



A5338

An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11982

This file contains the current ACTG A5338 protocol, which includes the following document:

- Clarification Memorandum #2, dated 3 August 2016
- Letter of Amendment #2, dated 25 January 2016
- Clarification Memorandum #1, dated 27 April 2015
- Letter of Amendment #1, dated 16 October 2015

Letter of Amendment #2 for:

A5338

An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11982

Letter of Amendment Date: 25 January 2016

ACTG Network Coordinating Center

Social & Scientific Systems, Inc.
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Phone: (301) 628-3000
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LETTER OF AMENDMENT

DATE: January 25, 2016

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5338 Protocol Team

SUBJECT: Letter of Amendment #2 for Protocol A5338, Version 1.0, 12/12/14 entitled "An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)"

The following information impacts the A5338 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also impact the Sample Informed Consent (SIC). Your IRB/EC is responsible for determining the process of informing subjects of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all the required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

The following are changes to A5338, Version 1.0, 12/12/14 (noted in strikethrough and bold):

1. In the required TB treatment regimen (Section 5.1.1), the following changes are made:

Required TB treatment (not provided through study):

- Rifampicin (RIF) ~~600 mg~~ **8 – 12 mg/kg** orally once daily **or as directed by the national guidelines for TB treatment.**
- Isoniazid (INH) ~~300 mg~~ **4 – 6 mg/kg** orally once daily **or as directed by the national guidelines for TB treatment.**

2. In Section 9.1, General Design Issues, the following changes are made in the 2nd paragraph:

A woman is eligible for this study if she is premenopausal between the ages of 18 and 46 and co-infected with HIV and TB. Women must be on: **(1) ~~both RIF- and (600 mg once daily) INH-containing TB treatment,~~ and (2) ~~EFV (600 mg once daily) - based cART at least 4 weeks before study entry.~~ (The participant must be on EFV-based cART for at least 4 weeks before study entry.) The dose of INH, RIF, and EFV is defined in section 5.1.1.**

The above information will be incorporated into the next protocol version as necessary if the protocol is amended.

Clarification Memo #2 for:

A5338

An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11982

Clarification Memo Date: 3 August 2016

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CLARIFICATION MEMO

DATE: August 3, 2016

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5338 Protocol Team

SUBJECT: Clarification Memo # 2 for Protocol A5338, Version 1.0, 12/12/14, entitled "An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)"

This clarification memo does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your institutional review board (IRB); however, as always, you must follow your IRB's policies and

procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this clarification memo with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately. These updates will be included in the next version of the A5338 protocol if it is amended at a future date.

The following are clarifications to A5338, Version 1.0, 12/12/14:

The use of ethambutol (EMB) does not exclude a woman from participating in the study. This is supported by the following sections of the protocol:

- Inclusion criterion 4.1.4: *Currently receiving RIF and Isoniazid (INH)-based TB therapy on at least 5 days per week schedule after completion of the intensive phase of TB treatment (minimum of 8 weeks of TB treatment) and expected to be on TB treatment for a minimum of 12 weeks after enrollment.*

This criterion does not exclude the use of EMB during the study.

- Exclusion criterion 4.2.3: *Use of any drugs other than RIF and EFV known to: 1) induce CYP3A4 system within 30 days and to 2) inhibit the CYP3A4 system with one week prior to study entry.*

Because EMB does not induce or inhibit the CYP3A4 system, its use is consistent with the language in the protocol.

Although the use of EMB is not prohibited, the sites are reminded to follow their country's TB treatment guidelines and to use EMB only if it is part of local standard of care for TB treatment.

Sites should inform the team if other TB medications will be used in the study. All TB medications used in the study should be recorded on study case report forms (CRFs).

Please contact the A5338 team at ACTG.COREA5338@fstrf.org with any questions.

Clarification Memo #1 for:

A5338

An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11982

Clarification Memo Date: 27 April 2015

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CLARIFICATION MEMO

DATE: April 27, 2015

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5338 Protocol Team

SUBJECT: Clarification Memo # 1 to the A5338 Protocol, Version 1.0, 12/12/14 entitled "An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)"

This clarification memo does not result in a change in the protocol informed consent document. The Division of AIDS does not require you to forward it to your IRB; however, as always, you must follow your IRB's policies and procedures. If IRB review of clarification memos is required at your site, please submit this document for review.

Each site should file a copy of this clarification memo with the protocol for reference.

The protocol clarifications contained in this memo should be implemented immediately. These updates will be included in the next version of the A5338 protocol if it is amended at a future date.

The following are clarifications (noted in either strikethrough or bold font) to protocol A5338, Version 1.0, 12/12/14:

1. Sites Participating in the Study, 2nd paragraph

This is a limited site study, open to select non-US sites. The approved sites are listed on the Protocol-Specific Web Page (PSWP).

2. Doses of ARV and TB medications to be collected in the CRF prior to PK in Section 10.2, 1st paragraph, 1st sentence

Doses of ~~all ARV and TB medications~~ **EFV, RIF, and INH** taken for **over** 48 hours prior to PK will be collected on the CRF at weeks **0, 2, 4, 6, 8, 10, and 12.**

Letter of Amendment #1 for:

A5338

An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)

A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

DAIDS ES # 11982

Letter of Amendment Date: 16 October 2015

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LETTER OF AMENDMENT

DATE: October 16, 2015

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5338 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5338, Version 1.0, 12/12/14 entitled "An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)"

The following information impacts the A5338 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also impact the Sample Informed Consent (SIC). Your IRB/EC is responsible for determining the process of informing subjects of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all the required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

The following are changes to A5338, Version 1.0, 12/12/14 (noted in strikethrough and bold font):

1. In the Exclusion Criteria (Section 4.2), the following changes are made:
 - a. Section 4.2.1 is revised to:

Receipt of DMPA ~~and~~ **or** any other injectable **contraceptive** ~~contraceptives~~ within 180 days prior to study entry.
 - b. Section 4.2.8 is revised to:

Any previous ~~Breast~~ breast cancer diagnosis.
2. In Pharmacy: Product Supply, Distribution, and Accountability (Section 5.3), the following changes are made to allow sites the option to use locally available depot medroxyprogesterone acetate (DMPA) instead of study-provided DMPA:
 - a. The following paragraph is added as the 3rd paragraph in Section 5.3.1

Sites may use locally available DMPA if drug importation issues or delays are anticipated or encountered. The locally available DMPA must be approved by the A5338 Core Team before it can be used for the study. No additional funding will be provided to sites for purchasing DMPA locally, and participants and the participants' insurers must not be billed for the product.
 - b. Section 5.3.2

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC **or any other source** and subsequently dispensed. ~~All unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor).~~ **Study product not obtained from the CRPMC should be disposed of in accordance with the disposal standard operating procedures at the site** after the study is completed or terminated. The site pharmacist at non-US Clinical Research Sites (CRSs) must follow the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities **for the destruction of unused study products obtained from the CRPMC.**
3. In the noncompliance criteria for premature study discontinuation (Section 8.1), the following changes are made to clarify the criteria for missed doses and pharmacokinetic (PK) sampling:

a. Section 8.1.3

Missed 2 or more of the RIF and/or EFV doses within one week prior to PK sampling at week 2, 4, 6, or 8 and did not return with acceptable adherence (ie, missed 2 or more of the RIF and/or EFV doses) for the rescheduled PK sampling for 2 consecutive study weeks.

b. Section 8.1.4

Missed 2 or more of the RIF and/or EFV doses within one week prior to PK sampling at week 10 or 12 and did not return with acceptable adherence (ie, missed 2 or more of the RIF and/or EFV doses) for the rescheduled PK sampling.

4. In Section 9.5, the following changes are made to add review by an independent Study Monitoring Committee (SMC) to the planned team monitoring:

The study team will monitor participant accrual to ensure the target number of evaluable participants is enrolled. Study sites will be required to report all participant dropouts and noncompliance, including missing PK sample times/visits to the study team as soon as they occur. The study team will make decisions on participant's replacement on conference calls or by emails. **The study team will also review data availability reports prepared by the study statisticians and/or laboratory data manager regularly, to ensure that samples for primary and secondary analyses are collected as anticipated.**

During the study, the safety and tolerability of the study medications will be monitored by means of adverse events reports representing laboratory and clinical data, ~~such as Toxicity Summary reports or Phase I/II reports~~ provided by ACTG DMC. ~~It is required for study sites to enter these data into the DMC database within a specified time period for data entry.~~ The study team will discuss these reports on regularly scheduled conference calls or by email. It is the responsibility of the study team to interpret the adverse event data and make any decisions needed to protect study participants from undue risk. Any concerns will be presented to the DAIDS Clinical Representative.

An ACTG-appointed Study Monitoring Committee (SMC) review will take place at the earliest of (a) approximately 50% accrual to the study, (b) 6 months after enrollment of the first participant, or (c) if two or more participants become pregnant on study treatment. Subsequent reviews will occur annually for as long as there are participants in follow-up.

5. In Pharmacology Study Design (Section 10.2), the following changes are made in the 1st and 2nd paragraphs to clarify the criterion for rescheduling a visit for PK sampling and the schedule of the medroxyprogesterone acetate (MPA) PK and plasma progesterone evaluations:

Doses of all ARV and TB medications taken for 48 hours prior to PK will be collected on the CRF at weeks 2, 4, 6, 8, 10, and 12. The participant should be contacted one week prior to the scheduled visit to reinforce the importance of 100% adherence to RIF and EFV and of her upcoming appointment. A participant who misses 2 or more doses of RIF and/or EFV within one week prior to the scheduled PK sampling at weeks 2, 4, 6, 8, 10, and 12 will have the visit rescheduled to one week later. For the week 10 and week 12 visits, the rescheduled PK sampling should be strictly within the original visit window for

that visit. The schedule for the remaining visit weeks should not be changed. The rules for replacing participants who do not complete the PK are described in sections 8.1 and 9.5.

A single 4 mL blood sample for PK will be collected just prior to DMPA injection at week 0 and at the scheduled visits at weeks 2, 4, 6, 8, 10, and 12. The blood sample will be centrifuged within 1 hour of collection to separate the plasma which will be stored at -70°C or colder until assay for MPA and/or progesterone.

6. In the Sample Informed Consent (SIC), the following changes are made in the “Why Would The Doctor Take Me Off This Study Early?” section to clarify the criteria for missed visits and missed doses that would lead to premature study discontinuation:
 - a. 1st bullet

You miss two study visits in a row **or you miss either the week 10 or week 12 visit.**
 - b. 2nd bullet

You do not take the RIF and/or EFV medications as you are supposed to and you then do not take the RIF and/or EFV prior to your rescheduled visit to collect the blood sample to measure the level of DMPA in your blood.

The above information will be incorporated into the next protocol version as necessary if the protocol is amended.

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A Limited Center Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

**The National Institute of Allergy
and Infectious Diseases**

non-IND Protocol

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**Final Version 1.0
December 12, 2014**



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APPENDIX I: SAMPLE INFORMED CONSENT	

SITES PARTICIPATING IN THE STUDY

This is a limited site study. The sites were selected based on the availability of potentially eligible subjects, close proximity of the site to a Tuberculosis (TB) clinic, integrated HIV/TB programs and interest in the study according to responses to a site feasibility survey.

The approved sites are listed on the Protocol-Specific Web Page (PSWP).

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STUDY MANAGEMENT

All questions concerning this protocol should be sent to actg.coreA5338@fstf.org via e-mail. The appropriate team member will respond with a "cc" to actg.coreA5338@fstf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol E-mail Group

Sites should contact the Computer Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5338 e-mail group. Include the protocol number in the e-mail subject line.

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

Clinical Management

For questions concerning entry criteria, toxicity management, concomitant medications, and coenrollment, contact the protocol team. Send an e-mail message to actg.coreA5338@fstf.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 protocol pharmacologist. Send an e-mail message to actg.coreA5338@fstf.org (ATTN: Helen McIlleron).

Data Management

For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRF), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the data manager. CRFs can be downloaded from the FSTRF website at www.fstrf.org.

- For transfers, reference the Patient Transfer from Site to Site SOP 119, and contact Kristine Coughlin directly.
- For other questions, send an e-mail message to actg.coreA5338@fstf.org (ATTN: Kristine Coughlin).
- Include the protocol number, PID, and a detailed question.

Participant Registration

For participant registration questions or problems and study identification number SID lists.

- Send an e-mail message to randu.support@fstf.org. Call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at 716-834-0900 x7301.

Computer and Screen Problems

Contact the SDAC/DMC programmers.

- Send an e-mail message to actg.support@fstf.org or call 716-834-0900 x7302.

Protocol Document Questions

For questions concerning the protocol document, contact the clinical trials specialist. Send an e-mail message to actg.coreA5338@fstf.org (ATTN: Jhoanna Roa and Laura Moran).

STUDY MANAGEMENT (Cont'd)

Copies of the Protocol

To request a hard copy of the protocol, send a message to ACTGNCC@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG Web site (<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.

Study Product

For questions or problems regarding study product, dose, supplies, records, and returns, call Michelle Wildman, protocol pharmacist, at 301-496-7913.

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.

Phone Calls

Sites are responsible for documenting any phone calls made to A5338 team members.

- Send an e-mail to actg.coreA5338@fstf.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
AUC	area under the concentration-time curve
BMI	body mass index
cART	combination antiretroviral therapy
COC	combined oral contraceptives
CPQA	clinical pharmacology quality assurance
DEXA	dual-energy x-ray absorptiometry
DMPA	depot medroxyprogesterone acetate (Depo-Provera)
FSH	follicle-stimulating hormone
INH	isoniazid
IUD	intrauterine device
LMP	last menstrual period
LTBI	latent TB infection
MPA	medroxyprogesterone acetate (Provera)
NLME	nonlinear mixed-effects
RIF	rifampicin
SHIV	simian HIV
STI	sexually transmitted infection

SCHEMA

A5338

An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)

DESIGN

This is a phase II open-label, single arm, multicenter, steady-state pharmacokinetic (PK) study of drug-drug interactions in HIV-infected women treated with depot medroxyprogesterone acetate (DMPA) while receiving an efavirenz (EFV)-based combination antiretroviral therapy (cART), rifampicin (RIF) and isoniazid (INH) during the treatment of active tuberculosis (TB).

Blood samples for DMPA PK analysis will be collected at pre-dose and every 2 weeks post DMPA administration. Progesterone levels will be tested every 2 weeks post DMPA administration.

DURATION

All participants will be followed for 12 weeks.

SAMPLE SIZE

46 evaluable participants

POPULATION

Premenopausal women 18 to 46 years of age who are co-infected with HIV and TB.

Women who participate in this study must be on EFV plus two or more nucleoside reverse transcriptase inhibitors (NRTIs) for at least 4 weeks and intend to continue on this regimen without modifications for the duration of the study. Women must be on the continuation phase of active TB treatment taking RIF and INH on a 5-day or more per week schedule.

REGIMEN

Depot medroxyprogesterone acetate (DMPA) 150 mg administered intramuscularly (IM) as a single-dose at study entry.

An optional dose of DMPA will be available at no cost to all qualifying study participants after all week 12 study evaluations are completed.

Study provided drug is DMPA only. ARV therapy and TB treatment medications will not be provided by this study.

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

Concurrent use of efavirenz (EFV) and rifampicin (RIF) will increase the clearance of medroxyprogesterone acetate (MPA) in HIV and TB coinfecting women, resulting in reduced plasma MPA concentrations and reduced contraceptive efficacy.

1.2 Primary Objectives

- 1.2.1 To estimate the optimal dosing frequency of depot MPA (DMPA) for HIV and TB coinfecting women taking EFV-based combination antiretroviral therapy (cART) and RIF-containing TB treatment based on a target MPA concentration >0.1 ng/mL.
- 1.2.2 To determine whether a 150 mg DMPA IM injection will be adequate to suppress ovulation through 12 weeks in women taking EFV-based cART and RIF-containing TB treatment based on serial plasma progesterone concentrations.

1.3 Secondary Objectives

- 1.3.1. To estimate the area under the concentration-time curve (AUC), trough concentration (C_{\min}), maximum concentration (C_{\max}), apparent clearance (CL/F), and half-life ($t_{1/2}$) of MPA in HIV and TB coinfecting women taking EFV-based cART and RIF-containing TB treatment.
- 1.3.2. To estimate time and variability in time to MPA C_{\min} reaching 0.1ng/mL or less in HIV and TB coinfecting women taking EFV-based cART and RIF-containing TB treatment.
- 1.3.3. To estimate the proportion of participants who maintain MPA levels above the minimum level thought to suppress ovulation (MPA 0.1ng/mL) through 12 weeks after DMPA administration.
- 1.3.4. To evaluate the toxicity and safety of concurrent RIF, EFV, and DMPA use.

1.4 Exploratory Objectives

- 1.4.1 To explore whether pharmacokinetic (PK) interactions between EFV, RIF, and/or DMPA are affected by human genetic polymorphisms that have been reported to affect metabolism of these drugs.
- 1.4.2 To explore body mass index (BMI) and body fat content over time and correlate with DMPA levels.
- 1.4.3 To explore relationship between DMPA and bone metabolism in the HIV and TB coinfecting women.

2.0 INTRODUCTION

2.1 Background

Tuberculosis (TB) remains the most common cause of morbidity in HIV-infected patients in resource-limited countries. In the pre-highly active antiretroviral therapy (HAART) era, patients with HIV with latent TB infection (LTBI) had about a 10% risk of developing TB disease annually, a proportion that is most important in areas of high TB prevalence. HIV, due to its ability to suppress the immune system, is a significant risk factor for development of active TB in patients with latent TB [1, 2]. The HIV epidemic has fueled the resurgence of the TB epidemic leading to a dramatic increase in TB infections in the resource limited countries [3]. 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 HIV infected [4, 5]. A large percentage of patients on TB treatment will require combination antiretroviral therapy (cART).

Globally, women comprise 52% of all people living with HIV. In Sub-Saharan Africa, women account for approximately 57% of all people living with HIV and the prevalence of HIV in women between the ages of 15 and 24 years remains more than twice as high as young men in the same age group [6, 7]. In settings of high HIV prevalence, young women aged 15 to 24 years experience tuberculosis rates 1.5 to 2 times higher than men in the same age group [7]. Decisions about contraception in a population of women infected with both TB and HIV are of paramount importance. In the setting of the treatment of active tuberculosis, preventing pregnancy becomes even more important because it allows women to attain a level of health that will support healthy future pregnancies. Treatment options for TB may be limited in pregnancy because of concerns about teratogenicity. Indeed, fetal exposure to RIF, although generally considered safe, is associated with bleeding disorders. Treatment of TB before pregnancy avoids TB exposure in the neonate, a condition associated with high infant mortality.

Millions of women around the world use DMPA (Depo-Provera), an intermediate-acting progesterone-only injectable contraceptive, for prevention of pregnancy because of its high efficacy rate and its ease and convenience of administration [8]. According to data from the United Nations (UN) and Africa, more than 50% of women choosing reversible contraception in Sub-Saharan Africa use DMPA. Unfortunately DMPA's safety and effectiveness among women coinfecting with TB and HIV is unknown since the interactions of TB treatment, cART, and DMPA have not been well studied. A pharmacological interaction between hormonal contraceptives and RIF was described in the 1970s, and unintended pregnancies reported, leading to national guidelines recommending alternative dosing schedules for DMPA without good evidence for these recommendations [9]. The requirement for a third drug (EFV) with potential interactions makes the contraceptive efficacy of DMPA even more difficult to predict.

While some studies suggest that women using progestin-only injectable contraceptive may be at increased risk of transmitting HIV to an uninfected partner, most other studies have not shown this association except for a recent observational study which suggested a relationship between the use of DMPA and HIV transmission to an

uninfected partner [10]. Further work indicated that this might be due to increased genital tract viral load in women using this method of contraception [11]. A pigtail macaque model looking at the effect of DMPA on simian HIV (SHIV) showed no increase in plasma viral load or vaginal shedding of SHIV [12] and a recent prospective study did not find an association between DMPA and cervical HIV in well-suppressed women on ART [13]. Several studies are underway that will elucidate the relationship between contraceptive method choice and infectivity (Clinical Trial on the Effects of Progestin-based Contraception in the Genital Tract of HIV-infected and Uninfected Women, [NCT02103660] and HIV-Target Cell Response in Women Initiating Various Contraceptive Methods in High HIV-Incidence Areas: Zim CHIC [NCT02038335]). A World Health Organization (WHO) expert group reviewed all available evidence and recommended that women at high risk for HIV infection and women living with HIV can continue to use all existing hormonal contraceptive methods including DMPA without restriction. Women using progesterone-only injectable contraceptive should also be advised to use condoms as an HIV preventive measure [14].

2.1.1 DMPA

Medroxyprogesterone acetate (MPA, Provera) is a 21-carbon synthetic progestin with high selectivity and activity resembling those of natural progesterone. MPA has been used extensively in combination with estrogens for oral hormone replacement therapy in postmenopausal women. Relative to progesterone, MPA undergoes substantially less first-pass hepatic metabolism when given orally. MPA has a plasma half-life of 24 hours, with hepatic metabolism to various polar compounds and their conjugates [1]. DMPA, given as a 150 mg intramuscular dose, inhibits ovulation for up to 14 weeks and is therefore, given every 3 months to ensure continuous contraception, with a typical use failure rate of 0.3% during the first year [15]. The apparent half-life of DMPA is approximately 50 days after the intramuscular (IM) injection. Peak plasma concentration (1 to 7 ng/mL) is reached within 3 weeks of the injection and decreases exponentially to become undetectable at 120 to 200 days after dosing. MPA levels stay above the concentration needed to suppress ovulation (0.1 ng/mL) for approximately 3 months [16, 17, 18]. MPA levels at 3 months (12 weeks, C_{min}) after injection ranges from 0.04 to 1.31 ng/mL and mean MPA C_{min} is 0.45 ng/mL with coefficient of variation (CV) of 53% when coadministered with NRTIs only and 0.37 ng/mL with CV of 57% when co-administered with EFV-containing regimen. Women may not ovulate for up to 6 months after the last DMPA dosing [19].

DMPA prevents conception by inhibiting gonadotropin release, leading to ovulation suppression and thinning of the endometrial lining. Luteal activity and ovulation, as indicated by a rise in serum progesterone to >5 ng/mL, occurs when the MPA concentration drops to <0.1 ng/mL [17, 20, 21].

DMPA is metabolized via the cytochrome p450 enzyme system [16] and induces the activity of CYP3A4. When given as an injectable, MPA induces activity of CYP3A4 by 25% [18]. PK studies of DMPA with selected antiretroviral agents have not demonstrated a reduced contraceptive efficacy as assessed through ovulation suppression measured by progesterone levels [16, 19]. Non-NRTIs

(NNRTIs) and protease inhibitors (PIs) have demonstrated significant interactions with combined oral contraceptives (COC), which might lead to decreased efficacy of the COC [22, 23]. Studies of interactions between ART and DMPA have not demonstrated any clinically significant changes in the levels of either selected cARTs or DMPA. Cohn et al. showed that there were similar levels of DMPA in women on selected cART regimens (nelfinavir [NFV], nevirapine [NVP] and EFV) compared to women not on cART [16, 24]. Another small study done recently also failed to show significant changes in the PK of DMPA in HIV-infected women on cART with zidovudine (ZDV), lamivudine (3TC), and EFV [19]. This cART combination did not increase DMPA-related adverse events nor did it decrease the effectiveness of DMPA [19]. DMPA has not been shown to significantly alter the levels of antiretroviral drugs. The levels of EFV remained unchanged compared to baseline in the Cohn et al. study [16]. Current guidelines do not recommend changes in dosing frequency for patients on EFV-containing cART who use DMPA.

It is unknown whether simultaneous treatment of HIV and TB affected the serum concentration, efficacy, or adverse effects (AEs) of DMPA.

There have been concerns about decreased effectiveness of DMPA in obese women. No pregnancies were documented in two large phase 3 trials that included 193 women (of 1787 total) with a body mass index (BMI) of >30 [25]. A detailed study designed to assess the efficacy of DMPA in obese women revealed fluctuating estrogen levels consistent with follicular development, but no evidence of ovulation [26]. Patients being treated for both TB and HIV may experience even more variability in estrogen and DMPA levels. Patients treated for TB typically gain weight. The proportion of fat gain in that setting is variable and may affect DMPA metabolism. In the exploratory objective, BMI and body fat content will be estimated over time and compared to DMPA levels.

Safety Profile:

DMPA is safe in HIV infected women. There were few toxicities in the ACTG A5093 study related to DMPA with abnormal menstrual bleeding being the most frequent and similar to non-HIV-infected populations [16, 24]. Watts et al. demonstrated no significant changes in the levels of circulating HIV viral load in patients after administration of DMPA [24].

The most common side effects are menstrual irregularities (bleeding or spotting), amenorrhoea (2.1%) abdominal pain/discomfort 11%, weight gain (37.7%), dizziness 6%, headache 17%, nervousness 11%, and decreased libido 6%.

DMPA users were found to gain more weight than users of other forms of hormonal contraceptives with a >10% weight gain demonstrated in some populations [27]. A prospective cohort found that after 18 months of use women with a BMI \geq 30 had a significantly higher mean weight increase (9.45 kg) compared to women with a BMI <25 (4.04 kg). A baseline assessment of BMI may predict weight gain expected with DMPA use [28].

Other less common adverse reactions include loss of bone mineral density, thromboembolic disorders, insomnia, depression, acne, breast pain, and arthralgia.

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 [29]. Menzies et al. demonstrated that regimens that contained RIF for only 1-2 months of TB treatment instead of 6 months had high failure rates with an increased chance of relapse and resistance development [30].

An oral dose of RIF is absorbed completely when taken on an empty stomach, and after 1.5 to 2 hours, a 600 mg dose yields a peak blood level of 8 to 20 mcg/mL. The half-life of RIF varies from 2 to 5 hours, and it is shortened by approximately 20 to 40% after the first week of daily treatment because of RIF's auto-induction of hepatic microsomal enzymes. The half-life is unaffected by renal impairment but is increased by liver disease or biliary obstruction. RIF is deacetylated to an enterohepatically recirculated active metabolite, and 50% to 60% is excreted in the feces. Up to 30% of a dose is excreted in the urine. Approximately 85% of circulating RIF is bound to plasma proteins, and is widely distributed throughout the body. Certain genetic polymorphisms have been associated with reduced concentrations of rifamycin antibiotics, including RIF [31].

RIF is a potent inducer of multiple cytochrome P450 enzymes, such as CYP3A and CYP2B6, and drug transporters can accelerate clearance of drugs metabolized via the cytochrome p450 system, including cART [18, 19, 22] with potential loss of efficacy of these drugs.

RIF reduces the concentrations of many antiretroviral medications, especially PIs like atazanavir (ATV) and lopinavir/ritonavir (LPV/r) [32], and NNRTIs like NVP. The effect of RIF on EFV concentrations appears to depend on the CYP2B6 metabolizer genotype of the patient. CYP2B6 genotype not only determines the plasma EFV concentration at a given time point but also the long-term effects of EFV auto-induction on plasma exposure. Individuals with the extensive-metabolizer phenotype tend to have a pronounced EFV auto-induction effect, which has influence on the long-term therapeutic outcome [33]. In patients coinfecting with TB and HIV, EFV-metabolizing enzymes are induced maximally during the first 4 weeks of RIF's use and EFV therapy does not induce the enzymes to any greater extent. This suggests that EFV has no significant additive or synergistic enzyme induction effect with on-going RIF therapy in

HIV/TB co-treated patients. That is to say, the duration of therapy influences long-term EFV auto-induction in the absence of RIF; however, in the presence of RIF, maximal induction occurs during the early stages of therapy, and prolonged EFV dosing does not further reduce EFV concentrations in these auto-inducers [34]. A study done in South Africa found no evidence of a decrease in EFV mid-dosing interval plasma concentration in the presence of RIF, and a high proportion of South Africans were found to have the CYP2B6 polymorphism which impairs metabolism of EFV [35]. Similar results were demonstrated in a study in South India which concluded that RIF did not significantly alter the steady-state PK of EFV in HIV-infected patients [35, 36]. Globally, among HIV-infected patients who require RIF-containing TB therapy, EFV-based cART is the preferred HIV regimen.

Safety Profile:

In the usual daily dose of 10 mg/kg (maximum 600 mg), RIF is well tolerated. It often causes harmless red-orange discoloration of tears, sweat, saliva, feces, and urine. Less than 4% of TB patients experience significant adverse reactions to RIF. Gastrointestinal 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 or isoniazid. 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 or thrice-weekly. 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 like oligomenorrhoea and amenorrhoea [37].

2.1.3 Efavirenz (EFV):

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

The single dose of the 600 mg EFV tablet administered to patients after a high-fat/high-calorie meal and while fasting was generally well tolerated. Even though the US FDA approved a revised label for EFV stating that the dose should be increased to 800 mg daily in patients also taking rifampin who weigh over 50 kg, the CDC recommends use of the standard 600 mg dose of EFV in patients being cotreated for TB regardless of their weight. The evidence for use of a higher dose of EFV in this clinical scenario is inconclusive, and the higher EFV dose has been associated with an increased incidence of neurotoxic side effects. There is large inter-individual variability in EFV metabolism, such that universally increasing the EFV dose in participants weighing over 50 kg may increase the incidence of EFV-related AEs.

Steady-state plasma EFV clearance is known to be affected by relatively frequent genetic polymorphisms, primarily in CYP2B6 (esp. rs3745274 and rs28399499) [38, 39, 40, 41, 42], and perhaps also in CYP2A6 [43]. Genotyping of CYP2B6 can be used to characterize individuals as belonging to slow, intermediate, and extensive EFV metabolizer groups. Metabolites of EFV lack anti-HIV activity.

Safety Profile:

The most significant AEs observed in patients receiving EFV were central nervous system (CNS) symptoms, psychiatric symptoms, and rash [44]. Fifty-three percent of individuals noted CNS complaints, which may include dizziness, insomnia, impaired concentration, somnolence, abnormal dreaming, euphoria, depression, confusion, agitation, amnesia, hallucinations, stupor, abnormal thinking, and depersonalization. In addition, convulsions have been observed in the presence of known medical history of seizures. CNS symptoms usually begin during the first 1 or 2 days of therapy and generally resolve after the first 2 to 4 weeks. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in 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. EFV can be reinitiated in persons interrupting therapy because of rash.

There is concern for potential teratogenic effects with EFV exposure in the first trimester of pregnancy. An increased incidence of neural tube defects has been observed in fetuses from EFV-treated monkeys that received doses resulting in plasma drug concentrations similar to those in humans given 600mg/day. There are also case reports of neural tube defects linked to first trimester EFV exposure in humans. Therefore, pregnancy should be avoided in women receiving EFV, and barrier contraceptives should always be used in combination with hormonal contraceptives to maximize pregnancy prevention.

Most new-onset AEs were reported as mild and transient. A greater percentage of patients who received EFV under fed conditions (91.3%) reported AEs compared with patients who received EFV under fasted conditions (73.9%). Patients who received EFV after the meal also reported individual AEs more frequently. The AEs that were reported by >10% of patients under fed conditions included dizziness (16, 69.6%), headache (7, 30.4%), impaired concentration (6, 26.1%), and nausea (3, 13%). The AEs that were reported by >10% of participants under fasted conditions included dizziness (10, 43.5%, headache (4, 17.4%), and impaired concentration (4, 17.4%). Two (10%) patients each reported an AE of moderate intensity that was considered to be of possible (headache, fasted) or probable (abdominal pain, fed) relationship to study medication. There were no serious AEs or deaths reported. No clinical laboratory

results were reported as AEs by the investigator. No one discontinued the study because of an AE.

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

2.2 Rationale

The high burden of TB in HIV-infected women, the increased prevalence of HIV in women of reproductive age, and the limited data on use of DMPA in women being treated simultaneously for TB and HIV make it crucially important to understand the clinical significance of interactions among DMPA, EFV, and RIF given the significant number of women who could benefit from this combination of medications [45]. It is not known whether patients taking RIF and EFV together eliminate MPA faster than women taking DMPA alone. This needs to be evaluated to determine the optimal frequency of DMPA injections in HIV/TB co-infected patients.

Given that women of reproductive potential are overrepresented in the population of HIV/TB coinfecting individuals and given the risk to the mother and fetus if pregnancy occurs during co-treatment of these infections, reliable contraception for this population of women is especially important. While it has been shown that RIF reduces the levels of both oral estrogen and progesterone [46, 47], its effect on injectable progestin has not been clearly characterized. Because MPA is extensively metabolized in the liver, largely by CYP3A, it is likely that RIF will reduce MPA concentrations when DMPA and RIF are coadministered [15]. Some country guidelines, including the 2004 South African guidelines, have recommended shortening the dosing interval of DMPA from 12 weeks to 8 weeks in patients concurrently taking RIF [48]. Even though these guidelines were revised in December 2012 to recommend use of DMPA with the 12-week dosing interval in patients on rifampicin, there has been no new data on the effectiveness of DMPA in these patients. Australian Centre for Disease Control (CDC) guidelines for control of Tuberculosis in the Northern Territory recommend use of methods of contraception in patients on RIF other than DMPA and COC [49]. Some country guidelines, however, recommend use of DMPA keeping the 12-week dosing interval, even though the effects on pregnancy risk are unknown in patients coinfecting with TB. The WHO document, Medical Eligibility Criteria for Contraceptive Use, recommends use of DMPA but advises medical followup by the provider [50]. However, there are still limited data on whether RIF has a negative impact on the effectiveness of DMPA [51], even when DMPA is given more frequently, and the optimal dosing frequency for DMPA has not been established in this population. This study, therefore, will focus on the effects of combined RIF-containing TB treatment and EFV-based cART on DMPA.

DMPA suppresses the pituitary-ovarian-uterine axis and consequently may result in a hypoestrogen state which may lead to bone resorption exceeding bone formation resulting in reduced bone mineral density especially in adolescence and early adulthood before full bone maturity is attained. This loss in bone mineral density is unlikely to happen in the first 12 weeks and appears to be the greatest in the first 2 years of use and plateaus thereafter. [52, 53] In 2004, the FDA issued a black box warning that the

reduced mineral density may not be completely irreversible and its effect in increased risk of osteoporotic bone fractures later in life is unknown [54]. Currently, bone mass measurement heavily relies on x-ray like DEXA scan which are expensive and not easily accessible in resource limited settings. Development of future assays for biomarkers of bone metabolism for early detection of reduced bone mass will be very useful. The mechanism for the bone loss has not been extensively studied, with very little data in HIV-infected women. Because of this, blood for bone biomarkers will be collected before and 12 weeks after receiving DMPA and future funding for analyses of these specimens will be sought. Of particular interest is the potential additive toxicity of tenofovir disoproxil fumarate (TDF)-containing regimens and other agents that increase bone resorption. This study is not powered to assess this interaction, but evaluation of the cART regimens may lead to the detection of a signal warranting further study.

This study will enroll women with known TB infection during the continuation phase of RIF-containing TB treatment regimen who are on a stable cART regimen consisting of at least 2 NRTIs and EFV. Women will be given DMPA after being on EFV-based cART for at least 4 weeks and on RIF-containing TB treatment for at least 8 weeks. PK assessments for MPA will be assessed pre-dose then every 2 weeks after starting DMPA administration, through week 12. The rationale for giving DMPA at this time point is: (1) RIF and EFV concentrations are near steady state and maximal induction effect will be achieved; and (2) RIF dosing frequency does not change during the continuation phase of TB treatment (whereas frequency and concurrent TB drugs may change between the intensive and the continuation phases). Initiating the study treatment within the four weeks after completion of intensive phase TB treatment allows a 12-week period required for completion of the study.

The results of this study are likely to be applicable to patients receiving RIF-containing TB treatment that are not being treated concurrently with EFV as well, given that addition of EFV to RIF is unlikely to increase induction of metabolizing enzymes significantly beyond the induction achieved with RIF alone.

3.0 STUDY DESIGN

A5338 is an open-label, non-randomized 12-week, single-arm study to determine the PK of single-dose DMPA among women with TB and HIV co-infection who are receiving RIF-containing TB treatment plus EFV-based cART. Biomarkers of suppression of ovulation will also be evaluated. Participants will be HIV and TB co-infected women who have completed the intensive phase and are already in the continuation phase of RIF-containing TB treatment and who have been on EFV-based cART for at least 4 weeks.

Women diagnosed with TB and who are not already receiving HIV treatment at the time of screening for eligibility may start cART at any time between 2 and 8 weeks after TB treatment has been initiated, at the discretion of the treating physician and health care provider at the local clinic and in accordance with national and local treatment guidelines. Women who develop TB while on ART may also participate in the study. At study entry, all participants will receive a single IM injection of DMPA.

We will estimate individual MPA elimination rates, and then examine if any participant has a plasma progesterone level >5 ng/mL by the time that the estimated MPA level reaches 0.1 ng/mL. If data allows, a correlation between plasma progesterone levels and MPA concentrations observed at study weeks 10 and 12 will be investigated to better understand a minimum threshold of MPA concentration level to prevent ovulation using plasma progesterone level. If MPA clearance is induced by the co-administered drugs, the study week 10 and later are thought to be the times when ovulation would be most likely to occur, and increased plasma progesterone levels would be seen.

We will estimate MPA area under the concentration-time curve (AUC) by collecting PK samples from baseline (week 0) pre-DMPA dosing through week 12 after DMPA dosing from all participants. We will determine whether potential PK interactions between EFV-based cART with RIF and DMPA affect the suppression of ovulation as measured by the proportion of participants whose progesterone level is >5 ng/mL at weeks 2, 4, 6, 8, 10, and 12. We will also determine the proportion of women who have sub-therapeutic concentrations of MPA (levels <0.1 ng/mL) at different time points. Using a combination of both sub-therapeutic concentrations of MPA and progesterone >5 ng/mL, we will be able to determine whether contraception is thought to be maintained throughout the 12-week study. Mathematical modeling will be employed to determine the optimal frequency of DMPA dosing in the setting of TB and HIV cotreatment.

Information about demographic factors that can affect drug concentrations such as age, sex, ethnicity, disease state, and concomitant drug use will be collected on all participants. Whole blood will be collected and stored for potential pharmacogenomics analyses including CYP2B6 genotyping. All participants will be strongly encouraged to use condoms and non-hormonal contraceptives for prevention of pregnancy and sexually transmitted infections (STI) if engaging in behaviors that put them at risk. The participants will be informed that the contraceptive effect of DMPA may be attenuated and participants who engage in activities that could lead to pregnancy will be required to use another non-hormonal contraceptive. Other forms of hormonal contraceptives will be prohibited. Women who have had a tubal ligation or other sterilization procedure, are currently using a non-hormonal intrauterine device (IUD) or those whose partners have had a vasectomy will be eligible for the study.

All participants will complete self-reported questionnaires to assess adherence to both TB therapy and cART, and to collect AEs commonly reported with DMPA, ie, irregular bleeding patterns. Adherence will also be assessed by review of patients' TB treatment records and participant's self-report.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

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

4.1.2 Current tuberculosis infection, confirmed or probable diagnosis.

Confirmed TB is defined as:

- demonstration of acid fast bacilli using the Ziehl Nielson or Auramine stain
OR
- a positive culture of *M. tuberculosis* OR
- a positive GeneXpert test in sputum, pleural and pericardial fluid, lymph node aspirate, cerebrospinal fluid or blood.

Probable TB is based on the clinician’s judgment where acid-fast bacilli are not demonstrable but sufficient clinical suspicion exists to initiate empiric TB therapy. A probable diagnosis may be based on the presenting clinical symptoms of fever for more than 2 weeks, unintentional weight loss of more than 10% of body weight, night sweats, positive TB contacts, radiographic findings, and the absence of another possible diagnosis.

4.1.3 Currently stable on EFV-based cART for at least 28 days.

See section 5.1.1 for cART initiation if a woman is not on HIV treatment at the time of screening and acceptable NRTIs.

4.1.4 Currently receiving RIF and Isoniazid (INH)-based TB therapy on at least 5 days per week schedule after completion of the intensive phase of TB treatment (minimum of 8 weeks of TB treatment) and expected to be on TB treatment for a minimum of 12 weeks after enrollment.

4.1.5 Premenopausal female with presumed normal ovarian function based on normal menstrual history and absence of previous ovarian dysfunction diagnosis.

NOTE: Clinical assessment and clinician’s opinion are acceptable for determining previous ovarian dysfunction diagnosis.

4.1.6 Last menstrual period (LMP) ≤ 35 days prior to study entry.

4.1.6.1 If LMP is > 35 days prior to study entry, serum follicle-stimulating hormone (FSH) must be ≤ 40 MIU/mL.

NOTE: Enrollment after the start of the monthly menstrual flow is preferred.

4.1.7 Negative serum or urine-HCG pregnancy test within 30 days prior to study entry and negative pregnancy test at entry at any network-approved laboratory that operates in accordance with Good Clinical Practices and participates in appropriate external quality assurance programs.

4.1.8 All participants must agree not to participate in a conception process (eg, 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 an additional reliable method of contraception while in the study. Acceptable forms of contraceptives include:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Non-hormonal IUD
- Bilateral tubal ligation
- Male partner vasectomy

4.1.9 Laboratory values within 30 days prior to study entry:

- Absolute neutrophil count ≥ 500 cells/mm³
- Platelet count $\geq 50,000$ platelets/mm³
- Hemoglobin ≥ 8.0 g/dL
- Aspartate transaminase (AST) and alanine aminotransferase (ALT) < 5 x upper limit of normal (ULN)
- Creatinine ≤ 1.5 x ULN
- Total bilirubin ≤ 2.0 x ULN

4.1.10 Women between the ages of 18 to 46 years

4.1.11 Ability and willingness to provide written informed consent

4.2 Exclusion Criteria

4.2.1 Receipt of DMPA and any other injectable contraceptives within 180 days prior to study entry.

- 4.2.2 Receipt of other hormonal contraceptives within 30 days prior to study entry.
- 4.2.3 Use of any drugs other than RIF and EFV known to: 1) induce CYP3A4 system within 30 days and to 2) inhibit the CYP3A4 system with one week prior to study entry.
- 4.2.4 ≤ 40 kg in weight.
- 4.2.5 Bilateral oophorectomy.
- 4.2.6 Less than 30 days postpartum at study entry.
- 4.2.7 Hypersensitivity to DMPA, MPA, or any of the other ingredients in DMPA.
- 4.2.8 Breast cancer.
- 4.2.9 Serious illness requiring systemic treatment and/or hospitalization within 21 days prior to study entry.
- 4.2.10 Karnofsky performance score < 70 within 14 days prior to study entry.
- 4.2.11 Use of any immunosuppressant medication including systemic corticosteroids within 30 days prior to study entry.

NOTE: Use of systemic or inhaled corticosteroids, such as for acute therapy for *Pneumocystis jirovecii* pneumonia (previously called *Pneumocystis carinii* pneumonia; PCP) or asthma exacerbation or TB Immune Reconstitution Inflammatory Syndrome (IRIS), and prednisone ≤ 10 mg (or equivalent) is permitted as a stable or tapering dose.

- 4.2.12 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
 - 4.2.13 History of deep venous thrombosis or pulmonary emboli.
- 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(s) 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 (DAIDS 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.

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 approvals 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. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification 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 will be asked to read and sign the approved protocol consent form.

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 Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database. At entry, participants will be registered according to standard ACTG DMC procedures.

4.4 Coenrollment Guidelines

Sites are encouraged to coenroll participants in A5243, "Plan for Obtaining Human Biological Samples at Non-U.S. Clinical Research Sites for Currently Unspecified Genetic Analyses". Coenrollment in A5243 does not require permission from the A5338 protocol chairs.

For specific questions and approval for coenrollment 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 a single dose of depot medroxyprogesterone acetate (DMPA). ARV and TB therapy are required; however they will NOT be supplied through the study.

5.1 Regimen, Administration, and Duration

5.1.1 Regimen

At study entry/week 0, participants will receive:

Depot medroxyprogesterone acetate (DMPA) 150 mg administered intramuscularly (IM) as a single-dose.

NOTE: An optional additional dose of DMPA will be provided at no cost to all study participants who successfully complete all 12 weeks of the study, experience no AEs from the first injection, are interested in continuing with DMPA outside of the protocol, and after confirmation of a negative pregnancy test.

Required ARV therapy (not provided through study):

- Efavirenz (EFV) 600 mg orally once daily in combination with 2 or more NRTIs.
- Two or more NRTIs

NOTES:

- a. Acceptable NRTIs include the following:
 - zidovudine (ZDV)
 - lamivudine (3TC)
 - emtricitabine (FTC)
 - didanosine (ddI)
 - stavudine (d4T)
 - abacavir (ABC)
 - tenofovir disoproxil fumarate (TDF)
 - b. Refer to section 5.4.2 for the prohibited NRTI combinations.
- Women who are not already receiving HIV treatment at the time of screening may initiate cART at any time between 2 and 8 weeks after starting TB treatment, at the discretion of the treating physician and health care provider at the local clinic.
 - ARV therapy will not be provided through the study. For participants requiring changes in ARV therapy during the study, see sections 6.2.4 and 8.2 for follow-up and study discontinuation.

Required TB treatment (not provided through study):

- Rifampicin (RIF) 600 mg orally once daily.

- Isoniazid (INH) 300 mg orally once daily.

NOTE: Pyridoxine (vitamin B₆), if recommended by local standard of care with INH, will not be supplied through the study and must be obtained locally by the site.

- Participants must be on the continuation phase of TB treatment with a minimum of 12 weeks of TB treatment remaining.

5.1.2 Administration

The 1 mL vial or the 1 mL pre-filled syringe of DMPA should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension. A total of 1 mL (150 mg) of DMPA should be injected deeply into the gluteal or deltoid muscle.

5.2 Study Product Formulation and Preparation

Depot medroxyprogesterone acetate (DMPA) is supplied in vials and pre-filled syringes, each containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension at a concentration of 150 mg/mL. The product must be stored at 20°C to 25°C (68°F to 77°F).

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

Depot medroxyprogesterone acetate (DMPA) will be supplied by Greenstone LLC.

Study product will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities.

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 US in NIAID (DAIDS)-supported and/or -sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at: <http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/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 and subsequently dispensed. All unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the

sponsor) after the study is completed or terminated. The site pharmacist at non-US Clinical Research Sites (CRSs) must follow the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities.

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent'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 updated ACTG Drug Interactions Database located at: http://tdm.pharm.buffalo.edu/home/di_search/Search.

5.4.1 Required Medications

EFV-based cART, RIF, and INH (refer to section 5.1.1)

5.4.2 Prohibited Medications

- NRTIs are allowed, however, the following NRTI combinations are prohibited:
 - ZDV and d4T
 - 3TC and FTC
 - ABC and ddl
 - ABC and TDF
 - 3TC and d4T
 - ddl and d4T
- Other prohibited medications are listed on the A5338 PSWP.

5.4.3 Precautionary Medications

Precautionary medications are listed on the A5338 PSWP.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events

Evaluation	Screening	Entry	On-Study (Weeks) and Visit Windows						Premature Study Discontinuation
		Week 0	2	4	6	8	10	12	
			±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	
Documentation of HIV-1 and TB infection	X								
Medical History	X								
Menstrual Baseline and Interval History	X	X	X	X	X	X	X	X	
Medication History	X								
Clinical Assessments	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X
Adherence Assessments (cART and TB medications)	X	X	X	X	X	X	X	X	X
Hematology	X			X				X	X
Chemistry	X			X				X	X
Liver Function Tests	X			X				X	X
Pregnancy Test	X	X		X				X	X
Plasma Progesterone Levels			X	X	X	X	X	X	X
Serum FSH (see section 6.3.8)	X								
CD4+/CD8+		X							
HIV-1 RNA		X						X	
DMPA Injection		X						X	
DMPA PK		X	X	X	X	X	X	X	
Whole blood for Drug Metabolism Genotype		X							
Stored Serum for Bone Metabolism Biomarkers		X						X	

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant's starting any study medications, treatments, or interventions. At the time of screening, participants must have completed the intensive phase and be in the continuation phase of TB treatment. Participants must require at least 12 more weeks of TB treatment at the time they receive the DMPA injection at study entry.

Site staff are encouraged to contact/liaise with primary care physicians at TB clinics for identification of eligible participants prior to completion of the intensive phase of TB treatment. Information about the location of the ARV clinic and planned timing of cART initiation should be obtained. The identified participants will be given appointments for the research clinic as soon as they are initiated on cART. Site staff will obtain contact details of these potential participants to remind them about scheduled screening appointments. Eligible participants will be enrolled as soon as eligibility is determined.

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 in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Entry Evaluations

Entry evaluations must be completed on the day of registration after eligibility is determined from the screening evaluations. Participant must begin treatment the same day of registration. Entry evaluations must be completed prior to DMPA administration.

Enrollment and completion of entry evaluations after the start of the monthly menstrual flow is preferred.

6.2.3 Post-Entry Evaluations

Post-entry evaluations occur after study entry and injection of DMPA. Study visits are scheduled as indicated in the Schedule of Events (SOE) in section 6.1. The final visit is the week 12 visit.

The visit windows for post-entry evaluations are ± 3 days for weeks 2, 4, 6, and 8, and ± 7 days for weeks 10 and 12. The evaluations at weeks 10 and 12 should be performed as close as possible to the ideal visit date. If the week 10 or week 12 PK sampling is rescheduled, the reschedule date must be within the original visit window for the visit. There must be at least 3 days between the PK samples collected at each visit.

NOTE: All PK visits must be scheduled to occur following at least 2 consecutive doses of RIF and EFV in those participants who take TB medications <7 days a week.

Participants who elect to receive a second dose of DMPA at week 12 (see section 6.3.11) will have no further follow-up after the second dose of DMPA is administered.

Women who wish to continue receiving DMPA after completing the study will be referred to a family planning program or a program at their local clinic.

6.2.4 Discontinuation Evaluations

Evaluations for Registered Participants Who Do Not Start Study Treatment

All case report forms (CRFs) must be completed and keyed for the period up to and including week 0.

Premature Study Discontinuation

Participants who prematurely discontinue from the study will have the premature discontinuation evaluations performed as per section 6.1 and then be taken off study.

6.3 Instructions for Evaluations

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 Web site for information about what must be included in the source document: <http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/sourcedocappndx.pdf>

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International Conference on Harmonisation (ICH) definitions for a serious adverse event.

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other important medical event (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 events listed above.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), which can be found on the DAIDS RSC Web site: <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

6.3.1 Documentation of HIV-1 and TB Infection

HIV-1 Infection

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

TB Infection

Section 4.1.2 specifies the clinical and laboratory requirements for confirmed or probable TB diagnosis. The TB diagnosis (ie, date of diagnosis and confirmed or probable) will be recorded on the CRF; however TB documentation will not be recorded.

6.3.2 Medical History

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

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Tuberculosis
- Documentation of hepatitis B (surface antigen and core antibody) at any time prior to entry
- Documentation of hepatitis C (antibody) at any time prior to entry

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

6.3.3 Menstrual Baseline and Interval History

Baseline History

Age of menarche and cycle length and frequency will be obtained at the screening visit and reported in the CRF.

Interval History

The last menstrual period (date of first day of bleeding) will be collected at every visit and reported in the CRF.

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 and reported in the CRF.

Medication History Table

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	Complete
Hormonal contraceptive therapies including barrier methods	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
Complementary and Alternative therapies	30 days prior to study entry
Dietary supplements	30 days prior to study entry
Other – In Vitro Fertilization (IVF)	30 days prior to study entry

6.3.5 Clinical Assessments

In addition to the visits specified in section 6.1, the clinical assessments (except height) should be performed when clinically indicated.

Complete Physical Exam

A complete physical examination will be conducted at screening and as part of clinical assessments performed when clinically indicated. The complete physical exam will include, at a minimum, an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema; and Karnofsky performance test. It will also include signs and symptoms, diagnoses, and vital signs (weight, height, temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Exam

A targeted physical examination is required at all study visits after screening. The targeted physical exam must include vital signs (temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant experienced.

Height

Height required to be reported on the CRF at study entry only.

Weight

Weight required at study entry and at all visits.

Waist Circumference

Waist circumference required at study entry and all on-study visits.

Signs and Symptoms

At entry, all grades that occurred 30 days before entry must be recorded in the source document and CRFs.

After entry:

- Grades 1 and 2 toxicities must be recorded in the source document.
- Grades 3 and 4 toxicities must be recorded in both the source document and CRF.
- Record all signs and symptoms that led to a change in treatment regardless of grade on both source document and CRF. Further evaluation will be required for those events that meet Expedited Adverse Event (EAE) or ICH reporting requirements.

Diagnoses

At the entry and post-entry visits, record all diagnoses identified by the ACTG criteria for clinical events and other diseases in the source document and CRFs.

HIV and TB Treatment Modifications

After entry, all modifications to antiretroviral medications and TB drugs including initial doses, subject-initiated, physician modifications and/or protocol-mandated interruptions, modifications, and permanent discontinuation will be recorded on the CRFs.

6.3.6 Concomitant Medications

At the entry and post-entry visits, record the new and discontinued medications in the source document and CRFs.

6.3.7 Adherence Assessments for cART and TB Medications

Adherence will be carefully assessed at screening, entry/day 0 and post entry visits using the ACTG self-report questionnaires completed by the participant or completed with the help of site staff (counselor- or nurse-driven). All participants will also have their TB treatment record reviewed to monitor adherence to treatment. Participants will be encouraged to maintain perfect adherence. Participants will be encouraged to bring documentation of TB treatment history, if available, TB medication, and cART at all study visits. 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 scheduling of participants, provision of medication, and monitoring of adherence to medication.

6.3.8 Laboratory Evaluations

At screening and entry all laboratory values must be recorded. For post-entry assessments, record all \geq Grade 3 laboratory values. All laboratory toxicities that led to a change in treatment, regardless of grade, must be recorded. Further evaluation will be required for those events that meet EAE or ICH reporting requirements. All protocol required labs will be done at the DAIDS-approved local lab unless otherwise specified.

Hematology

Perform hemoglobin, hematocrit, white blood cell count (WBC), absolute neutrophil count (ANC), and platelets as clinically indicated in addition to the visits specified in section 6.1.

Blood Chemistries

Perform electrolytes (sodium, potassium, chloride, and bicarbonate), creatinine, and blood urea nitrogen as clinically indicated in addition to the visits specified in section 6.1.

Liver Function Tests (LFTs)

Perform total bilirubin, AST (SGOT), and ALT (SGPT), albumin as clinically indicated in addition to the visits specified in section 6.1.

Pregnancy Test

At screening, serum or urine β -HCG (urine test must have a sensitivity of ≤ 25 mIU/mL) may be used.

Urine β -HCG may be used at the entry, post-entry, and premature study discontinuation visits and when clinically indicated.

There must be a negative pregnancy test within 30 days prior to study entry as well as at the time of study entry.

Perform as clinically indicated in addition to the visits specified in section 6.1.

Plasma Progesterone Levels

This will be done at a central lab. For details, please see the LPC found on the A5338 PSWP.

Serum FSH

At screening must be performed on women with LMP >35 days. For details, please see the current laboratory processing chart (LPC) found on the A5338 PSWP.

6.3.9 Immunologic Studies

CD4+/CD8+

Obtain CD4+ and CD8+ cell counts and percentages at study entry from a laboratory that possesses a CLIA certification or equivalent.

6.3.10 Virologic Studies

Plasma HIV-1 RNA

HIV-1 RNA must be performed by a laboratory certified by the DAIDS Virology Quality Assurance (VQA) Program at study entry and at week 12.

6.3.11 DMPA Injection

DMPA 150 mg will be administered intramuscularly (IM) as a single-dose at entry/week 0 after all blood samples for week 0 have been drawn.

Participants who successfully completed all their study requirements will be offered an extra dose of DMPA at no cost after all evaluations for the week 12 visit are completed, if in the opinion of the investigator the second DMPA dose does not present unnecessary risk to the participant. DMPA dose should be given after DMPA level and other blood work have been drawn.

6.3.12 Pharmacokinetic Assays

MPA Levels

Plasma will be obtained for MPA levels. For details, please see section 10.2 and the LPC found on the A5338 PSWP.

6.3.13 Whole Blood for Drug Metabolism Genotype

A single whole blood sample will be obtained at entry from all study participants for human genotyping of polymorphisms that have been associated with metabolism and/or transport of the study drugs, including EFV (eg, CYP2B6), RIF (eg, SLCO1B1), and DMPA. The samples will be processed at the Vanderbilt DNA Resources Core Laboratory. See the LPC on the A5338 PSWP for details regarding processing and shipping.

If at Entry/week 0 the whole blood for drug metabolism genotype it is not obtained, this sample may be obtained at any later visit week.

6.3.14 Metabolic Studies

Biomarkers of Bone Metabolism

Serum will be collected and stored for future studies of biomarkers of bone metabolism. For details, please see the LPC found on the A5338 PSWP.

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Toxicity

Toxicities will be evaluated and managed by the study team in close consultation with the participants' primary care clinicians. Ongoing communication between the ACTG study staff and the participants' clinicians will be encouraged. If either the study team or primary care clinician becomes aware of an adverse event, he/she will contact the other within 24 hours of awareness.

For participants who experience toxicities that require treatment interruption or changes, a detailed letter with the results will be sent to primary care physicians by the study staff informing them about the toxicities and planned management from the study perspective.

If TB medication or cART is held for toxicity by the primary care physician, participants must inform the study team. Information about these treatment modification/interruptions must be recorded on the source document and CRF.

Grades 1 and 2: can be managed as per standard of care by the study doctor.

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

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

7.2 Pregnancy

If a participant becomes pregnant on study, she will continue to be followed on study and on cART and TB treatment, and have the study evaluations performed following the visit schedule in section 6.1, except the PK evaluation, until she completes the study. After she completes the study, she will be followed for safety until the outcome of her pregnancy is known.

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 a CRF at the end of the pregnancy.

Pregnancy Outcomes and Reporting

A Pregnancy Outcomes CRF should be completed for all participants who become pregnant. The intrapartum complications and/or pregnancy outcome should be recorded on the CRFs.

Sites are encouraged to report prospectively any pregnancy to The Antiretroviral Pregnancy Registry if such occurs during this study. More information is available at www.apregistry.com; Fax: 44-1628-789-666 or 910-256-0637; Phone: 910-679-1598.

7.3 Breastfeeding

Sites should follow local guidelines to prevent Mother-to-Child Transmission (MTCT) during breastfeeding.

8.0 CRITERIA FOR PREMATURE STUDY DISCONTINUATION

8.1 Participant meets one or more of the criteria for noncompliance.

8.1.1 Failure by the participant to attend 2 consecutive visits at week 2, 4, 6, or 8.

8.1.2 Failure by the participant to attend any of the week 10 or week 12 visit.

8.1.3 Missed 2 or more of the RIF and EFV doses within one week prior to PK sampling at week 2, 4, 6, or 8 and did not return with acceptable adherence (ie, missed 2 or more of the RIF and EFV doses) for the rescheduled PK sampling for 2 consecutive study weeks.

8.1.4 Missed 2 or more of the RIF and EFV doses within one week prior to PK sampling at week 10 or 12 and did not return with acceptable adherence (ie, missed 2 or more of the RIF and EFV doses) for the rescheduled PK sampling.

NOTE: A participant who prematurely discontinues from the study due to noncompliance will be replaced.

8.2 Participant requires a change in the cART or TB regimen during the 12 weeks on study.

8.2.1 For the purposes of this study, a cART change that will warrant replacement of the participant includes:

- Addition of another NNRTI or a PI resulting in a NNRTI/PI or any PI combination therapy.
- Any substitution within the NNRTI class.
- Addition of an integrase inhibitor or entry inhibitor to the regimen.

NOTE: Participants may stay on study if they change or discontinue one or more of their NRTIs since this class of medications is not thought to affect the metabolism of DMPA or EFV. See section 5.4.2 for the NRTI combinations that are not allowed in this study.

8.2.2 For the purposes of this study, a TB regimen change that will warrant replacement of the participant includes:

- Stopping RIF secondary to toxicity or resistance.
- Addition of other TB medications to the study TB regimen of RIF and INH.

8.3 Request by the participant to withdraw.

- 8.4 Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- 8.5 Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- 8.6 At the discretion of the IRB/Ethics Committee, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, or investigator.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a phase II, open-label, single arm, PK study to investigate effects of coadministered EFV and RIF on PK of DMPA in HIV- and TB-coinfected women and to evaluate whether the current dosing frequency of DMPA is adequate to suppress ovulation in women when taken together with an EFV- and RIF-containing regimen.

A woman is eligible for this study if she is premenopausal between the ages of 18 and 46 and co-infected with HIV and TB. Women must be on both RIF (600 mg once daily)-containing TB treatment and EFV (600 mg once daily)-based cART at least 4 weeks before study entry.

After HIV- and TB-coinfected women undergo screening evaluations for study eligibility, PK samples for MPA concentrations from eligible women will be taken at study entry. After entry, PK samples for MPA concentrations will be taken every 2 weeks during the 12-week study period. Blood samples for plasma progesterone levels will be collected from all the eligible women for investigating evidence of ovulation during the 12 weeks of DMPA administration.

Eligible women will also undergo study visits for safety labs at weeks 4 and 12. Signs and symptoms will be assessed at bi-weekly study visits.

9.2 Outcome Measures

9.2.1 Primary Outcome Measures

MPA concentration levels obtained at 2, 4, 6, 8, 10, and 12 weeks after DMPA is administered. The 12 week measurement will be the measurement obtained closest to 84 days after DMPA is administered. The allowable window for the measurement is ± 7 days, as stated in section 6.2.3.

Plasma progesterone levels obtained at 2, 4, 6, 8, 10, and 12 weeks after DMPA is administered.

9.2.2 Secondary Outcome Measures

9.2.2.1 Estimation of MPA PK parameters in HIV and TB co-infected women taking EFV and RIF:

MPA PK parameters AUC over the 12 weeks (AUC_{0-12wk}), C_{min} , C_{max} , apparent clearance (CL/F), and half-life ($t_{1/2}$) calculated using standard non-compartmental method: These PK parameters will be calculated based on the MPA concentrations obtained every 2 weeks over the 12 weeks. MPA concentration obtained at entry (prior to DMPA administration) will be evaluated as confirmation that no DMPA was taken prior to study entry.

9.2.2.2 Estimation of time and variability in time to reach MPA 0.1 ng/mL:

Times (weeks) where elimination slopes estimated fitting \log_e -linear regression models to the individual MPA concentrations obtained in the elimination phase reach MPA level of 0.1 ng/mL: The exact sampling time (weeks) will be used.

9.2.2.3 Estimation of the proportion of participants reaching MPA level <0.1 ng/mL at specified time points:

MPA concentration levels obtained at study weeks 6, 8, and 10. Since the week 12 measurements will be evaluated as the primary outcomes (section 9.2.1), the MPA measurements at study weeks 6, 8, and 10 after DMPA administration will be studied for any earlier sign of MPA levels <0.1 ng/mL.

9.2.2.4 Evaluation of toxicity and safety:

All adverse events with toxicity Grade ≥ 3 from signs/symptoms and chemistry and hematology laboratory analyses.

9.2.3 Exploratory Outcome Measures

9.2.3.1 Human genetic variants/polymorphisms that are known to affect PK of EFV (eg, CYP2B6) and RIF (eg, SLCO1B1).

9.2.3.2 Participants' BMIs and body fat percentages collected over the study period of 12 weeks. Body fat percentages will be estimated using age, body weight, height, and waist circumference.

9.3 Randomization and Stratification

Since this study has a single study arm, no randomization will be employed. There will be no stratification for participants.

9.4 Sample Size and Accrual

It is known that DMPA, EFV, and RIF drugs share some common metabolic pathways via the CYP3A4 enzyme system: MPA is metabolized by and induces CYP3A4 activity; RIF is primarily metabolized by CYP2B6 system but also by CYP3A4 and induces CYP3A4 and CYP2B6 enzyme activities; EFV is primarily metabolized by CYP2B6 and both induces and inhibits CYP3A4 enzyme activity (mixed and unpredictable activity). Therefore, it is anticipated that co-administration with EFV and RIF will induce clearance of MPA concentration, resulting in lower MPA concentrations during the elimination phase, compared to those seen when DMPA is administered alone. Thus, DMPA may need to be administered more frequently when used together with EFV and RIF.

The study hypothesis is that concurrent use of EFV and RIF increases the clearance of MPA, resulting in reduced MPA concentrations. The study will evaluate whether more frequent DMPA dosing is needed when DMPA is administered in combination with EFV and RIF in HIV- and TB-infected women. The evaluation of dosing frequency will be conducted by estimating the proportion of women with MPA levels <0.1 ng/mL 12 weeks post-dose (at the end of the dosing cycle). The critical value 0.1 ng/mL for MPA levels was chosen based on published papers including studies by Mishell [17] and Smit et al. [55]. These studies indicate that when MPA level falls below 0.1 ng/mL, serum progesterone level rises and the probability of ovulation increases.

In ACTG DMPA studies A5093 and A5283 in HIV-infected women, of the 79 PK evaluable participants, 5 women had MPA levels <0.1 ng/mL at 12 weeks after a single dose of DMPA was administered. None of these 5 women, however, had any evidence of ovulation (serum progesterone levels remained below 5 ng/mL). In a study by Smit et al. [56] in 94 women, all but one woman had MPA levels above 0.1 ng/mL at 12 weeks after DMPA administration. These 94 women had received either a single dose or multiple doses of DMPA. Therefore, based on the single dose studies, the proportion of women with MPA levels <0.1 ng/mL (sub-therapeutic MPA levels) 12 weeks post-dose is thought to be about 6% in normal DMPA use, although a study conducted by Trussell [57] showed that there is a contraceptive failure rate of about 0.3% when DMPA is used correctly.

The primary analysis outcome will be the proportion of women with sub-therapeutic MPA levels (<0.1 ng/mL) at 12 weeks. A one-sided binomial test with significance level 0.05 will be used to test the null hypothesis that the proportion of women with sub-therapeutic MPA level is 6% or less. A sample size of 42 women provides 90% power to reject the null hypothesis if the proportion of women with sub-therapeutic MPA levels in this study is at least 21% (this is 15% or higher increase from the 6% threshold). With a sample size of 42 women, the underlying true proportion will be declared as statistically significant increase if 6 or more women have sub-therapeutic MPA levels at 12 weeks (this is equivalent to saying that 90% CI for the underlying proportion is entirely above the 6% threshold). Based on the results from a PK study of oral contraceptives containing ethinyl estradiol (estrogen) and norethindrone (progestin) which are metabolized by CYP3A4 enzyme [58], the study team considers that the underlying proportion of women with sub-therapeutic MPA levels of 21% or higher (15% or higher

increase from the 6% threshold) is plausible in the setting of coadministration with EFV and RIF.

The statistical power was also examined to see if the sample size will achieve a plausible power to detect a clinically meaningful decrease (30%) in MPA concentration at 12 weeks (MPA C_{min}) as one of the secondary objectives. With a significance level of 0.05, a one-sided t-test showed about 91% and 84% power to detect a 30% decline when the coefficient of variation (CV) is 60% and 70%, respectively (in the ACTG study A5093, CV of MPA C_{min} was approximately 57% when coadministered with EFV). We note that this power was examined in \log_e -scale since it is known that PK parameter C_{min} has a \log -normal distribution.

To protect against 10% loss of the primary outcomes after study accrual is closed, the study will enroll a total of 46 women. (In the ACTG DMPA 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.)

A participant is considered to be evaluable for the primary objective if the participant completes the MPA PK sampling during the study period of 12 weeks after DMPA administration. The participant replacement criteria are described in sections 8.1 and 8.2.

The study team anticipates that the study will enroll approximately 4 participants per month and it will take approximately 12 months to meet the target enrollment for the study.

9.5 Monitoring

The study team will monitor participant accrual to ensure the target number of evaluable participants is enrolled. Study sites will be required to report all participant dropouts and noncompliance, including missing PK sample times/visits to the study team as soon as they occur. The study team will make decisions on participant's replacement on conference calls or by emails.

During the study, the safety and tolerability of the study medications will be monitored by means of adverse events reports representing laboratory and clinical data, such as Toxicity Summary reports or Phase I/II reports provided by ACTG DMC. It is required for study sites to enter these data into the DMC database within a specified time period for data entry. The study team will discuss these reports on regularly scheduled conference calls or by email. It is the responsibility of the study team to interpret the adverse event data and make any decisions needed to protect study participants from undue risk. Any concerns will be presented to the DAIDS Clinical Representative.

9.6 Analyses

A detailed statistical analysis plan will be developed after protocol Version 1.0 is finalized and before the study is open to accrual. The following will provide a summary of analyses that will state key analysis approaches.

9.6.1 Analyses of Primary Outcome Measurements

The proportion of participants with sub-therapeutic MPA levels (<0.1 ng/mL) will be estimated based on the participants who complete the PK sampling at 12 weeks after DMPA administration. A 90% confidence interval (CI) will be provided for proportion using Clopper-Pearson exact method for binomial measurements. This CI will provide us reasonable evidence that the true proportion is greater than the threshold (6%), by determining whether the 90% CI is entirely above the threshold.

Individual-specific MPA concentration-time curves in the elimination phase will be estimated by fitting \log_e -linear regression models to the data of MPA concentrations obtained at time of maximum MPA concentration and later. These estimated individual elimination curves will then be used to estimate the times (weeks) where MPA concentration levels reach at 0.1 ng/mL. We will present descriptive statistics of these estimated weeks including mean, SD, median, interquartile range, minimum and maximum. Mixed-effects model analysis (allowing individual elimination slope to be both fixed and random variable) with repeated measurements within individual participants will also be performed to estimate the times for comparison purposes with the results obtained using the \log -linear regression models fitted for individual participants. These modeling approaches will provide the population mean estimate of the time where MPA concentration level reaches at 0.1 ng/mL with 90% CI, which will guide us to determine optimal dosing frequency of DMPA in the study population. Details of these modeling approaches will be described in the statistical analysis plan that will be generated separately and approved by study team.

Descriptive statistics of plasma progesterone levels will be tabulated by study week. If there are participants with progesterone levels >5 ng/mL, the proportion and percentage of participants with progesterone levels >5 ng/mL will be tabulated by study week.

Relationships of plasma progesterone levels with MPA concentration levels will be investigated by exploratory plots and using nonlinear regression models to better understand a lower limit of therapeutic MPA level that could prevent ovulation. This analysis will be based on MPA and plasma progesterone levels observed at week 10 and 12. If MPA clearance is truly induced by the coadministered drugs, MPA levels at these times may be low enough that plasma progesterone may have risen. We note that if plasma progesterone levels have not begun to rise by week 10/12, this analysis may have a poor statistical power.

9.6.2 Analyses of Secondary Outcome Measurements

9.6.2.1 Estimation of MPA PKs in presence of EFV and RIF:

MPA PK parameters AUC_{0-12wk} , concentration at week 12 (trough concentration, C_{min}), C_{max} , CL/F , and $T_{1/2}$ will be estimated using non-

compartmental approach and descriptive statistics of these PK parameters will be presented. For the purpose of evaluating whether these PK parameters are significantly different from those in women not on the companion drugs, those PK parameters will be compared to those from the historic controls (A5093 Control Arm) using nonparametric two-sample Wilcoxon test. GMRs in MPA PK parameters of co-administration over administration-alone and associated 90% CIs will also be presented to provide magnitude of the differences as a supplementary analysis.

9.6.2.2 Estimation of time and variability in time to reach a MPA 0.1 ng/mL:

Times (weeks) and variability in times to reach MPA 0.1 ng/mL will be estimated using the analysis methods described in section 9.6.1.

9.6.2.3 Estimation of the proportion of participants reaching MPA level <0.1 ng/mL:

The proportion and percentage of participants with MPA concentration levels <0.1 ng/mL will be summarized by each of the study weeks 8 and 10. 90% CI for proportion at each week will be presented using Clopper-Pearson exact method.

9.6.2.4 Evaluation of toxicity and safety:

Signs and symptoms, chemistry and hematology with toxicity Grade ≥ 3 will be tabulated by study week.

9.6.3 Analyses of Exploratory Outcome Measurements

9.6.3.1 Inter-individual differences in PK parameters between EFV, DMPA, and/or RIF when stratified by human genetic variants that are known to predict altered pharmacokinetics of EFV (eg, CYP2B6) and RIF (eg, SLCO1B1) will be investigated using descriptive statistics of PK parameters categorized by metabolizer status (based on the human genetic variants) and performing a nonparametric ordered test (eg, Jonckheere-Terpstra trend test) in PK parameters for the priori ordering of metabolizer groups in the co-administration if data allows.

9.6.3.2 Associations of MPA PK parameters with baseline BMI and/or body fat percentage will be examined using visual plots (eg, scatter plots) and investigated using linear or nonlinear regression models. Changes of BMIs and body fat percentages at study week 12 from baseline will be descriptively summarized.

10.0 PHARMACOLOGY PLAN

Women stable on an EFV and 2 NRTIs-based regimens, who are on RIF and INH, and who have not received DMPA within the last 180 days, will receive one dose of DMPA at

study entry. An optional dose of DMPA will be available at no cost to all study participants, after all week 12 study evaluations are completed. Refer to section 5.1.1 for the allowed NRTIs and section 5.4.2 for the prohibited NRTI combinations.

The primary PK analysis is described in section 9.6. The secondary PK analysis employing a population approach and nonlinear mixed effects modelling is described in this section.

10.1 Pharmacology Objectives

Using nonlinear mixed-effects (NLME) modeling, the population PK of MPA will be described in the population in order:

10.1.1 To describe the structural PK model for MPA given in the DMPA formulation.

10.1.2 To identify and quantify the effects of covariates influences on PK (eg, weight [including total, fat and lean components], age, time on TB treatment, time on ART, adherence to ART and TB treatments, CYP2B6 genotype, etc.).

10.1.3 To characterize between subject and random unexplained components of the PK variability.

10.1.4 To predict the time at which the proportion of women with MPA <0.1 ng/L matches that at 12 weeks from historical data.

10.2 Pharmacology Study Design

Doses of all ARV and TB medications taken for 48 hours prior to PK will be collected on the CRF at weeks 2, 4, 6, 8, 10, and 12. The participant should be contacted one week prior to the scheduled visit to reinforce the importance of 100% adherence to RIF and EFV and of her upcoming appointment. A participant who misses 2 or more doses of RIF and EFV within one week prior to the scheduled PK sampling at weeks 2, 4, 6, 8, 10, and 12 will have the visit rescheduled to one week later. For the week 10 and week 12 visits, the rescheduled PK sampling should be strictly within the original visit window for that visit. The schedule for the remaining visit weeks should not be changed. The rules for replacing participants who do not complete the PK are described in sections 8.1 and 9.5.

A single 4 mL blood sample for PK will be collected just prior to DMPA injection at week 0 and at the scheduled visits at weeks 2, 4, 6, 8, 10, and 12. The blood sample will be centrifuged within 1 hour of collection to separate the plasma which will be stored at -70°C or colder until assay for MPA and progesterone.

The ACTG Pharmacology Specialty Laboratory at the University of Cape Town will use liquid chromatography-tandem mass spectrometry (LC MS/MS) to measure MPA and progesterone in the plasma. The assay methods will be validated and submitted to Clinical Pharmacology Quality Assurance (CPQA) for review.

10.3 Primary and Secondary Data, Modeling, and Data Analysis

The concentration vs. time data for DMPA will be analyzed using NLME modelling using the software NONMEM (Version 7.2) [57].

The modelling approach will follow a stepwise procedure to first identify the structural model best describing the data, and then incorporate the effect of the study covariates such as weight, age, and effect of concomitant anti-retroviral and anti-tuberculosis treatment.

Various structural pharmacokinetic models will be evaluated, focusing on correctly characterizing the absorption after intra-muscular injection. The tested models will include one, two, and three compartments disposition with first-order elimination and zero-, first-order, or saturable absorption.

Statistically significant variability and correlation estimates for the PK parameters will be included and the covariates of interest will be evaluated with respect to their impact on the PK parameters and their variability.

Allometric scaling [59] will be used to account for the effect of body size on the PK parameters, using total body weight or fat-free mass. Other covariate effects will be evaluated and included if they significantly improve the ability of the model to describe the data. The effect of adherence to and time on ART and TB regimens, and CYP2B6 genotype (if available), will be investigated on clearance.

Concentrations below the limit of quantification will be included in the analysis and handled with established methods [60].

The tools used for model development and graphical and statistical diagnostics will include Xpose, and Perl Speaks NONMEM, and Pirana [61].

The PK profiles will be analyzed using post-hoc Bayesian methods to extract information such as peak concentration, overall exposure (AUC), and time above target concentration. Simulations will be employed to explore the pharmacokinetic profiles, their variability in a population, and how they are affected by weight, concomitant anti-retroviral or anti-tuberculosis treatment, other covariates found significant, and possibly under different dosing scenarios, and to predict the time at which the proportion of women with MPA <0.1 ng/L matches that at 12 weeks from historical data.

10.4 Anticipated Outcomes

The anticipated outcomes are described in the section above. They are the model outputs: firstly the population PK of MPA will be described using the primary model parameters and secondary measure estimates. Covariate effects on the model parameters will be identified and quantified. The model will ascribe variability (due to fixed effects, inter individual and random unexplained variability) with accuracy. Secondly, simulations will predict the optimal dosing frequency to achieve a target trough concentration of >0.1 ng/mL in the target proportion of women.

10.5 Pharmacogenomics – Host Genetic Analysis

Inter-individual differences in host genes (eg, those that encode drug-metabolizing and transporter proteins) have been associated with inter-individual differences in plasma PK of EFV [38, 39, 40, 41, 42, 43] and RIF [62]. The study will therefore evaluate human genetic polymorphisms that are known to affect steady-state plasma PK of EFV and RIF. Among study participants that receive EFV and RIF, analyses of PK data will take into consideration such polymorphisms. If additional polymorphisms are reported to affect sex hormones, these may also be studied.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

Case report forms (CRF) will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon registration.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 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.

11.3 Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study 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.

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

11.4 Expedited Adverse Event Reporting to DAIDS

11.4.1 Adverse Event Reporting 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 <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Events Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2 Reporting Requirements for this Study

- The 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 depot medroxyprogesterone acetate (DMPA).
- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are: Injection related AEs.

11.4.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification, August 2009), must be used and is available on the DAIDS RSC Web site at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. This table will be used for all genital and menstrual symptoms.

11.4.4 Expedited AE Reporting Period

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

12.0 HUMAN PARTICIPANTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix I) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, and this fact will be documented in the participant's record.

12.2 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, NIAID, and OHRP, or other government agencies as part of their duties.

12.3 Study Discontinuation

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

13.0 PUBLICATION OF RESEARCH FINDINGS

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

14.0 BIOHAZARD CONTAINMENT

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

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APPENDIX I

DIVISION OF AIDS AIDS CLINICAL TRIALS GROUP (ACTG)

SAMPLE INFORMED CONSENT

For protocol:

An Open-Label, Non-Randomized Study of Pharmacokinetic Interactions Among Depot Medroxyprogesterone Acetate (DMPA), Rifampicin (RIF), and Efavirenz (EFV) in Women Co-Infected with Human Immunodeficiency Virus (HIV) and Tuberculosis (TB)
Final Version 1.0, 12/12/14

SHORT TITLE FOR THE STUDY: DMPA in HIV/TB (PRIDE-HT), Final Version 1.0, 12/12/14

INTRODUCTION

You are being asked to take part in this research study because you are a woman infected with the human immunodeficiency virus (HIV), the virus that causes AIDS; have tuberculosis (TB); are taking particular anti-HIV and anti-TB medications; will continue to take TB treatment for at least 3 months; and are able to get pregnant. This study is sponsored by the United States (US) 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?

This study is being done to evaluate the effect of HIV and TB treatment on a commonly used birth control method. This study is being done on women who are infected with HIV and TB and are taking efavirenz (EFV; Sustiva®; an anti-HIV medication), rifampicin (RIF; an anti-TB medication) and isoniazid (INH; an anti-TB medication). The purpose of this study is to find out the best schedule to give depot medroxyprogesterone acetate (DMPA; a hormonal birth control method that is given as a shot every 3 months) in women with HIV and TB who are also taking EFV and RIF. This study will also try to find out if a 150 mg injection of DMPA is effective in preventing ovulation, the process by which the ovaries (the ovaries are part of the female reproductive system) release an egg for fertilization, for 12 weeks in women who are taking EFV and RIF. Another purpose of this study is to find out if it is safe to take RIF, EFV and DMPA at the same time.

For this study, DMPA will be provided in the form of an injection. DMPA is approved by the United States Food and Drug Administration (US FDA) for prevention of pregnancy. The list of risks of DMPA is included in this document; the risks are the same that would be encountered when DMPA is used outside of the study.

This study will not provide any anti-HIV or anti-TB medications. The anti-HIV and anti-TB medications that participants have to take to be in this study have been approved by the US FDA and are not being tested in this study.

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

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 1-2 hours. 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.
- Your TB infection status will be confirmed.
- You will be asked about your age at the time of your first menstrual period, the first day of your last menstrual period, and how often and usual number of days of your menstrual periods.
- You will be asked questions about your medical history and any medications you are taking. You will also be asked about any anti-TB medications you have ever taken; anti-HIV and hormonal birth control medications you have taken within the last year and other medications you have taken within the last 30 days.
NOTE: You must be taking EFV, RIF and INH to be eligible for the study.
- You will have a complete physical exam, including obtaining your height and weight.
- You will be asked about adherence to your anti-HIV and anti-TB medications (how correctly you are taking your medications).
- You will have about 1 tablespoon (15 mL) of blood drawn for routine lab tests for safety. You will be told the results of these tests when they become available.
- You will be asked to give a urine sample or have 1 teaspoon (5 mL) of 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.
- If it has been more than 35 days since your last menstrual period, you will have an additional 2 teaspoons (10 mL) of blood drawn to measure the amount of follicle-stimulating hormone (FSH) in your blood. In women, FSH is the hormone that helps control the menstrual cycle and the production of eggs in the ovaries. You will be told the result of the test when it becomes available.

If you do not enroll into the study

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), clinical (for example, disease condition, diagnosis), and laboratory (for example, pregnancy test, FSH) 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.

Entry

If you are eligible for the study, you will be contacted to come in for an entry visit, ideally right after the start of your menses. This visit will last about 1-2 hours. At this visit:

- You will be asked about your menstrual period and if there has been a change in your menstrual period since the screening visit.
- You will have a brief physical exam, which will include obtaining your weight and waist measurement, and you will be asked about your health and any changes in your medicines since your last visit.
- You will be asked about adherence to your anti-HIV and anti-TB medications.
- You will have about 1 tablespoon (15 mL) of blood drawn to measure your viral load (the amount of HIV in your blood) and your CD4+/CD8+ cell count (cells that help fight infection). You will be told the results of these tests when they become available.
- You will be asked to give a urine sample or have 1 teaspoon (5 mL) of 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.
- You will have about 1 teaspoon (4 mL) of blood drawn to measure the level of DMPA in your blood. You will not receive the result of this test.
- You will have 2 tablespoons (30 mL) of blood drawn and stored for future study-related bone test (to check signs of bone health) and 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.

After all of these evaluations are completed, you will receive your DMPA injection.

Study Visits

After your entry visit, you will come to the clinic again 2, 4, 6, 8, 10, and 12 weeks after the visit at which you received DMPA. These study visits will last about 30 minutes to 1 hour.

During most on-study visits:

- You will be asked when you had your last menstrual period.
- You will have a brief physical exam, which will include obtaining your weight and waist measurement, and you will be asked about your health and any changes in your medicines since your last visit.
- You will be asked about adherence to your anti-HIV and anti-TB medications.
- You will have 2 teaspoons (10 mL) of blood drawn to measure the amount of progesterone in your blood. Progesterone is a female hormone produced by the ovaries when a mature egg is released (from the ovary) and is ready to be fertilized (ovulation). You will not receive the result of this test.

- You will have about 1 teaspoon (4 mL) of blood drawn to measure the level of DMPA in your blood.

In addition, during the week 4 and week 12 on-study visits:

- You will have about 1 tablespoon (15 mL) of blood drawn for routine lab tests for safety. You will be told the results of these tests when they become available.
- You will be asked to give a urine sample or have 1 teaspoon (5 mL) of blood drawn to see if you are pregnant. You will be told the result of the test when it becomes available.
- At the week 12 visit only, you will have an additional 2 tablespoons (30 mL) of blood drawn to measure your viral load and stored for future study-related bone tests.

You must inform the study doctor if your primary care physician temporarily stops any of your anti-HIV and anti-TB medications because of a harmful side effect while you are in the study.

If You Have to Stop the Study Early

If you leave the study early, you will be asked to come to the clinic for an additional study visit. This visit will last about 1 hour. At this visit:

- You will have a brief physical exam, which will include obtaining your weight, and you will be asked about your health and any changes in your medicines since your last visit.
- You will be asked about adherence to your anti-HIV and anti-TB medications.
- You will have about 1 tablespoon (15 mL) of blood drawn for routine lab tests for safety. You will be told the results of these tests when they become available.
- You will be asked to give a urine sample or have 1 teaspoon (5 mL) of blood drawn to see if you are pregnant. You will be told the result of the test when it becomes available.
- You will have 2 teaspoons (10 mL) of blood drawn to measure the amount of progesterone in your blood.

Other

The blood samples collected for the test to measure the level of DMPA in your blood may be shipped for storage and testing in South Africa.

The blood samples collected for future study-related bone test and genetic test may be shipped for storage in the United States until the tests are performed.

Some of your blood that is left over after all required study testing is done may be stored (with usual protectors of identity) and used for ACTG-approved HIV-related research. These leftover blood samples may be shipped for storage in the United States for an indefinite period of time. Results of testing performed on these blood samples may not be given to you.

Please indicate now if you agree to have your left-over blood samples stored for future ACTG-approved HIV-related research. You may change your mind at any time and your samples will be destroyed.

_____ YES

_____ NO

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 46 women will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 12 weeks (about 3 months).

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:

- You miss two study visits in a row.
- You do not take the RIF and EFV medications as you are supposed to and you then do not take the RIF and EFV prior to your rescheduled visit to collect the blood sample to measure the level of DMPA in your blood.
- The blood sample to measure the level of DMPA in your blood could not be collected for two study visits in a row or at the week 10 or week 12 study visit (for example, because you missed the visit).
- You do not take your anti-HIV and anti-TB medications as you are supposed to.
- You have a severe adverse reaction to your anti-TB and anti-HIV medications and your primary care physician has taken you off these drugs.
- You need a treatment that you may not take while on the study.
- Your primary care physician no longer thinks that participating in the study is in your best interest or continuing in the study may cause you harm.
- The doctor in charge of the study believes that you may not be able to comply with the study, and that this may cause you harm or injury, or may affect the results of the study.
- You are not able to complete the study visits as required by the study.
- The study is stopped or cancelled.

If I have to permanently leave the study, how would DMPA be provided?

If you complete all 12 weeks of the study, you may be able to receive an additional one dose of DMPA at no cost to you after all the evaluations at week 12 are completed. After you have completed your study participation, the study will not be able to continue to provide you with DMPA that you received on the study. If continuing to take these or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

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

Risks of DMPA

- Changes in menstrual periods
- Conditions that may lead to the development of blood clots (thromboembolic disorders) involving deep veins of the legs, lung, and brain (stroke)
- Headache
- Nervousness
- Dizziness
- Difficulty falling and/or staying asleep
- Depression (a mood disorder that causes a persistent feeling of sadness and loss of interest that interferes with your everyday life)
- Swelling/water retention
- Changes in vaginal secretions
- Pain in the stomach area or belly
- Jaundice (a yellowing of the skin) and abnormal liver function tests
- Breast tenderness
- Sensitive skin, hives, and rash
- Acne
- Loss of scalp hair
- Delayed return to fertility
- Weight gain
- Thinning of the bones (Loss in bone density)
- Joint pain
- Pregnancy
- Low sex drive

Studies of women who have used different forms of contraception found that women who used DMPA over long periods of time had no increased risk of developing cancer of the breast, ovary, uterus, cervix or liver. However, women under 35 years of age whose first exposure to DMPA was within the previous 4 to 5 years may have a slightly increased risk of developing breast cancer similar to that seen with oral contraceptives.

At least one research study in humans has suggested an increased rate of HIV infection to the uninfected partners of DMPA users, while other studies have found no such relationship. A large clinical trial addressing the issue of DMPA and the risk of transmitting HIV is currently ongoing, and the WHO has issued guidelines saying that women with HIV can use DMPA without restrictions.

If you experience any of the side effects of DMPA, you must contact the study staff who will advise you to come to the clinic for assessment. Depending on the severity of your symptoms, the study doctor will either manage your symptoms or refer you to the hospital for care. If symptoms are mild, the study doctor will give you treatment but for severe symptoms, you will be referred to the hospital immediately.

Risks of Drawing Blood

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

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 secret from people close to you. 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 in this regard.

Other Information

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.

ARE THERE RISKS RELATED TO PREGNANCY?

Women who become pregnant while receiving DMPA may have an increased risk of delivering a baby that has birth defects. For this reason, we do not recommend that you allow yourself to become pregnant while using this medication. It is not known if taking DMPA together with anti-HIV and anti-TB drugs affects the levels of DMPA in your blood.

DMPA injections should not be taken during pregnancy. Pregnant women may not join the study. If you are having sex that could lead to pregnancy, you must agree not to become pregnant.

If you decide to participate in this study, you must use at least one barrier method of birth control during this study because it is unknown if various combinations of anti-HIV and anti-TB medications make DMPA less effective. You should NOT use DMPA as your ONLY method of birth control.

You may choose one or more of the birth control methods listed below:

- Male condom with or without spermicide (a cream or gel that kills sperm)
- Female condom with or without spermicide
- Diaphragm or cervical cap with spermicide
- Non-hormonal intrauterine device (IUD)
- Bilateral tubal ligation (surgery that involves blocking the fallopian tubes [the part of the female reproductive system that carries the eggs from the ovary to the uterus or womb] to prevent the egg from being fertilized)
- Male partner vasectomy (surgery that prevents the release of sperm from the male partner)

You must NOT use birth control pills during this study.

If you can become pregnant, you must have a pregnancy test before you enter this study. The test must be negative. 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. Your choice will not affect your usual medical care provided by your doctor. You may be allowed to join future research studies, if you qualify.

If you become pregnant while on study, you will continue taking your anti-HIV and anti-TB medications and continue to be seen at the scheduled study visits until you complete the study. You will have the study evaluations performed at each visit except the test to measure the level of DMPA in your blood.

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.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, it is unlikely that there will be any direct benefit to you. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and TB, and improve our understanding of the use of DMPA in HIV-infected women.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- treatment with prescription drugs available to you or at your local clinic
- treatment with experimental drugs, if you qualify
- no treatment

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

WHAT ABOUT CONFIDENTIALITY?

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, Office for Human Research Protections, (insert name of site) institutional review board (IRB)/ethics committee (EC), National Institutes of Health (NIH), local National Health Organization, other government agencies, study staff, and study monitors.

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

WHAT ARE THE COSTS TO ME?

Study drugs, exams, and lab tests will be provided without charge. 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.

WILL I RECEIVE ANY PAYMENT?

[Insert site-specific information on compensation to study participants]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. 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 National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

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 subject, contact:

- name or title of person on the IRB/EC (a local board or committee that reviews, approves and monitors research studies involving humans) 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