100%	93%	108%	100%	(83%, 120%)	90%	115%	100%	(75%, 133%)
95%	87%	103%	95%	(79%, 115%)	83%	108%	95%	(72%, 127%)
90%	84%	96%	89%	(74%, 107%)	81%	102%	90%	(68%, 120%)
85%	79%	93%	85%	(71%, 102%)	74%	95%	84%	(63%, 112%)

Alternative Hypothesis (True GMR)	CV=0.90			
	Q1 Observed GMR	Q3 Observed GMR	Median Observed GMR	Typical 90% CI (median LCB and UCB)
100%	88%	116%	102%	(73%, 141%)
95%	83%	110%	96%	(69%, 134%)
90%	76%	103%	89%	(64%, 124%)
85%	74%	97%	86%	(61%, 119%)

Summary of Table 10.4-3. Under modest departures from equivalence, the 90% CI about estimated GMRs observed to be 85% or closer to equivalence (100%) are expected to be bounded above the BE LCB of 70%.

The effective sample size for randomized Group A (15) is based on the secondary objective for a superiority hypothesis (rather than equivalence testing as in the primary study objectives), comparing the randomized Groups A and B (n=30). Here, the ratio is B/A so that the anticipated raw scale ratios are >100 and the significance level has been adjusted to 0.05 so that a 2-sided 95% CI is calculated and compared to see if the confidence interval excludes 100. There is at least 80% power to conclude a difference between the randomized groups for LNG AUC when the true difference between groups is that the increased dose has at least 47% larger AUC of LNG than the standard-dose (or estimated ratio 147.5). A 95% CI for this estimated ratio would be (112, 194).

A participant is considered to be evaluable for the primary objective if the participant completes the 8 hour PK sampling after LNG EC administration. The participant replacement criteria are described in section 9.0. Participants who are not evaluable for the primary outcome for any reason during the period of study accrual will be replaced.

Considering the sample size calculations above, and to protect against 10% loss of the primary outcomes after study accrual is closed, (e.g., problems related to laboratory analysis), the adjusted sample size for this four-group study is 116 female participants—33 each in Groups B-D, and 17 in Group A. (In another ACTG contraception study, A5093, the loss of the primary outcomes of week 12 was 9.8% [6 of 61 participants] due to either sample specimen loss or assay results not available.)

Complete accrual to all study groups is anticipated to take between 1 year to 18 months. However, it is not assumed for this accrual to be uniform over this time period. Due to differences in regulatory approvals in different locations, it is anticipated that accrual during the first 6 months of the study may by exclusively from US sites. But it is anticipated that accrual will be rapid following the approval of the study at non-US CRSs. As an example, in a recent ACTG PK study investigating DDIs between ART and another contraceptive (A5316: NCT01903031), accrual within the first 6 months following first enrollment was only within the US and accounted for only 20% of total study accrual. However, in the following 6 month period when sites from an additional 6 countries were available, over 55% of the total study sample was accrued (and thus 77% of total study accrual occurred within 1 year). Therefore, it is anticipated that only 20% of the total sample size (or 23) women might be enrolled during the first 6 months following first participant enrollment, and that the remaining accrual will occur in the subsequent 6-12 months (which assumes enrollment of 8-16 women per month over this time period). Please see below for contingencies regarding a possible additional interim review if the total accrual at 12 months following first enrollment is <50% of the total sample size (i.e., fewer than 58 women).

10.5 Data and Safety Monitoring

10.5.1 Interim Monitoring Guidelines

This study will be formally monitored at least annually by an ACTG-appointed SMC (via the standing committee for the ARTS TSG). The first interim review will occur no more than one year after the enrollment of the first participant or 3 months after 25 women have completed the study, whichever occurs earlier. An additional SMC review may be triggered if the accrual at one year is less than 50% of total expected accrual (e.g., fewer than 58 of 116 women across all 4 arms). This additional review, under the contingency of very slow accrual, would provide an opportunity for the SMC to review the available estimate of coefficient of variation of the AUC of LNG(0-8hrs) in order to see if the calculated CV varies greatly from the CV estimate used above to support the study size/design. Due to the two-stage testing workflow to achieve PK parameter estimates from blood samples, and the desire not to increase the study budget by requiring expedited shipping or testing, the timeframe for this additional review could be 6 months or longer.

Outside of this additional review contingency plan, there are no plans to initiate PK testing prior to completion of a primary objective, and thus no planned early looks at the primary efficacy outcome.

An unplanned interim review will be triggered if, at any time, any participant experiences an SAE that is attributed to LNG (by adjudication by the core team and DAIDS clinical representative), or if more than five women need to be replaced (as per the guidelines for replacement as described in section 9.2) in the overall study sample. An SMC review can also be requested at any time at the request of the team or sponsor.

Note: Eligibility and enrollment issues that cause participant replacement will not be included as an SMC trigger. The participant replacement interim review trigger will be determined based strictly on criteria stated in section 9.2 (Premature Study Discontinuation) of the protocol.

Any/all SMC reviews will include administrative/trial conduct data as well as safety data according to the safety-related outcomes enumerated above.

Routine monitoring reports are distributed to core team and are detailed in the study monitoring plan (SMP): screening, accrual, data delinquency, study status, data and sample completeness, with attention to intensive PK sampling for the primary efficacy outcome. The routine safety monitoring report is distributed to the DAIDS Clinical Representative and a subset of the core team (to include the study chairs) every 3 months.

Further details about monitoring of this study are available in the SMP.

10.6 Analyses

If accrual to study groups is such that one primary objective is able to be addressed before the other due to unequal accrual rates, then the team will plan to perform final analyses that include completely accrued groups, even if accrual is still occurring to groups required for the other primary objective. This is because it is anticipated that each primary objective can be published independently.

10.6.1 Primary Efficacy Analysis

The primary efficacy outcome of AUC of LNG PK over 8 hours will be calculated using the trapezoidal rule (i.e., noncompartmental technique) as described in section 11.3 below, using all observed data. As women not taking LNG will not have PK samples drawn, and any woman not having complete data to assess 8 hour AUC for any reason will be replaced, these observed data will be per-protocol and will have already excluded women for non-adherence to LNG or other protocol deviations that prevent primary outcome assessment. If participant self-reported short term non-adherence to the other targeted medications (either ARVs or RIF) were such that the PK samples should not have been collected, but were collected in error, then these women will also be replaced, and samples will not be sent for PK testing. Please see section 11.0 of the protocol for more information on the derivation of the primary efficacy outcome.

Each of the two primary objectives will be analyzed as follows. Assessing if increased dose of LNG overcomes DDI with EFV will be assessed by a comparison of randomized Group B to directly assigned Group C. Assessing if increased dose of LNG overcomes DDI with RIF will be assessed by a comparison of directly assigned Group D to directly assigned Group C. Therefore, in each of these primary objectives, the direct assignment Group C (i.e., women on DTG ARV regimen with standard-dose LNG**)** serves as the control group. Neither of these parallel group comparisons is based on randomization, and thus prior to primary analysis, the distribution of potential baseline confounding factors will be examined between pairwise groups for imbalance. A key factor is race; BMI is not expected to have significant imbalance due to enrollment limits placed on each group for women with BMI ≥ 30 kg/m^2.

Descriptive analysis will include the following: a) plots of the concentrations of LNG over time for will be provided to inform the derivation of the primary AUC outcome and other PK parameters (secondary outcomes); b) plots of the summary statistics of concentrations over time by treatment group; c) descriptive statistics of the primary outcome, including mean, standard deviation, median, interquartile range, minimum, and maximum of the primary outcome, will be presented by each study group.

The between group statistic that compares AUC(0-8hr of LNG) is the geometric mean ratio (GMR). The geometric mean and 95% confidence interval about the geometric mean of the primary outcome will be provided by each group. The GMR between Groups B and C (for the EFV objective) and between Groups D and C (for the RIF objective) will be presented. The 90% confidence intervals about the two pairwise GMRs will be compared to the FDA reference standard for bioequivalence in order to determine if LNG AUC is similar between AUC of LNG increased dose versus standard dose in each of the primary objective comparisons. Note that because of the high variability of the PKs of LNG, the bioequivalence interval will be (70%, 143%).

10.6.2 Primary Safety Analysis

Occurrence of the safety outcomes (i.e., number of participants meeting a safety outcome) as defined above will be enumerated and summarized by individual study group. Safety outcomes may be summarized separately by severity grade or type (category or MedDRA grouping) of adverse event.

The secondary objective of comparing safety between standard and increased doses will be achieved by a comparison of the relative number of participants with safety outcome in Groups A+C (or collectively the standard-dose groups) versus the relative number of participants with this outcome in Groups B+D (or collectively the increased dose groups). The statistical hypothesis test for this comparison will be a Fisher’s exact test. This comparison may also be repeated as 2 additional pairwise comparisons, especially if analyses of primary objectives

are analyzed separately: (1) randomized Group A versus randomized Group B, which is a randomized comparison and is restricted to HIV+ women taking EFV (2) assigned Group C versus assigned Group D.

Since this study is not powered to compare occurrence of AEs between LNG double dose versus single dose, inference related to comparisons above will focus on describing the magnitude and range of plausible values of observed differences between groups, and will not conclude similarity based on the absence of significant differences by Fisher's exact test.

10.6.3 Secondary Outcomes Analysis

The secondary objective of comparing increased dose of LNG EC to standard-dose among women on EFV (randomized comparison), will use analyses parallel to the primary outcome analysis as described above. However, since the hypothesis for this objective is superiority (rather than equivalence), the statistical inference for examination of the confidence interval about the GMR will focus whether this interval includes or excludes 1 (in which a significance difference can be concluded). Conclusions will focus on the estimations and plausible values of the GMR between LNG doses within this EFV comparison. Note this comparison is not subject to confounding because it is randomized comparison. A similar, non-randomized comparison will be performed between randomized Group A and control, directly assigned Group C.

Analyses for other PK parameters of LNG will follow an analysis plan parallel to the primary outcome as described above. Note that derivation of these PK parameter outcomes are according to specifications in section 11.0 below.

Other adverse events (that do not meet the primary safety outcome) and side effects between single dose and double dose may be compared either separately by group, or collapsed over group by LNG dosing (single vs. double).

Further details are outlined in the study's Statistical Analysis Plan (SAP).

10.6.4 Exploratory Outcomes Analysis

All host genotypes will be treated as ordinal variables (as 3 levels for individual SNPs, and either 3 or 12 levels for composite *CYP2B6/CYP2A6* genotypes). For each SNP or genotype, associations with PK concentrations with the AUC of LNG will be evaluated. The primary focus will be on SNPs/genotypes with very strong a *priori* evidence for effect on drug exposure (i.e., *CYP2B6*/*CYP2A6* SNPs for efavirenz, *UGT1A1* for dolutegravir). For example, we will explore whether *CYP2B6*/*CYP2A6* genotypes that are known to predict higher plasma efavirenz concentrations are also associated with lower levonorgestrel concentrations.

Side effects, tolerance, and acceptability of LNG will be summarized across participants grouped by LNG dose.

Further details are outlined in the study's Exploratory Statistical Analysis Plan.

11.0 PHARMACOLOGY PLAN

11.1 Pharmacology Objectives

See section 1.0 for study objectives.

11.2 Pharmacology Study Design

This is a pharmacology study, thus, the pharmacology study design is specified in the overall study design described in section 6.3.9.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

LNG analysis

The PK parameters for LNG include: maximum concentration (C_{max}), time to maximum concentration (T_{max}), minimum concentration (C_{min}), **time to minimum concentration (T_{min}),** oral clearance (CL/F), volume of distribution (Vd), elimination half-life (T1/2), and area under the concentration-time curve over 8 hours (AUC_{0-8h}), 24 hours (AUC_{0-24h}), 48 hours (AUC_{0-48h}), and to infinity (AUC_{inf}). Standard noncompartmental techniques will be used to determine these PK parameters using the software package Phoenix WinNonLin (Certara®). The AUC (including the primary outcome) will use the linear up/log down version of the trapezoidal rule. This version of the trapezoidal rule uses linear interpolation between untransformed data up to C_{max}, and between log-transformed data from C_{max} through C_{last} [81, 82]. C_{max} will be taken as the maximum observed concentration. T_{max} is the time at which C_{max} occurs. C_{min} will be taken as the minimum observed concentration after the observed dose. Apparent oral clearance will be calculated as CL/F = dose/AUC_{0-24} or CL/F = dose/AUC_{0-48}. The T1/2 will be determined using regression analysis when possible.

ART or RIF exposure in plasma

EFV, DTG, or RIF will be quantitated from aliquots of the same samples collected to assess LNG according to section 6.3.9. The concentrations will be at a single time point; therefore, no PK parameters will be calculated.

For participants receiving EFV: EFV will be measured in a plasma sample collected 12-20 hours after the last dose of EFV. Efavirenz should be administered in the evening prior to PK visits.

For participants receiving DTG or RIF: DTG or RIF will be measured in a plasma sample collected 20-28 hours after the last dose of DTG or RIF. If DTG or RIF is being administered in the morning, the pre-LNG dose sample at entry should be collected prior to administration of DTG or RIF.

See MOPS for further discussion of dose timing in relation to PK sampling at entry.

Hair analysis
Hair levels will be evaluated as continuous variables, possibly using logarithmic transformation if their distribution is skewed. Values below the detection limit will be counted as equal to the detection limit. We will examine scatterplots and calculate Spearman correlation coefficients for hair levels with plasma concentrations, we will also examine the correlation between SNPs in the genes implicated in EFV metabolism (e.g., CYP2B6) and hair concentrations of EFV.

Pharmacogenetic analyses
For all study participants who provide DNA for genetic testing, assays will be performed for polymorphisms in genes relevant to study drugs and concomitant medications (e.g., CYP2B6/CYP2A6 SNPs for efavirenz, UGT1A1 for dolutegravir). Associations will be explored between selected genetic polymorphisms and outcome measures as described in section 10.0.

11.4 Anticipated Outcomes

These PK studies will provide information on plasma concentrations of LNG when used as EC in participants taking EFV or RIF. The PK data for LNG will fill gaps in our knowledge, about possible EC options in women receiving EFV-based ART and RIF-based TB treatments.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization/registration.

12.2 Role of Data Management

12.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

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

12.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, other local, US, and international regulatory entities for confirmation of the study data.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (Appendices I-III) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or parent, legal guardian, or person with power of attorney for participants who cannot consent for themselves, such as those below the legal age of consent). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, parent, or legal guardian, and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, or other local, US, and international regulatory entities as part of their duties.

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, or other country-specific government agencies as part of their duties to ensure that research participants are protected.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies.

15.0 BIOHAZARD CONTAINMENT

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

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

16.0 REFERENCES

1. Joint United Nations Programme on HIV/AIDS. Global AIDS Update 2016. Geneva: UNAIDS; 2016.
2. Joint United Nations Programme on HIV/AIDS. When women lead, change happens. Geneva: UNAIDS; 2017.
3. World Health Organization. Global Tuberculosis Report 2015. Geneva: WHO; 2015.
4. U.S. Agency for International Development. Fact Sheet: The Twin Epidemics: HIV and TB Co-infection. U.S. Agency for International Development (USAID); 2014. [Online]. Available: https://www.usaid.gov/news-information/fact-sheets/twin-epidemics-hiv-and-tb-co-infection. [Accessed: 06-Oct-2017].
5. De Cock KM, Soro B, Coulibaly IM, Lucas SB. Tuberculosis and HIV infection in sub-Saharan Africa. JAMA 1992;268:1581-7.
6. Wilkinson D, Moore DA. HIV-related tuberculosis in South Africa--clinical features and outcome. S Afr Med J 1996;86:64-7.
7. Swaminathan S, Ramachandran R, Baskaran G, et al. Risk of development of tuberculosis in HIV-infected patients. Int J Tuberc Lung Dis 2000;4:839-44.
8. Narain JP, Raviglione MC, Kochi A. HIV-associated tuberculosis in developing countries: epidemiology and strategies for prevention. Tuber Lung Dis 1992;73:311-21.
9. Kobayashi K, Haruta T, Maeda H, Kubota M, Nishio T. Cerebral hemorrhage associated with vitamin K deficiency in congenital tuberculosis treated with isoniazid and rifampin. Pediatr Infect Dis J 2002;21:1088-90.
10. Rifadin (rifampin) [package insert]. Bridgewater, NJ: Sanofi-Aventis, US LLC; 2017.
11. Batur P, Cleland K, McNamara M, Wu J, Pickle S; EC Survey Group, Emergency contraception: A multispecialty survey of clinician knowledge and practices. Contraception 2016;93:145-52.
12. World Health Organization. Emergency Contraception. Geneva: WHO; 2017. [Online]. Available: http://www.who.int/mediacentre/factsheets/fs244/en/. [Accessed: 03-Nov-2017].
13. Decker MR, Benning L, Webere KM, et al. Physical and sexual violence predictors. Am J Prev Med 2016;51:731-42.
14. Bernstein M, Phillips T, Zerbe A, et al. Intimate partner violence experienced by HIV-infected pregnant women in South Africa: a cross-sectional study. BMJ Open 2016;6:e011999.
15. World Health Organization. Responding to intimate partner violence and sexual violence against women. WHO clinical and policy guidelines. Geneva: WHO; 2013.
16. Global Community Advisory Board; ACTG Community Science Subcommittee; Wei C. Recruitment and retention of women in ACTG trials: a guidebook of best practices. Women's Enrollment Initiative; 2014.

17. Lukhaimane TA, Adam Y. Women's willingness to use emergency contraception: Experience at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa. S Afr Med J 2015;105:266-7.
18. World Health Organization. Immunization, Vaccines and Biologicals: HIV/AIDS. Geneva: WHO; 2008. [Online]. Available: http://www.who.int/immunization/topics/hiv/en/. [Accessed: 03-Nov-2017].
19. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance. Geneva: WHO; 2018.
20. Gupta A, Juneja S, Vitoria M, et al. Projected uptake of new antiretroviral (ARV) medicines in adults in low- and middle-income countries: a forecast analysis 2015-2025. PLoS One 2016;11:e0164619.
21. Plan B One-Step Tablet (levonorgestrel) [package insert]. Pomona, NY: Duramed Pharmaceuticals (Barr Pharmaceuticals); 2009.
22. Polis CB, Schaffer K, Blanchard K, Glasier A, Harper CC, Grimes DA. Advance provision of emergency contraception for pregnancy prevention: a meta-analysis. Obstet Gynecol 2007;110:1379-88.
23. Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 2010;375:555-62.
24. Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and efavirenz. Infect Dis Obstet Gynecol 2012;2012:137192. doi: 10.1155/2012/137192. Epub 2012 Feb 28.
25. Hansen LB, Saseen JJ, Teal S.B. Levonorgestrel-only dosing strategies for emergency contraception. Pharmacotherapy 2007;27:278-84.
26. Johansson E, Brache V, Alvarez F, et al. Pharmacokinetic study of different dosing regimens of levonorgestrel for emergency contraception in healthy women. Hum Reprod 2002;17:1472-6.
27. Sivin I, Lahteenmaki P, Mishell DR Jr, et al. First week drug concentrations in women with levonorgestrel rod or Norplant capsule implants. Contraception 1997;56:317-21.
28. Sivin I, Lahteenmaki P, Ranta S, et al. Levonorgestrel concentrations during use of levonorgestrel rod (LNG ROD) implants. Contraception 1997;55:81-5.
29. Sivin I, Wan L, Ranta S, et al. Levonorgestrel concentrations during 7 years of continuous use of Jadelle contraceptive implants. Contraception 2001;64:43-9.
30. Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception 2016;94:52-7.
31. Praditpan P, Hamouie A, Basaraba CN, et al. Pharmacokinetics of levonorgestrel and ulipristal acetate emergency contraception in women with normal and obese body mass index. Contraception 2017;95:464-9.

32. European Medicines Agency, Emergency contraceptives, INN-levonorgestrel, ulipristal acetate, Assessment report. 2014. [Online]. Available: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Emergency_contraceptives_31/WC500176385.pdf. [Accessed: 19-Jun-2018].
33. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999;3(10 Suppl 2):S231-S279.
34. Menzies D, Benedetti A, Paydar A, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med 2009;6:e1000146.
35. World Health Organization. Treatment of Tuberculosis Guidelines. Geneva: WHO; 2009.
36. Wang J, Sonnerborg A, Rane A, et al. Identification of a novel specific CYP2B6 allele in Africans causing impaired metabolism of the HIV drug efavirenz. Pharmacogenet Genomics 2006;16:191-8.
37. Rotger M, Colombo S, Furrer H, et al.; Swiss HIV Cohort Study. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenet Genomics 2005;15:1-5.
38. Sustiva (efavirenz) [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2017.
39. LeBel M, Masson E, Guilbert E, et al. Effects of rifabutin and rifampicin on the pharmacokinetics of ethinylestradiol and norethindrone. J Clin Pharmacol 1998;38:1042-50.
40. Barditch-Crovo P, Trapnell CB, Ette E, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. Clin Pharmacol Ther 1999;65:428-38.
41. Back DJ, Breckenridge AM, Crawford FE, et al. The effect of rifampicin on norethisterone pharmacokinetics. Eur J Clin Pharmacol 1979;15:193-7.
42. Arora VK, Bedi RS, Arora R. Rifampicin induced menstrual disturbances. Indian J Chest Dis Allied Sci 1987;29:63-4.
43. Haas DW, Ribaudo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group Study. AIDS 200418:2391-400.
44. Haas DW, Smeaton LM, Shafer RW, et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir: an adult AIDS Clinical Trials Group Study. J Infect Dis 2005;192:11:1931-42.
45. Rotger M, Tegude H, Colombo S, et al. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. Clin Pharmacol Ther 2007;81:557-66.
46. di Iulio J, Fayet A, Arab-Alameddine M, et al. In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. Pharmacogenet Genomics 2009;19:300-9.

47. Scarsi KK, Darin KM, Chappell CA, Nitz SM, Lamorde M. Drug-drug interactions, effectiveness, and safety of hormonal contraceptives in women living with HIV. Drug Saf 2016;39:1053-72.

48. Scarsi KK, Darin KM, Nakalema S, et al. Unintended pregnancies observed with combined use of the levonorgestrel contraceptive implant and efavirenz-based antiretroviral therapy: a three-arm pharmacokinetic evaluation over 48 weeks. Clin Infect Dis 2016;62:675-82.

49. Reese MJ, Savina PM, Generaux GT, et al. In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor. Drug Metab Dispos 2013;41:353-61.

50. Song IH, Borland J, Chen S, Wajima T, Peppercorn AF, Piscitelli SC. Dolutegravir has no effect on the pharmacokinetics of oral contraceptives with norgestimate and ethinyl estradiol. Ann Pharmacother 2015;49:784-89.

51. Medicines and Healthcare products Regulatory Agency. Levonorgestrel-containing emergency hormonal contraception: advice on interactions with hepatic enzyme inducers and contraceptive efficacy - GOV.UK. 2016. [Online]. Available: https://www.gov.uk/drug-safety-update/levonorgestrel-containing-emergency-hormonal-contraception-advice-on-interactions-with-hepatic-enzyme-inducers-and-contraceptive-efficacy. [Accessed: 22-Sep-2017].

52. European Medicines Agency. European Medicines Agency - Human medicines - Levonelle 1500 microgram tablets and associated names. 2016. [Online]. Available: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Levonelle_1500_microgram_tablets_and_associated_names/human_referral_000405.jsp&mid=WC0b01ac05805c516f. [Accessed: 19-Sep-2017].

53. U.S. Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (CDER). Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry. 2017. [Online]. Available: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. [Accessed: 19-Jun-2018].

54. U.S. Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research (CDER). Guidance for Industry Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations Guidance for Industry. 2014. [Online]. Available: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. [Accessed: 19-Jun-2018].

55. Neary M, Lamorde M, Olagunju A, et al. The effect of gene variants on levonorgestrel pharmacokinetics when combined with antiretroviral therapy containing efavirenz or nevirapine. Clin Pharmacol Ther 2017;102:529-36.

56. Glasier A, Cameron ST, Blithe D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. Contraception 2011;84:363-7.

57. Society of Adolescent Health and Medicine. Position paper. Emergency contraception for adolescents and young adults: guidance for health care professionals. J Adolesc Health 2016;58:245-8.

58. American Academy of Pediatrics. Policy statement. Emergency contraception. Pediatrics 2012;130:1174-82.

59. Palermo T, Bleck J, Westley E. Knowledge and use of emergency contraception: a multicountry analysis. Int Perspect Sex Reprod Health 2014;40:79-86.

60. Drugs and lactation database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); Specialized Information Services Division. [cited 2018 Sep 18]. Available from: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

61. Hale TW, Rowe H. Medications and mothers' milk. 17th ed. New York: Springer Publishing Company; 2016.

62. Willetts SJ, MacDougall M, Cameron ST. A survey regarding acceptability of oral emergency contraception according to the posited mechanism of action. Contraception 2017;96:81-8.

63. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med 2015;5:470-82.

64. Podsadecki TJ, Vrijens BC, Tousset EP, Rode RA, Hanna GJ. "White coat compliance" limits the reliability of therapeutic drug monitoring in HIV-1-infected patients. HIV Clin Trials 2008;9:238-46.

65. Nettles RE, Kieffer TL, Parsons T, et al. Marked intraindividual variability in antiretroviral concentrations may limit the utility of therapeutic drug monitoring. Clin Infect Dis 2006;42:1189-96.

66. Hickey MD, Salmen CR, Tessler RA, et al. Antiretroviral concentrations in small hair samples as a feasible marker of adherence in rural Kenya. J Acquir Immune Defic Syndr 2014;66:311-5.

67. Baxi SM, Liu A, Bacchetti P, et al. Comparing the novel method of assessing PrEP adherence/exposure using hair samples to other pharmacologic and traditional measures. J Acquir Immune Defic Syndr 2015:68:13-20.

68. Prasitsuebsai W, Kerr SJ, Truong KH, et al. Using lopinavir concentrations in hair samples to assess treatment outcomes on second-line regimens among Asian children. AIDS Res Hum Retroviruses 2015;31:1009-14.

69. Koss CA, Natureeba P, Mwesigwa J. Hair concentrations of antiretrovirals predict viral suppression in HIV-infected pregnant and breastfeeding Ugandan women. AIDS 2015;29:825-30.

70. Castillo-Mancilla JR, Zheng JH, Rower JE, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retroviruses 2013;29:384-90.

71. Gandhi M, Greenblatt RM. Hair it is: the long and short of monitoring antiretroviral treatment. Ann Intern Med 2002;137:696-7.

72. Gandhi M, Ameli N, Bacchetti P, et al.; Women's Interagency HIV Study (WIHS). Protease inhibitor levels in hair strongly predict virologic response to treatment. AIDS 2009;23:471-8.

73. van Zyl GU, van Mens TE, McIlleron H, et al. Low lopinavir plasma or hair concentrations explain second-line protease inhibitor failures in a resource-limited setting. J Acquir Immune Defic Syndr 2011;56:333-9.

74. Gandhi M, Ameli N, Bacchetti P, et al. Atazanavir concentration in hair is the strongest predictor of outcomes on antiretroviral therapy. Clin Infect Dis 2011;52:1267-75.

75. Baxi SM, Greenblatt RM, Bacchetti P, et al. Nevirapine concentration in hair samples is a strong predictor of virologic suppression in a prospective cohort of HIV-infected patients. PLoS One 2015;10:e0129100.

76. Chawana TD, Gandhi M, Nathoo K, et al.; Adolescent Treatment Failure (ATF) Study Team. Defining a cut-off for atazanavir in hair samples associated with virological failure among adolescents failing second-line antiretroviral treatment. J Acquir Immune Defic Syndr 2017;76:55-9.

77. Pintye J, Bacchetti P, Teeraananchai S, et al. Brief Report: Lopinavir hair concentrations are the strongest predictor of viremia in HIV-infected Asian children and adolescents on second-line antiretroviral therapy. J Acquir Immune Defic Syndr 2017;76:367-71.

78. Majeed S, West S, Jiang S, et al. Confirmation of the drug-drug interaction (DDI) potential between cobicistat-boosted antiretroviral regimens and hormonal contraceptives. [Oral Abstract #O_05/#5.] 18th International Workshop on Clinical Pharmacology of Antiviral Therapy, June 14-17 2017, Chicago, IL; 2017.

79. Begley R, Anderson K, Watkins T, et al. Lack of drug-drug interaction between filgotinib, a JAK-1 selective inhibitor, and a representative hormonal contraceptive medication, levonorgestrel/ethinyl estradiol. [ACR Meeting Abstracts 1459]. 2017 ACR/ARHP Annual Meeting, November 3-8, 2017. San Diego, CA; 2017.

80. Davit BM, Chen ML, Conner DP, et al. Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products by the US Food and Drug Administration. AAPS J 2012;14:915-24.

81. Gabrielsson J, Weiner D. Pharmacokinetic and pharmacodynamic data analysis: concepts and applications. 3rd ed. Stockholm: Swedish Pharmaceutical Press; 2002.

82. Pharsight Corporation. WinNolin® User's Guide. Version 5.3. St. Louis: Pharsight Corporation. Available: https://support.certara.com/forums/index.php?app=core&module=attach&section=attach&attach_id=3024. [Accessed: 16-Aug-2018].

APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For protocol: A5375

An Open-Label, Phase II Pharmacokinetic Study to Evaluate Double-Dose Levonorgestrel Emergency Contraception in Combination with Efavirenz-Based Antiretroviral Therapy or Rifampicin-Containing Anti-Tuberculosis Therapy

FINAL Version 2.0, 10/30/20

SHORT TITLE FOR THE STUDY: Optimize LNG EC

SUMMARY

PURPOSE: **Emergency contraception is birth control that prevents pregnancy. Girls and women use it after having unprotected sex. Levonorgestrel (LNG) emergency contraception is commonly known as Plan B® One-Step, or the Morning After Pill. This study will test if a higher dose of LNG needs to be used to prevent pregnancy in girls and women who are taking some types of anti-HIV or anti-TB medications. This study will also test if a higher dose of LNG is safe.**

STUDY TREATMENT: **You will take a dose of LNG emergency contraception by mouth. LNG emergency contraception will be provided by the study.**

The United States Food and Drug Administration (US FDA) has approved LNG for prevention of pregnancy.

NUMBER OF PARTICIPANTS: **There will be 116 participants in this study. There will be 17 participants in Group A, and 33 participants in each of Groups B, C, and D.**

LENGTH OF STUDY: **The study will last about 4 weeks. During this time, you will need to come to the clinic for about 3 visits.**

REQUIRED ACTIVITIES: **<u>Blood and Urine Collections</u>**
At most visits, some blood will be collected from a vein in your arm. You may be asked to provide a urine sample.

At the entry visit, you will be asked to remain at the clinic all day for an intensive pharmacokinetic (PK) blood sampling. For this

intensive PK sampling, you will have blood drawn several times over a period of 8 hours to measure the amount of LNG in your blood. To avoid many needle sticks, a small tube (intravenous device) may be placed into a vein in your arm and left in place during your stay. You will be able to move around and should not have any significant pain or discomfort once the tube is in place.

RISKS: **The following side effects have been associated with using LNG: nausea, lower stomach pain, tiredness, headache, dizziness, breast pain, vomiting, and diarrhea. Some individuals will have menstrual changes such as spotting or bleeding before their next period. Some individuals may have a heavier or lighter next period, or a period that is early or late.**

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

BENEFITS: **You will receive no benefit from being in this study.**

OTHER CHOICES: **Instead of being in this study, you have the option of continuing with your current treatment or starting a new treatment under the care of your regular doctor or other health care provider.**

INTRODUCTION

You are being asked to take part in this research study because you are a girl at least 16 years of age or a woman and:

1. You are living with human immunodeficiency virus (HIV-1) and you have been taking a combination of antiretroviral drugs (ARV) that includes either efavirenz (EFV) or dolutegravir (DTG)

   OR

2. You are living with tuberculosis (TB) infection, and you have completed the intensive phase of TB therapy and are now completing the continuation phase of TB treatment that requires taking isoniazid (INH) and rifampicin (RIF) daily.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

Emergency contraception is birth control that prevents pregnancy. Girls and women use it after having unprotected sex. Levonorgestrel (LNG) emergency contraception is commonly known as Plan B® One-Step, or the Morning After Pill. This study will test if a higher dose of LNG needs to be used to prevent pregnancy in girls and women who are taking some types of anti-HIV or anti-TB medications. This study will also test if a higher dose of LNG is safe.

The United States Food and Drug Administration (US FDA) has approved LNG for prevention of pregnancy.

LNG works mainly by stopping the release of an egg from the ovary. It may also work by preventing fertilization of an egg, or by preventing attachment to the uterus. Girls and women can use emergency contraception to prevent pregnancy if regular birth control was used incorrectly or fails, or no birth control was used. LNG will not disrupt an existing pregnancy and using LNG does not affect your ability to have a baby in the future. After you take LNG as part of this study, you may attempt to get pregnant again as soon as your next menstrual cycle (after your next period), if you want to.

Efavirenz (EFV) is a medication commonly used to treat HIV. Rifampicin (RIF) is a medication commonly used to treat tuberculosis. Both of these medications lower the amount of LNG in your blood by about half. This may make LNG not work as well as it normally would. It is unknown if the current dose of LNG emergency contraception, in combination with EFV or RIF, is enough to prevent a pregnancy. To learn if a higher dose is needed to prevent pregnancy, you will take either a regular dose or a double dose of LNG emergency contraception.

Dolutegravir (DTG) is an anti-HIV medication that does not lower the amount of LNG in your blood. It is being used as a comparison to the other groups.

In this study, you will not be taking LNG for contraception (to prevent pregnancy), you will be volunteering to take it so that we can evaluate the impact of your other medications on the amount of LNG in your blood. You will take a dose of LNG emergency contraception by mouth. After you take the dose of LNG, the amount of LNG that is in your blood will be measured. This study will also take a hair sample that will tell researchers how often you have taken EFV, INH, and DTG over the past few weeks.

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

Information Collected at Screening

There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, routine lab tests for safety) information will be collected from you.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may determine whether there are patterns and/or common reasons why people do not join a study.

If you decide to take part in this research study, you will be asked to sign this consent form. A screening visit will be done to make sure you are eligible to join the study. If you are found eligible, you will have one entry visit that will last 9-10 hours, a 1 hour visit 24 hours after entry, and a 1 hour visit 48 hours after entry. You will be asked to take a questionnaire over the phone 1 week, 2 weeks, and 4 weeks after entry.

<u>If you do not enroll into the study</u>
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, pregnancy test) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

<u>If you enter the study</u>
- At the study entry visit, you will be assigned to a study group. There are four study groups. Two will receive a standard dose of LNG, and two will receive twice the standard dose of LNG. You will not be able to choose your study group, but you will know what study group you are in.
- If you are taking EFV for HIV treatment, you will be randomly assigned (like a coin flip) to one of two possible doses of LNG. Some women will take a standard dose of LNG, other women will take twice the standard dose of LNG. More women will be assigned to take twice the standard dose, so it is more likely that you will be in this group.
- If you are taking DTG for HIV treatment, you will be assigned to receive a standard dose of LNG.
- If you are taking RIF for TB treatment, you will be assigned to receive twice the standard dose of LNG.

You will have blood samples taken during the study to measure the amount of LNG in your blood.

You will have a small sample of hair cut from your head so that we can measure levels of the anti-TB or anti-HIV drugs in this small hair sample. You may decline this procedure.

You will be asked questions about how well you take your anti-HIV or anti-TB medications and if you have any concerns about taking LNG.

You will be asked to use a reliable form of non-hormonal birth control every time you have sex that could lead to pregnancy until the study is completed. You may not enter the study if you have had sex that could lead to pregnancy within 14 days prior to starting the study.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used for study-required pharmacologic, pharmacogenetic (testing of material passed from parent to child that determines the makeup of the body and mind that can affect your response to the study drugs), and virologic testing.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

Your blood and/or hair specimens may be used for commercial profit. If this happens, there is no plan to share any money with you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

Please refer to Attachment I-A to consent for use of your samples in other studies.

A5375 Study Visits
The study staff can answer any questions you have about individual study visits, and how long they will last, or about the tests that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

Table 1: Study Schedule

Evaluation or Procedure	Screening	Entry Visit	Study Visits		Follow-Up Calls			Clinically Indicated Visit	Early Study Discontinuation
		Day 0	Day 1	Day 2	Day 7	Day 14	Day 28		
	1 hour	9-10 hours	1 hour	1 hour	30 minutes	30 minutes	30 minutes	1 hour	30 minutes
Documentation of HIV Status	√								
Medical/ Medication History	√	√							
Questions About Your Menstrual Cycle	√	√			√	√	√		√
Diagnoses Questions		√	√	√	√	√	√	√	√
Medication Questions		√	√	√			√	√	√

Evaluation or Procedure	Screening	Entry Visit	Study Visits		Follow-Up Calls			Clinically Indicated Visit	Early Study Discontinuation
		Day 0	Day 1	Day 2	Day 7	Day 14	Day 28		
	1 hour	9-10 hours	1 hour	1 hour	30 minutes	30 minutes	30 minutes	1 hour	30 minutes
Acceptability and Practicality Questionnaire		√		√		√	√		√
Adherence Assessment	√	√	√	√					
Physical Exam	√	√						√	
Blood Collection	√	√							
Pregnancy Testing	√	√						√	
Hair Collection		√							
LNG EC Administration		√							
Pharmacokinetic Sampling		√	√	√					

Screening

If you would like to be in this study, after you have read and signed this informed consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. This visit will take about 1 hour [*Site to insert site-specific information about duration of study visit]*. Up to 18 mL (1.4 tablespoons) of blood will be drawn at this visit.

- Your HIV infection status will be confirmed. If there is no record available, another HIV test will be done. You may have to sign a separate consent form before this is done.
- You will be asked questions about your medical and medication history and any medications you are currently taking. You will be asked about your menstrual period.
- You will be asked about adherence to your anti-HIV or anti-TB medications (how correctly you are taking your medications).
- You will have a physical exam.
- You will have blood drawn for routine lab tests for safety. You will be told the results of these tests when they become available.
- You will give a urine sample or have blood drawn to see if you are pregnant. This test must show that you are not pregnant for you to enroll in the study. You will be told the result of the test when it becomes available.

Entry Visit (Day 0)

If you are eligible for the study and you choose to enroll, you will come back to the clinic for an entry visit. This visit will last about 9 or 10 hours *[Site to insert site-specific information about duration of study visit]*. Up to 75 mL (5.8 tablespoons) of blood will be drawn at this visit.

- You will be asked about: your medical history and any medications you are taking, **birth control that you are taking or have taken in the last 4 months**, your menstrual period

and if there has been a change in your menstrual period since the screening visit, and adherence to your anti-HIV or anti-TB medications.
- You will have a physical exam, including measuring your neck, waist, and hips.
- If you are HIV positive, you will have blood drawn to test how much HIV is in your blood, and to test how many CD4 cells (infection-fighting cells) are in your blood. You will be told the results of these tests when they become available.
- You will have blood drawn and stored for a genetic test (a test of your DNA [genes] to better understand how fast your body removes the study drugs from your blood). Genetic testing looks at differences in people's genes. Your body, like all living things, is made up of cells, and cells contain deoxyribonucleic acid, also known as "DNA." DNA is like a string of information put together in a certain order. Parts of the string make up "genes." Genes contain instructions on how to make your body work and fight disease. The testing in this study will only look at certain genes that are known to have an effect on how your body uses hormones. The tests will not look at any other genes. You will not receive the results of these tests.
- You will give a urine sample or have blood drawn to see if you are pregnant. This test must show that you are not pregnant for you to remain in the study. You will be told the result of the test when it becomes available.
- You will have a small sample of hair (about 50 strands) cut from your head to measure levels of the HIV or TB drugs in this hair sample. Humans lose about 100 hairs from their head every day naturally, so this amount of hair removal should not be noticeable. If you decide not to provide a hair sample, you can still be in the study. Results of this testing will not be available to you since hair levels are still a research tool.
- You will take a dose of LNG emergency contraception by mouth.
- You will be asked to remain at the clinic all day for an intensive pharmacokinetic (PK) blood sampling. For this intensive PK sampling, you will have blood drawn over 8 hours to measure the amount of LNG in your blood. To avoid many needle sticks, a small tube (intravenous device) **may** be placed into a vein in your arm and left in place during your stay. You will be able to move around and should not have any significant pain or discomfort once the tube is in place. Blood will be taken before you take the LNG emergency contraception dose, and then at 30 minutes, 1, 1.5, 2, 3, 4, 6, and 8 hours after you take the LNG emergency contraception dose.
- You will be asked if you have any problems or concerns after taking the LNG emergency contraception dose.

<u>Study Visits (Days 1 and 2)</u>
After the entry visit, you will come back to the clinic for two more study visits. The first will be 1 day after your entry visit, and the second will be 2 days after your entry visit. These study visits will last about 1 hour. Up to 6 mL (0.4 tablespoons) of blood will be drawn at this visit.
- You will have about blood drawn for PK blood sampling.
- You will be asked about: your adherence to medications, changes in your medications and diagnoses, the acceptability and practicality of emergency contraception, and any problems or concerns you have after taking the LNG emergency contraception dose.

During the COVID-19 outbreak, the Day 1 and Day 2 study visits may be conducted over the phone. If the visit is conducted over the phone, a member of the study staff will call you. Visits that are conducted over the phone will not include blood draws.

Follow-up
A member of the study staff will call you 7 days after study entry to ask you about your menstrual period. You will also be asked about changes in your diagnoses.

A member of the study staff will call you 14 and 28 days after study entry to ask you about: changes in your diagnoses and (on day 28 only) your medications, your menstrual period, the acceptability and practicality of emergency contraception, and any problems or concerns you have after taking the LNG emergency contraception dose.

Clinically Indicated Visit
If you become pregnant or have an adverse event, you may be asked to return to the clinic for a physical exam and pregnancy test, and to discuss any changes in your medications or diagnoses.

Early Study Discontinuation (Leaving the Study Early)
If you leave the study early, you will be asked questions about your menstrual period, changes in your medications or diagnoses, questions to determine the acceptability and practicality of emergency contraception, and questions about any problems or concerns you have after taking the LNG emergency contraception dose.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 116 women **and girls who are 16 years of age or older** will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 4 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:

- The study is stopped or cancelled
- You are not able to attend the study visits as required by the study
- You have a positive pregnancy test before you take the LNG dose for the study
- Your primary care doctor requests that you be taken off the study

After the study:

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

WHAT ARE THE RISKS OF THE STUDY?

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

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

Risks of Levonorgestrel (LNG, Plan B® One-Step)
The following side effects have been associated with the use of LNG:

- Nausea
- Lower stomach (abdominal) pain
- Tiredness
- Headache
- Dizziness
- Breast pain
- Vomiting
- Diarrhea

Some women will have menstrual changes such as spotting or bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late.

- If your period is more than a week late, you should get a pregnancy test

Risks of Drawing Blood
Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

Risks of Hair Collection
There is a small risk of cutting or nicking the scalp during the hair collection, although this is extremely rare.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your HIV or TB status, or information about your sexual activity, secret from people close to you. This may include your parent or guardian if you are under 18 years old. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns about this.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the drug or drug combinations in this study harm unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant until you complete the study. You may not enter the study if you have had sex that could lead to pregnancy within 14 days prior to starting the study.

You and your partner must use reliable birth control that you discuss with the study staff. You must continue to use birth control while in the study. You may choose one of the birth control methods below:

- Male condom with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal IUD
- Bilateral tubal ligation
- Male partner vasectomy

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. A pregnancy test may not detect a very early pregnancy, which is why the study team asks that you not enter the study if you have had sex that could lead to pregnancy within 14 days of study entry.

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

Breastfeeding

Breastfeeding women will be included only after their infants are at least 6 months old. Birth control like LNG is allowed during breastfeeding. During long-term use of drugs like LNG, called progestins, the amount of progestin in infant blood is only 1-6% of the amount in maternal blood. No side effects of progestins have been found on breastfeeding (quality or quantity of milk), or on the health or development of the infant due to this low progestin exposure.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You will receive no benefit from being in this study. Information learned from this study may help other women who have HIV or TB.

WHAT ABOUT CONFIDENTIALITY?

For Sites in the US
We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time**.**

For Sites outside the US
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, and their designees.

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

WHAT ARE THE COSTS TO ME?

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

There is no cost to you for LNG, study-related visits, physical examinations, laboratory tests, or other study procedures.

Anti-HIV and anti-TB medicines will not be provided by the study.

WILL I RECEIVE ANY PAYMENT?

You may be reimbursed for your time and travel expenses as part of your participation in this study. *(Site to insert site-specific information about payment.)*

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of your being in this study, you will be given immediate treatment for injuries and be referred for further treatment, if necessary.
[*Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry Clinical Trials Insurance (CTI), this must be indicated in the informed consent.]*

- ***This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.***
- ***The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH.***

You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your rights as a research participant, contact:

- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

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

Participant's Name (print)	Participant's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

ATTACHMENT I-A: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called "extra samples." The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any information that has been collected about you. This means that no one looking at the labels or at other information will know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your extra samples will be stored.
[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. [Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.] IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher's location. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you.

You may withdraw your consent for research on your extra samples at any time, and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

Research without Human Genetic Testing

If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples

OR

____ (initials) I understand but I do not agree to this storage and possible use of my samples

Research with Human Genetic Testing

The ACTG has two different studies that collect samples for genetic testing.

If you live in the US, this study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

If you live outside of the US, this study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.

Your site might ask you if you would like to participate in one of these studies if it is being done where you live. If you would like to participate, you will sign a separate consent form.

Your extra samples will not be used for human genetic testing unless you sign a consent for A5128 or A5243.

APPENDIX II: SAMPLE PARENTAL INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For protocol: A5375

An Open-Label, Phase II Pharmacokinetic Study to Evaluate Double-Dose Levonorgestrel Emergency Contraception in Combination with Efavirenz-Based Antiretroviral Therapy or Rifampicin-Containing Anti-Tuberculosis Therapy

FINAL Version 2.0, 10/30/20

SHORT TITLE FOR THE STUDY: Optimize LNG EC

SUMMARY

PURPOSE: **Emergency contraception is birth control that prevents pregnancy. Girls and women use it after having unprotected sex. Levonorgestrel (LNG) emergency contraception is commonly known as Plan B® One-Step, or the Morning After Pill. This study will test if a higher dose of LNG needs to be used to prevent pregnancy in girls and women who are taking some types of anti-HIV or anti-TB medications. This study will also test if a higher dose of LNG is safe.**

STUDY TREATMENT: **Your child will take a dose of LNG emergency contraception by mouth. LNG emergency contraception will be provided by the study.**

The United States Food and Drug Administration (US FDA) has approved LNG for prevention of pregnancy.

NUMBER OF PARTICIPANTS: **There will be 116 participants in this study. There will be 17 participants in Group A, and 33 participants in each of Groups B, C, and D.**

LENGTH OF STUDY: **The study will last about 4 weeks. During this time, your child will need to come to the clinic for about 3 visits.**

REQUIRED ACTIVITIES: **<u>Blood and Urine Collections</u>**
At most visits, some blood will be collected from a vein in your child's arm. Your child may be asked to provide a urine sample.

At the entry visit, your child will be asked to remain at the clinic all day for an intensive pharmacokinetic (PK) blood sampling. For this

intensive PK sampling, your child will have blood drawn several times over a period of 8 hours to measure the amount of LNG in her blood. To avoid many needle sticks, a small tube (intravenous device) may be placed into a vein in your child's arm and left in place during her stay. She will be able to move around and should not have any significant pain or discomfort once the tube is in place.

RISKS: **The following side effects have been associated with using LNG: nausea, lower stomach pain, tiredness, headache, dizziness, breast pain, vomiting, and diarrhea. Some individuals will have menstrual changes such as spotting or bleeding before their next period. Some individuals may have a heavier or lighter next period, or a period that is early or late.**

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

BENEFITS: **Your child will receive no benefit from being in this study.**

OTHER CHOICES: **Instead of being in this study, your child has the option of continuing with her current treatment or starting a new treatment under the care of her regular doctor or other health care provider.**

INTRODUCTION

You are being asked to let your child take part in this research study because your child is a girl who is at least 16 years of age and:

1. Your child is living with human immunodeficiency virus (HIV-1) and she has been taking a combination of antiretroviral drugs (ARV) that includes either efavirenz (EFV) or dolutegravir (DTG)

   OR

2. Your child is living with tuberculosis (TB) infection, and she has completed the intensive phase of TB therapy and is now completing the continuation phase of TB treatment that requires taking isoniazid (INH) and rifampicin (RIF) daily.

This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to let your child be a part of this study, we want you to know about the study.

This is a consent form for your child to participate in the study. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to let your child take part in this study, you will be

asked to sign this consent form. You will get a copy to keep. We will also talk to your child about the study and ask her if she agrees to participate in the study.

WHY IS THIS STUDY BEING DONE?

Emergency contraception is birth control that prevents pregnancy. Girls and women use it after having unprotected sex. Levonorgestrel (LNG) emergency contraception is commonly known as Plan B® One-Step, or the Morning After Pill. This study will test if a higher dose of LNG needs to be used to prevent pregnancy in girls and women who are taking some types of anti-HIV or anti-TB medications. This study will also test if a higher dose of LNG is safe.

The United States Food and Drug Administration (US FDA) has approved LNG for prevention of pregnancy.

LNG works mainly by stopping the release of an egg from the ovary. It may also work by preventing fertilization of an egg, or by preventing attachment to the uterus. Girls and women can use emergency contraception to prevent pregnancy if regular birth control was used incorrectly or fails, or no birth control was used. LNG will not disrupt an existing pregnancy and using LNG does not affect your **c**hild's ability to have a baby in the future. After your child takes LNG as part of this study, she may attempt to get pregnant again as soon as her next menstrual cycle (after her next period), if she wants to.

Efavirenz (EFV) is a medication commonly used to treat HIV. Rifampicin (RIF) is a medication commonly used to treat tuberculosis. Both of these medications lower the amount of LNG in the blood by about half. This may make LNG not work as well as it normally would. It is unknown if the current dose of LNG emergency contraception, in combination with EFV or RIF, is enough to prevent a pregnancy. To learn if a higher dose is needed to prevent pregnancy, your child will take either a regular dose or a double dose of LNG emergency contraception.

Dolutegravir (DTG) is an anti-HIV medication that does not lower the amount of LNG in the blood. It is being used as a comparison to the other groups.

In this study, your child will not be taking LNG for contraception (to prevent pregnancy), your child will be volunteering to take it so that we can evaluate the impact of your child's other medications on the amount of LNG in your child's blood. Your child will take a dose of LNG emergency contraception by mouth. After your child takes the dose of LNG, the amount of LNG that is in your child's blood will be measured. This study will also take a hair sample that will tell researchers how often your child has taken EFV, INH, and DTG over the past few weeks.

WHAT DOES MY CHILD HAVE TO DO IF SHE IS IN THIS STUDY?

<u>Information Collected at Screening</u>
There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (for example, age, gender,

race), clinical (for example, disease condition, diagnosis), and laboratory (for example, routine lab tests for safety) information will be collected from your child.

We will collect this information even if your child does not enroll in this study. This information is collected so that ACTG researchers may determine whether there are patterns and/or common reasons why people do not join a study.

If you decide to let your child take part in this research study, you will be asked to sign this consent form. A screening visit will be done to make sure your child is eligible to join the study. If your child is found eligible, she will have one entry visit that will last 9-10 hours, a 1 hour visit 24 hours after entry, and a 1 hour visit 48 hours after entry. Your child will be asked to take a questionnaire over the phone 1 week, 2 weeks, and 4 weeks after entry.

<u>If your child does not enroll into the study</u>
If you or your child decide not to take part in this study or if your child does not meet the eligibility requirements, we will still use some of your child's information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, pregnancy test) information is being collected from your child so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

<u>If your child enters the study</u>
- At the study entry visit, your child will be assigned to a study group. There are four study groups. Two will receive a standard dose of LNG, and two will receive twice the standard dose of LNG. Your child will not be able to choose her study group, but she will know what study group she is in.
- If your child is taking EFV for HIV treatment, she will be randomly assigned (like a coin flip) to one of two possible doses of LNG. Some women will take a standard dose of LNG, other women will take twice the standard dose of LNG. More women will be assigned to take twice the standard dose, so it is more likely that your child will be in this group.
- If your child is taking DTG for HIV treatment, she will be assigned to receive a standard dose of LNG.
- If your child is taking RIF for TB treatment, she will be assigned to receive twice the standard dose of LNG.

Your child will have blood samples taken during the study to measure the amount of LNG in her blood.

Your child will have a small sample of hair cut from her head so that we can measure levels of the anti-TB or anti-HIV drugs in this small hair sample. Your child may decline this procedure.

Your child will be asked questions about how well she takes her anti-HIV or anti-TB medications and if she has any concerns about taking LNG.

Your child will be asked to use a reliable form of non-hormonal birth control every time your child has sex that could lead to pregnancy until the study is completed. Your child may not enter

the study if she has had sex that could lead to pregnancy within 14 days prior to starting the study.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY CHILD'S SAMPLES AND INFORMATION ARE USED FOR?

Some of your child's blood will be stored and used for study-required pharmacologic, pharmacogenetic (testing of material passed from parent to child that determines the makeup of the body and mind that can affect your response to the study drugs), and virologic testing.

Identifiers will be removed from your child's samples and from any private information that has been collected about her. This means that no one looking at the labels or at other information will be able to know that the samples or information came from your child.

Your child's blood and/or hair specimens may be used for commercial profit. If this happens, there is no plan to share any money with you or your child.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, your child should not join this study.

Please refer to Attachment II-A to consent for use of your child's samples in other studies.

A5375 Study Visits

The study staff can answer any questions you have about individual study visits, and how long they will last, or about the tests that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

Appendix II Table 1: Study Schedule

Evaluation or Procedure	Screening	Entry Visit	Study Visits		Follow-Up Calls			Clinically Indicated Visit	Early Study Discontinuation
		Day 0	Day 1	Day 2	Day 7	Day 14	Day 28		
	1 hour	9-10 hours	1 hour	1 hour	30 minutes	30 minutes	30 minutes	1 hour	30 minutes
Documentation of HIV Status	√								
Medical/ Medication History	√	√							
Questions About Your Menstrual Cycle	√	√			√	√	√		√
Diagnoses Questions		√	√	√	√	√	√	√	√
Medication Questions		√	√	√			√	√	√
Acceptability and Practicality Questionnaire		√		√		√	√		√
Adherence Assessment	√	√	√	√					
Physical Exam	√	√						√	
Blood Collection	√	√							
Pregnancy Testing	√	√						√	
Hair Collection		√							
LNG EC Administration		√							
Pharmacokinetic Sampling		√	√	√					

Screening

If you agree to let your child be in this study, after you have read and signed this informed consent form, your child will come to the clinic for a screening visit to make sure your child meets the requirements for joining the study. This visit will take about 1 hour [*Site to insert site-specific information about duration of study visit]*. Up to 18 mL (1.4 tablespoons) of blood will be drawn at this visit.

- Your child's HIV infection status will be confirmed. If there is no record available, another HIV test will be done. You may have to sign a separate consent form before this is done.

- Your child will be asked questions about her medical and medication history and any medications she is currently taking. Your child will be asked about her menstrual period.
- Your child will be asked about adherence to her anti-HIV or anti-TB medications (how correctly she is taking her medications).
- Your child will have a physical exam.
- Your child will have blood drawn for routine lab tests for safety. *[Site to insert site-specific information about sharing test results with adolescents and parents/guardians.]*
- Your child will give a urine sample or have blood drawn to see if she is pregnant. This test must show that she is not pregnant for her to enroll in the study. *[Site to insert site-specific information about sharing test results with adolescents and parents/guardians.]*

Entry Visit (Day 0)

If your child is eligible for the study and you choose to let her enroll, she will come back to the clinic for an entry visit. This visit will last about 9 or 10 hours *[Site to insert site-specific information about duration of study visit]*. Up to 75 mL (5.8 tablespoons) of blood will be drawn at this visit.

- Your child will be asked questions about: her medical history and any medications she is taking, **birth control that she is taking or has taken in the last 4 months**, her menstrual period and if there has been a change in her menstrual period since the screening visit, and adherence to her anti-HIV or anti-TB medications.
- Your child will have a physical exam, including measuring her neck, waist, and hips.
- If your child is HIV positive, she will have a blood drawn to test how much HIV is in her blood, and to test how many CD4 cells (infection-fighting cells) are in her blood. *[Site to insert site-specific information about sharing test results with adolescents and parents/guardians.]*
- Your child will have blood drawn and stored for a genetic test (a test of your child's DNA [genes] to better understand how fast her body removes the study drugs from your blood). Genetic testing looks at differences in people's genes. Our bodies, like all living things, are made up of cells, and cells contain deoxyribonucleic acid, also known as "DNA." DNA is like a string of information put together in a certain order. Parts of the string make up "genes." Genes contain instructions on how to make our bodies work and fight disease. The testing in this study will only look at certain genes that are known to have an effect on how our bodies use hormones. The tests will not look at any other genes. Your child will not receive the results of these tests.
- Your child will be asked to give a urine sample or have blood drawn to see if she is pregnant. This test must show that she is not pregnant for her to remain in the study. *[Site to insert site-specific information about sharing test results with adolescents and parents/guardians.]*
- Your child will have a small sample of hair (about 50 strands) cut from her head to measure levels of the HIV or TB drugs in this hair sample. Humans lose about 100 hairs from their head every day naturally, so this amount of hair removal should not be noticeable. If your child decides not to provide a hair sample, she can still be in the study. Results of this testing will not be available to your child since hair levels are still a research tool.
- Your child will take a dose of LNG emergency contraception by mouth.
- Your child will be asked to remain at the clinic all day for an intensive pharmacokinetic (PK) blood sampling. For this intensive PK sampling, she will have blood drawn over 8 hours to

measure the amount of LNG in your blood. To avoid many needle sticks, a small tube (intravenous device) **may** be placed into a vein in her arm and left in place during her stay. Your child will be able to move around and should not have any significant pain or discomfort once the tube is in place. Blood will be taken before she takes the LNG emergency contraception dose, and then at 30 minutes, 1, 1.5, 2, 3, 4, 6, and 8 hours after she takes the LNG emergency contraception dose.

- Your child will be asked if she has any problems or concerns after taking the LNG emergency contraception dose.

Study Visits (Days 1 and 2)
After the entry visit, your child will come back to the clinic for two more study visits. The first will be 1 day after her entry visit, and the second will be 2 days after her entry visit. These study visits will last about 1 hour. Up to 6 mL (0.4 tablespoons) of blood will be drawn at this visit.

- Your child will have blood drawn for PK blood sampling.
- Your child will be asked about: her adherence to medications, changes in her medications or diagnoses, the acceptability and practicality of emergency contraception, and any problems or concerns she has after taking the LNG emergency contraception dose.

During the COVID-19 outbreak, the Day 1 and Day 2 study visits may be conducted over the phone. If the visit is conducted over the phone, a member of the study staff will call your child. Visits that are conducted over the phone will not include blood draws.

Follow-up
A member of the study staff will call your child 7 days after study entry to ask her about her menstrual period, and about changes in her diagnoses.

A member of the study staff will call your child 14 and 28 days after study entry to ask her about: changes in her diagnoses and (on day 28 only) her medications, her menstrual period, the acceptability and practicality of emergency contraception, and any problems or concerns she has after taking the LNG emergency contraception dose.

Clinically Indicated Visit
If your child becomes pregnant or has an adverse event, she may be asked to return to the clinic for a physical exam and pregnancy test, and to discuss any changes in her medications or diagnoses.

Early Study Discontinuation (Leaving the Study Early)
If your child leaves the study early, she will be asked about: changes in her medications or diagnoses, her menstrual period, the acceptability and practicality of emergency contraception, and any problems or concerns she has after taking the LNG emergency contraception dose.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 116 women and girls **who are 16 years of age or older** will take part in this study.

HOW LONG WILL YOUR CHILD BE IN THIS STUDY?

Your child will be in this study for about 4 weeks.

WHY WOULD THE DOCTOR TAKE YOUR CHILD OFF THIS STUDY EARLY?

The study doctor may need to take your child off the study early without your permission if:

- The study is stopped or cancelled
- Your child has a positive pregnancy test before she takes the LNG dose for the study
- Your child is not able to attend the study visits as required by the study
- Your child's primary care doctor requests that she be taken off the study

After the study:

After your child has completed her study participation, the study will not be able to continue to provide your child with the LNG she received on the study. If similar drugs/agents would be of benefit to your child, the study staff will discuss how your child may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY TO YOUR CHILD?

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

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your child's safety, you must tell the study doctor or nurse about all medications your child is taking before she starts the study and also before she starts any new medications while on the study. Also, you must tell the study doctor or nurse before your child enrolls in any other clinical trials while on this study.

Risks of Levonorgestrel (LNG, Plan B® One-Step)
The following side effects have been associated with the use of LNG:

- Nausea
- Lower stomach (abdominal) pain
- Tiredness
- Headache
- Dizziness
- Breast pain
- Vomiting
- Diarrhea

Some women will have menstrual changes such as spotting or bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late.

- If your child's period is more than a week late, she should get a pregnancy test

Risks of Drawing Blood
Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

Risks of Hair Collection
There is a small risk of cutting or nicking the scalp during the hair collection, although this is extremely rare.

Risks of Social Harm
It is possible that participating in this study will make it difficult for your child to keep her HIV or TB status, secret from people close to her. This may lead to unwelcome discussions about or reactions to your child's HIV or TB status. Please talk with the study staff if you have any concerns about this.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the drug or drug combinations in this study harm unborn babies. If your child is are having sex that could lead to pregnancy, she must agree not to become pregnant until she completes the study. Your child may not enter the study if she has had sex that could lead to pregnancy within 14 days prior to starting the study.

Your child and her partner must use reliable birth control that she discusses with the study staff. Your child must continue to use birth control while in the study. Your child may choose one of the birth control methods below:

- Male condom with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal IUD
- Bilateral tubal ligation
- Male partner vasectomy

If your child can become pregnant, she must have a pregnancy test before she enters this study. The test must show that she is not pregnant. If your child thinks she may be pregnant at any time during the study, she must tell the study staff right away. The study staff will talk to your child about her choices. A pregnancy test may not detect a very early pregnancy, which is why the study team asks that your child not enter the study if she has had sex that could lead to pregnancy within 14 days of study entry.

If your child becomes pregnant while on study, the study staff would like to obtain information from her about the outcome of the pregnancy (even if it is after her participation in the study ends). If your child is taking anti-HIV drugs when she becomes pregnant, her pregnancy will be reported to an international database that collects information about pregnancies in women

taking anti-HIV drugs. This report will not use your child's name or other information that could be used to identify her.

Breastfeeding
Breastfeeding women will be included only after their infants are at least 6 months old. Birth control like LNG is allowed during breastfeeding. During long-term use of drugs like LNG, called progestins, the amount of progestin in infant blood is only 1-6% of the amount in maternal blood. No side effects of progestins have been found on breastfeeding (quality or quantity of milk), or on the health or development of the infant due to this low progestin exposure.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Your child will receive no benefit from being in this study. Information learned from this study may help other women and girls who have HIV or TB.

WHAT ABOUT CONFIDENTIALITY?

For Sites in the US
We will do everything we can to protect your child's privacy. In addition to the efforts of the study staff to help keep your child's personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your child's name or identify your child personally.

Your child's records may be reviewed by the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, and their designees. Having a Certificate of Confidentiality does not prevent you from releasing information about your child and your child's participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time**.**

For Sites outside the US
Efforts will be made to keep your child's personal information confidential. We cannot guarantee absolute confidentiality. Your child's personal information may be disclosed if required by law. Any publication of this study will not use your child's name or identify your child personally.

Your child's records may be reviewed by the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties, (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, and their designees.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify your child. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE THE COSTS TO ME?

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

There is no cost to you for LNG, study-related visits, physical examinations, laboratory tests, or other study procedures.

Anti-HIV and anti-TB medicines will not be provided by the study.

WILL **MY CHILD** RECEIVE ANY PAYMENT?

Your child may be reimbursed for **her** time and travel expenses as part of **her** participation in this study. *(Site to insert site-specific information about payment to adolescents.)*

WHAT HAPPENS IF YOUR CHILD IS INJURED?

If your child is injured as a result of your being in this study, your child will be given immediate treatment for injuries and be referred for further treatment, if necessary.
[*Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry Clinical Trials Insurance (CTI), this must be indicated in the informed consent.]*

- ***This site has clinical trials insurance. This insurance will allow the site to provide your child with monetary compensation if your child suffers harm as a result of participating in this research study.***
- ***The cost for this treatment will be charged to you/your child or your child's insurance company. There is no program for compensation either through this institution or the NIH.***

You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE YOUR CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to let your child take part in this study or to remove your child from this study at any time. **Your child may choose to leave the study at any time.** Your decision will not have any impact on your child's participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which your child is otherwise entitled.

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- Name of the investigator or other study staff
- Telephone number of above

For questions about your child's rights as a research participant, contact:

- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

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

Child Participant's Name (print)	Child Participant's Date of Birth
Parent/Legal Guardian Name (print) (As appropriate)	Parent/Legal Guardian Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

ATTACHMENT II-A: PARENTAL CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called "extra samples." The ACTG will only allow your child's extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your child's samples and from any information that has been collected about your child. This means that no one looking at the labels or at other information will know that the samples or information came from your child.

Extra samples are stored in a secure central place called a repository. Your child's samples will be stored in the ACTG repository located in the United States.

There is no limit on how long your child's extra samples will be stored.
[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]

When a researcher wants to use your child's samples and information, their research plan must be approved by the ACTG. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. [Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.] IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your child's samples to the researcher's location. This means that researchers who are not part of the protocol team may use your child's samples without asking you or your child again for consent.

You will not be paid for your child's samples. Also, a researcher may make a new scientific discovery or product based on the use of your child's samples. If this happens, there is no plan to share any money with you or your child.

You may withdraw your consent for research on your extra samples at any time, and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your child's extra samples may be stored (with usual protection of your child's identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my child's samples

OR

____ (initials) I understand but I do not agree to this storage and possible use of my child's samples

Research with Human Genetic Testing

The ACTG has two different studies that collect samples for genetic testing.

If you live in the US, this study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

If you live outside of the US, this study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.

Your site might ask you if you would like your child to participate in one of these studies if it is being done where you live. If you would like your child to participate, you will sign a separate consent form.

Your child's extra samples will not be used for human genetic testing unless you sign a consent for A5128 or A5243.

APPENDIX III: SAMPLE ASSENT FORM

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For protocol: A5375

An Open-Label, Phase II Pharmacokinetic Study to Evaluate Double-Dose Levonorgestrel Emergency Contraception in Combination with Efavirenz-Based Antiretroviral Therapy or Rifampicin-Containing Anti-Tuberculosis Therapy

FINAL Version 2.0, 10/30/20

SHORT TITLE FOR THE STUDY: Optimize LNG EC

SUMMARY

PURPOSE: **Emergency contraception is birth control that prevents pregnancy. Girls and women use it after having unprotected sex. Levonorgestrel (LNG) emergency contraception is commonly known as Plan B® One-Step, or the Morning After Pill. This study will test if a higher dose of LNG needs to be used to prevent pregnancy in girls and women who are taking some types of anti-HIV or anti-TB medications. This study will also test if a higher dose of LNG is safe.**

STUDY TREATMENT: **You will take a dose of LNG emergency contraception by mouth. LNG emergency contraception will be provided by the study.**

The United States Food and Drug Administration (US FDA) has approved LNG for prevention of pregnancy.

NUMBER OF PARTICIPANTS: **There will be 116 women and girls who are 16 years of age or older in this study. There will be 17 people in Group A, and 33 people in each of Groups B, C, and D.**

LENGTH OF STUDY: **The study will last about 4 weeks. During this time, you will need to come to the clinic for about 3 visits.**

REQUIRED ACTIVITIES: **<u>Blood and Urine Collections</u>**
At most visits, some blood will be collected from a vein in your arm. You may be asked to provide a urine sample.

At the entry visit, you will be asked to remain at the clinic all day for an intensive pharmacokinetic (PK) blood sampling. For this intensive PK sampling, you will have blood drawn several times over a period of 8 hours to measure the amount of LNG in your blood. To avoid many needle sticks, a small tube (intravenous device) will be placed into a vein in your arm and left in place during your stay. You will be able to move around and should not have any significant pain or discomfort once the tube is in place.

RISKS: **The following side effects have been associated with using LNG: nausea, lower stomach pain, tiredness, headache, dizziness, breast pain, vomiting, and diarrhea. Some individuals will have menstrual changes such as spotting or bleeding before their next period. Some individuals may have a heavier or lighter next period, or a period that is early or late.**

Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

BENEFITS: **You will receive no benefit from being in this study.**

OTHER CHOICES: **Instead of being in this study, you have the option of continuing with your current treatment or starting a new treatment under the care of your regular doctor or other health care provider.**

INTRODUCTION

You are being asked to take part in this research study because you are a girl at least 16 years of age and:

1. You are living with human immunodeficiency virus (HIV-1) and you have been taking a combination of antiretroviral drugs (ARV) that includes either efavirenz (EFV) or dolutegravir (DTG)

   OR,

2. You are living with tuberculosis (TB) infection, and you have completed the intensive phase of TB therapy and are now completing the continuation phase of TB treatment that requires taking isoniazid (INH) and rifampicin (RIF) daily.

Your parent/guardian will be informed about this study and asked to sign a separate form giving their consent for you to take part. As a participant in this study, we would like you to know about the study too, and to be given a chance to ask any questions you may have about it. You will be asked to sign this assent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Emergency contraception is birth control that prevents pregnancy. Girls and women use it after having unprotected sex. Levonorgestrel (LNG) emergency contraception is commonly known as Plan B® One-Step, or the Morning After Pill. This study will test if a higher dose of LNG needs to be used to prevent pregnancy in girls and women who are taking some types of anti-HIV or anti-TB medications. This study will also test if a higher dose of LNG is safe.

The United States Food and Drug Administration (US FDA) has approved LNG for prevention of pregnancy.

LNG works mainly by stopping the release of an egg from the ovary. It may also work by preventing fertilization of an egg, or by preventing attachment to the uterus. Girls and women can use emergency contraception to prevent pregnancy if regular birth control was used incorrectly or fails, or no birth control was used. LNG will not disrupt an existing pregnancy and using LNG does not affect your ability to have a baby in the future. After you take LNG as part of this study, you may attempt to get pregnant again as soon as your next menstrual cycle (after your next period), if you want to.

Efavirenz (EFV) is a medication commonly used to treat HIV. Rifampicin (RIF) is a medication commonly used to treat tuberculosis. Both of these medications lower the amount of LNG in your blood by about half. This may make LNG not work as well as it normally would. It is unknown if the current dose of LNG emergency contraception, in combination with EFV or RIF, is enough to prevent a pregnancy. To learn if a higher dose is needed to prevent pregnancy, participants will take either a regular dose or a double dose of LNG emergency contraception.

Dolutegravir (DTG) is an anti-HIV medication that does not lower the amount of LNG in your blood. It is being used as a comparison to the other groups.

In this study, you will not be taking LNG for contraception (to prevent pregnancy), you will be volunteering to take it so that we can evaluate the impact of your other medications on the amount of LNG in your blood. You will take a dose of LNG emergency contraception by mouth. After you take the dose of LNG, the amount of LNG that is in your blood will be measured. This study will also take a hair sample that will tell researchers how often you have taken EFV, INH, and DTG over the past few weeks. You can refuse to give a hair sample**.**

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

People who take part in this study will be asked to be part of it for 4 weeks. A screening visit will be done to make sure you are eligible to join the study. If you are found eligible, you will have one entry visit that will last 9-10 hours, a 1 hour visit 24 hours after entry, and a 1 hour visit 48 hours after entry. You will be asked to take a questionnaire over the phone 1 week, 2 weeks, and 4 weeks after entry.

The study staff can tell you more about the study visits and what exactly will be done at the visits. They can also talk more with you and your parent/guardian about the study medicines

and the possible effects of these medicines. They will also tell you about health problems that they would like you to report to them. You are welcome to ask any questions you may have at any time.

We would also like you to know that information collected in this study will be kept confidential (private) and only those people who are doing the study and are overseeing the study will be able to see your information. [*Sites should also include a statement here describing the extent to which information reported by children/adolescents will be shared with their parents/guardians*].

Taking part in this study is your choice. This means you can say yes or no to being part of the study. No matter what decision you make, and even if your decision changes, nothing bad will happen to you or your family. You will not lose medical care, legal rights, or any benefits that you are otherwise entitled to.

WHAT ARE THE RISKS OF THE STUDY?

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

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

<u>Risks of Levonorgestrel (LNG, Plan B® One-Step)</u>
The following side effects have been associated with the use of LNG:

- Nausea
- Lower stomach (abdominal) pain
- Tiredness
- Headache
- Dizziness
- Breast pain
- Vomiting
- Diarrhea

Some women will have menstrual changes such as spotting or bleeding before their next period. Some women may have a heavier or lighter next period, or a period that is early or late.

- If your period is more than a week late, you should get a pregnancy test

Risks of Drawing Blood
Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

Risks of Hair Collection
There is a small risk of cutting or nicking the scalp during the hair collection, although this is extremely rare.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your HIV or TB status, or information about your sexual activity, secret from people close to you. This may include your parent or guardian. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns about this.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known if the drug or drug combinations in this study harm unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant until you complete the study. You may not enter the study if you have had sex that could lead to pregnancy within 14 days prior to starting the study.

You and your partner must use reliable birth control that you discuss with the study staff. You must continue to use birth control while in the study. You may choose one of the birth control methods below:

- Male condom with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal IUD
- Bilateral tubal ligation
- Male partner vasectomy

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must show that you are not pregnant. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. A pregnancy test may not detect a very early pregnancy, which is why the study team asks that you not enter the study if you have had sex that could lead to pregnancy within 14 days of study entry.

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

Breastfeeding
Breastfeeding women will be included only after their infants are at least 6 months old. Birth control like LNG is allowed during breastfeeding. During long-term use of drugs like LNG, called progestins, the amount of progestin in infant blood is only 1-6% of the amount in maternal blood. No side effects of progestins have been found on breastfeeding (quality or quantity of milk), or on the health or development of the infant due to this low progestin exposure.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

You will receive no benefit from being in this study. Information learned from this study may help other women who have HIV or TB.

SIGNATURE PAGE

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

_____
Child Participant's Name and Surname (print)

_____
Child Participant's Date of Birth

_____
Child Participant's Signature and Date

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

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

APPENDIX IV: PROHIBITED AND PRECAUTIONARY MEDICATIONS

Some drugs on these lists that can be used topically may be allowed on a case-by-case basis, after discussion with and approval by the protocol team via e-mail as described in the Study Management section.

1.0 PROHIBITED MEDICATIONS

1.1 Other Hormones

All Groups: Efavirenz, Dolutegravir, Rifampicin

- Delestrogen
- Depotestrogen
- Desogestrel
- Drospirenone
- Estradiol cypionate
- Estradiol Valerate
- Estrogens, Conjugated
- Estrogens, Esterfied
- Ethinyl Estradiol
- Ethynodiol Diacetate
- Etonogestrel
- Gestodene
- Hydroxyprogesterone
- Levonorgestrel
- Medroxyprogesterone
- Norelgestromin
- Norethindrone
- Norgestimate
- Norgestrel
- Progesterone
- Testosterone

1.2 Other Concomitant Medications

Group A and B: Efavirenz

- Amodiaquine
- anticonvulsants (carbamezepine, Eslicarbazepine, felbamate, fosphenytoin, Lamotrigine, Oxcarbazepine, Perampanel, phenytoin)
- Astemizole
- Azole Antifungals (Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)
- barbiturates (phenobarbital, primidone)
- Bepridil
- cat's claw

- Cisapride
- dexamethasone
- Dihydroergotamine
- Enzalutamide
- Ergotamine
- Griseofulvin
- integrase strand transfer inhibitors (including dolutegravir, elvitegravir, raltegravir, bictegravir)
- Macrolides (Clarithromycin, erythromycin)
- maraviroc
- Midazolam
- Mitotane
- Other Nonnucleoside reverse transcriptase inhibitors (including nevirapine, rilpivirine, delavirdine, doravirine)
- Protease inhibitors (HIV or HCV)
- Rifamycins (including rifampin, rifapentine & rifabutin)
- St John's Wort
- Terfenadine

Group C: Dolutegravir

- **A**frican potato
- anticonvulsants (carbamezepine, Eslicarbazepine, felbamate, fosphenytoin, Lamotrigine, Oxcarbazepine, Perampanel, phenytoin)
- Azole Antifungals (Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)
- barbiturates (phenobarbital, primidone)
- Dofetilide
- Enzalutamide
- Macrolides (Clarithromycin, erythromycin)
- maraviroc
- Mitotane
- Nonnucleoside reverse transciptase inhibitors (including efavirenz, nevirapine, rilpivirine, delavirdine, doravirine)
- Other integrase strand transfer inhibitors (including elvitegravir, raltegravir, bictegravir)
- protease inhibitors (HIV or HCV)
- Rifamycins (including rifampin, rifapentine & rifabutin)
- St John's Wort

Group D: Rifampicin

- anticonvulsants (carbamezepine, Eslicarbazepinefelbamate, fosphenytoin, Lamotrigine, Oxcarbazepine, Perampanel, phenytoin)
- Azole Antifungals (Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)
- barbiturates (phenobarbital, primidone)

- Enzalutamide
- Halothane
- integrase strand transfer inhibitors (including dolutegravir, elvitegravir, raltegravir, bictegravir)
- Macrolides (Clarithromycin, erythromycin)
- maraviroc
- Mitotane
- Nonnucleoside reverse transciptase inhibitors (including efavirenz, nevirapine, rilpivirine, delavirdine, doravirine)
- Other Rifamyacins (rifabutin & rifapentine)
- protease inhibitors (HIV or HCV)
- St. John's Wort

2.0 PRECAUTIONARY MEDICATIONS

Groups A and B: Efavirenz

- Aprepitant
- Artemether/lumefantrine
- Atovaquone/proguanil
- Azole antifungals (itraconazole, posaconazole)
- Bosentan
- clopidogrel
- diltiazem
- Fosaprepitant
- garlic
- ginkgo biloba
- GLP-1 agonists (exenatide, lixisenatide)
- hops
- Lesinurad
- malabar nut tree
- Mycophenolate
- nefazodone
- pioglitazone
- Proguanil
- Prucalopride
- quercetin
- Telithromycin
- ticlopidine
- Topiramate
- Triazolam

Group C: Dolutegravir

- antacids - follow product labeling for instructions on separation with DTG
- Aprepitant
- Artemether/lumefantrine

- buffered medications - follow product labeling for instructions on separation with DTG
- divalent cations (e.g., Ca++, Fe++) - follow product labeling for instructions on separation with DTG
- Fosaprepitant
- garlic
- GLP-1 agonists (exenatide, lixisenatide)
- Lesinurad
- malabar nut tree
- MVI - follow product labeling for instructions on separation with DTG
- Mycophenolate
- Prucalopride
- sucralfate - follow product labeling for instructions on separation with DTG
- Topiramate

Group D: Rifampicin

- antacids - follow product labeling for instructions on separation with RIF
- Aprepitant
- Artemether/lumefantrine
- cotrimoxazole
- Fosaprepitant
- GLP-1 agonists (exenatide, lixisenatide)
- Lesinurad
- Mycophenolate
- probenecid
- Prucalopride
- Topiramate