

IMPAACT P1026s
(DAIDS Document ID 10040)
**Pharmacokinetic Properties of Antiretroviral Therapy During
Pregnancy**

A Multicenter International Trial of the
International Maternal Pediatric Adolescent AIDS
Clinical Trials Group (IMPAACT)

**This file contains the current IMPAACT P1026s protocol,
which is comprised of the following documents,
presented in reverse chronological order:**

- **Clarification Memorandum #1, dated 1 June 2018**
- **Letter of Amendment #2, dated 13 April 2018**
- **Letter of Amendment #1, dated 14 December 2016**
- **Protocol Version 10.0, dated 2 February 2016**

Clarification Memorandum #1 for:

IMPAACT P1026s Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum, Version 10.0, dated 2 February 2016

IND # 64,535
DAIDS ES # 10040

Clarification Memorandum Date: 1 June 2018

Information/Instructions to Study Sites

This Clarification Memorandum (CM) has been approved by the NIAID and NICHD Medical Officers. Institutional Review Board/Ethics Committee (IRB/EC) approval of this CM is not required by the sponsor prior to implementation; however, sites may submit it to the responsible IRBs/ECs for their information or, if required by the IRBs/ECs, for their approval prior to implementation.

None of the clarifications being made impact the sample informed consent forms and the benefit-to-risk ratio for participants is not affected in any way.

This CM should be maintained in each site's essential documents file for IMPAACT P1026s. It is the responsibility of the Investigator of Record to ensure that all study staff are made aware of and follow this CM. The content of this CM will be incorporated into any future amendment of the IMPAACT P1026s protocol.

Summary of Clarification, Rationale and Implementation

The purpose of this CM is to specify use of Version 2.1 of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events for grading severity of adverse events in IMPAACT P1026s.

In protocol Section 6.3, Grading Severity of Events, the following modifications are made, with deletions indicated in strikethrough and additions shown in bold text:

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, ~~Version 2.0, dated November 2014~~, **Corrected Version 2.1, dated July 2017** (which can be at the following website: **<http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>**) ~~<http://rsc.tech-res.com/safetyandpharmacovigilance/>~~ must be followed.

Letter of Amendment #2 for:

**IMPAACT P1026s
Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and
Postpartum**

Version 10.0, dated 2 February 2016

**IND # 64,535
DAIDS ES # 10040**

Letter of Amendment Date: 13 April 2018

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT P1026s study and must be submitted to site Institutional Review Boards (IRBs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB and regulatory entity requirements must be followed.

Upon obtaining IRB approval and any other applicable regulatory entity approvals, each site should immediately begin implementing this LoA. After the IRB-approved updated site-specific informed consent form (ICF) is made available, all study participants still in follow-up must be re-consented at their next scheduled study visit, and all new participants must be consented using the updated site-specific ICF.

Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this LoA.

Please file this LoA, all associated IRB and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1026s. If the IMPAACT P1026s protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

IMPAACT P1026s
Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum

Version 10.0, dated 2 February 2016

IND # 64,535
DAIDS ES # 10040

Version 10.0, Letter of Amendment #2
Dated 13 April 2018

Letter of Amendment Signature Page

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

Signature of Investigator of Record

Date

Name of Investigator of Record
(printed)

Summary of Modifications and Rationale

The following modifications are included in this LoA:

1. Updates language regarding regulatory entities and drug companies supporting the study that may review study records: Per ICH GCP E6 4.8.10(n) and DAIDS requirements, it is mandatory that all DAIDS-sponsored and/or supported trials include language that informs participants that other US, local, and international regulatory entities may also review study records. Protocol Section 11.2 and the sample ICF have been updated accordingly. As noted in the instructions above, current study participants must be re-consented using the updated site-specific ICF.
2. Other minor updates, clarifications, and corrections have been incorporated.

Implementation

Detailed modifications of the protocol text are shown below in general order of appearance in the protocol. Deletions in the protocol text are indicated by strikethrough, and additions are indicated in bold.

- Protocol Team Roster:

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- Section 11.2, Subject Confidentiality:

[...] Clinical information will not be released without written permission of the subject, except as necessary, for **inspection, monitoring, and/or auditing during or after the conduct of the study by authorized representatives of the study sponsors and their contractual monitors, IMPAACT, by the U.S. FDA, site drug regulatory authorities, the site IRBs/ECs, OHRP and other applicable U.S., local, and international regulatory entities.** ~~the NIAID, or the local or national IRB or Ethics Committee.~~ **Data or information from the study may be shared with drug companies, who have agreements with the protocol team and or U.S. NIH, or regulatory entities, but individual participants will not be identified.**

- The changes noted below apply to Sample Consent Forms - Appendices VI-A, VI-B, VI-C and VI-D:

WHAT ABOUT CONFIDENTIALITY?

For U.S. Sites, 2nd paragraph:

People who may review your/your baby's records include: the U.S. Food and Drug Administration (FDA) **and other U.S., local and international regulatory entities;** (insert Name of Site) IRB, National Institutes of Health (NIH), **drug companies supporting the study**, the Office for Human Research Protections (**OHRP**), study staff, and study monitors. Any publication of this study will not use your/your baby's name or identify you/your baby personally.

For sites outside the U.S., 2nd paragraph:

Your/your baby's records may be reviewed by the Ministry of Public Health in your country, the FDA **and other U.S., local and international regulatory entities;** the Office of Human Research Protections (OHRP), the NIH, (*insert name of site*) IRB, Ethics Committee (EC), **drug companies supporting the study**, study staff, and study monitors.

Letter of Amendment #1 for:

**IMPAACT P1026s
Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and
Postpartum**

**IND # 64,535
DAIDS ES # 10040**

Letter of Amendment Date: 14 December 2016

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) affects the IMPAACT P1026s study and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from other site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, this LoA is to be implemented immediately. Study sites must submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for IMPAACT P1026s.

If the IMPAACT P1026s protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.

Summary of Modifications and Rationale

The following modifications are included in this LoA:

- One of the three tenofovir alafenamide fumarate (TAF) antepartum arms for HIV-infected pregnant women not on tuberculosis treatment has been corrected for consistency with the formulations of this drug that are currently approved by the United States Food and Drug Administration (FDA). These formulations are as follows:
 - Genvoya® – TAF 10 mg co-formulated with elvitegravir and emtricitabine
 - Odefsy – TAF 25 mg co-formulated with rilpivirine and emtricitabine
 - Descovy® – TAF 25 mg co-formulated with emtricitabine (may be taken with or without cobicistat or ritonavir boosting)
- Instructions for collection of vaginal secretions have been updated.
- Disallowed medicines for the newly added TAF arms have been updated.
- Other minor updates, clarifications, and corrections have been incorporated.

Implementation

Detailed modifications of the protocol text are shown below in general order of appearance in the protocol. Deletions in the protocol text are indicated by strikethrough, and additions are indicated in bold.

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2. Schema:

Study Arms, Antiretrovirals (ARVs) without tuberculosis (TB) Treatment (10 Arms): HIV-infected pregnant women ≥ 20 weeks gestation NOT on tuberculosis treatment receiving one or more of the following ARV drugs/drug combinations (sixth bullet point):

- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 800/100 mg b.i.d. until 30 weeks gestation; then 800/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 900/100 mg b.i.d. until 30 weeks gestation; then 900/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- dolutegravir 50 mg q.d.
- tenofovir alafenamide fumarate (TAF) 25 mg q.d. without cobicistat or ritonavir boosting
- tenofovir alafenamide fumarate (TAF) 10 mg q.d. with cobicistat
- tenofovir alafenamide fumarate (TAF) ~~40~~ **25** mg q.d. with **cobicistat or** ritonavir **boosting**
- elvitegravir/cobicistat 150/150 mg q.d.
- darunavir/cobicistat 800/150 mg q.d.
- atazanavir/cobicistat 300/150 mg q.d.
- Participants outside of Thailand only: efavirenz 600 mg q.d.

3. Section 3.11, Enrollment Procedures, Maternal Antepartum Enrollment (during pregnancy):

Pregnant women who meet the eligibility criteria, as specified, in Section 4.1 will enroll in P1026s prior to or at the time of pharmacokinetic sampling. The initial PK sampling visit ~~must~~ **should** occur within 5 days of participant enrollment. **If the PK visit cannot be done within 5 days contact the protocol team for permission to perform the sampling visit after 5 days.** See Appendix I-A through I-C for a complete description of the procedures to be performed for each study arm, and Section 10 Data Collection Requirements, for a description of data to be collected.

4. Section 3.21, Genital Tract Viral Load and Drug Concentrations, last sentence (added):

HIV-infected pregnant women not on TB drugs will have vaginal samples for ARV concentrations obtained at the second and third trimester and the 6-12 postpartum PK sampling visits. Samples will be obtained pre-dose and at 1, 2, and 4 hours after dosing. Samples for drug concentrations will be obtained with the soft plastic aspirator without speculum placement or by another appropriate technique and can be collected by the participant or by a clinician. Samples will be stored and batch shipped for testing. Since target drug concentrations for vaginal samples have not been determined, real time testing and reporting of vaginal specimen results to the sites will not be done. A single vaginal swab will also be obtained without speculum placement for viral load testing once during each PK visit. No vaginal specimens will be collected if contraindicated by a pregnancy complication such as placenta previa or premature rupture of membranes. **Also, no specimens should be collected from women who are menstruating or have vaginal bleeding.**

5. Section 3.4, Intrapartum Pharmacokinetic Sampling, 2nd sentence:

A single maternal specimen will be drawn at the time the cord is clamped, **unless it is medically contraindicated, in which case it can be obtained as soon as possible.**

6. Section 4.1, Maternal Inclusion Criteria:

4.111 HIV-infected pregnant women $\geq$ 20 weeks gestation NOT on tuberculosis treatment receiving one or more of the following ARV drugs/drug combinations (sixth bullet point):

- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 800/100 mg b.i.d. until 30 weeks gestation; then 800/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 900/100 mg b.i.d. until 30 weeks gestation; then 900/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- dolutegravir 50 mg q.d.
- tenofovir alafenamide fumarate (TAF) 25 mg q.d. without cobicistat or ritonavir boosting
- tenofovir alafenamide fumarate (TAF) 10 mg q.d. with cobicistat
- tenofovir alafenamide fumarate (TAF) ~~10~~ 25 mg q.d. with **cobicistat or ritonavir boosting**
- elvitegravir/cobicistat 150/150 mg q.d.
- darunavir/cobicistat 800/150 mg q.d.
- atazanavir/cobicistat 300/150 mg q.d.
- Participants outside of Thailand only: efavirenz 600 mg q.d.

5. Section 7.0, Disallowed Medicines:

7.1 NRTIs

For tenofovir alafenamide fumarate, **the following medicines are disallowed:** ~~no medicines are disallowed.~~

- **Anticonvulsants:** carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- **Antimycobacterials:** rifabutin, rifampin, rifapentine
- **Herbal products:** St. John's wort (*Hypericum perforatum*)
- **Protease inhibitors:** tipranavir/ritonavir

7.3 PIs, 10th Bullet:

- Neurleptic: **lurasidone**, pimozide

7.33 Ritonavir, 2nd Bullet:

- **Antifungal: voriconazole**

7.4 Integrase Inhibitors, 15th Bullet:

- Neuroleptic: **lurasidone**, pimozide

7.6 Combined Oral Contraceptives (COCs) and Etonogestrel Implant, 1st and 6th Bullets:

- Anticonvulsants: barbiturates, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate
- Psychostimulants; modafinil

6. Appendices IA, IB, I-AMR, IC, ID, II and III, Schedules of Evaluations:

— Appendix IA, footnotes 9 and 13

9. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System. **The PK sampling visit can be performed more than 5 days after enrollment with permission from the protocol team.**

13. Draw at the time the cord is clamped, **unless it is medically contraindicated, in which case draw can be obtained as soon as possible.**

— Appendix IB, Schedule of Evaluations for Women on ARV Medicines with Tuberculosis Treatment, footnotes 8, 12 and 14:

8. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System. **The PK sampling visit can be performed more than 5 days after enrollment with permission from the protocol team.**

12. Draw at time the cord is clamped, **unless it is medically contraindicated, in which case, the draw can be obtained as soon as possible.** For this arm, collection of maternal delivery sample can be omitted if there are circumstances that prohibit collection (i.e. delivery at non-study facility, delivery during non-business hours).

14. For participants treated with any injectable TB medication the audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the **P1026s Protocol Specific Web Page at <http://impaactnetwork.org/studies/P1026s.asp>** ~~LPG~~ for additional information.

— Appendix IC, Schedule of Evaluations for HIV-Uninfected Women with Tuberculosis Treatment, footnotes 6 and 10:

6. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5

days after enrollment using the Subject Enrollment System. **The PK sampling visit can be performed more than 5 days after enrollment with permission from the protocol team.**

10. For participants treated with any injectable TB medication the audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the **P1026s Protocol Specific Web Page at <http://impaactnetwork.org/studies/P1026s.asp>** ~~LPG~~ for additional information.

— Appendix I-D, footnote 12:

12. The participant must be on the ARV of interest for at least 2 weeks prior to the initial PK sampling and not using any hormonal contraceptive method during that time. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System. **The PK sampling visit can be performed more than 5 days after enrollment with permission from the protocol team.**

— Appendix I-AMR, Title:

ADDITIONAL MONITORING REQUIREMENTS FOR WOMEN ON DRV/r AND LPV

— Appendix II, Schedule of Evaluations for Infants, footnote 9:

9. Only for infants of mothers treated with any injectable TB medication. The audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the **P1026s Protocol Specific Web Page at <http://impaactnetwork.org/studies/P1026s.asp>** ~~LPG~~ for additional information.

— Appendix III, Maternal Intensive PK Sampling Schedule for ARV Medicines, Tuberculosis Treatment and Hormonal Contraceptives, row 8:

tenofovir alafenamide fumarate 40- 25 mg q.d. with cobicistat or ritonavir boosting	24 hour sampling during optional 2nd trimester, during 3rd trimester and 6-12 weeks postpartum
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IMPAACT P1026s

**PHARMACOKINETIC PROPERTIES OF ANTIRETROVIRAL AND RELATED
DRUGS DURING PREGNANCY AND POSTPARTUM**

(DAIDS Document ID 10040)

A Multi-center Trial of the
International Maternal Pediatric Adolescent AIDS
Clinical Trials (IMPAACT) Network

Sponsored By:

The National Institute of Allergy and Infectious Diseases
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
The National Institute of Mental Health (NIMH)

IND # 64,535 held by NIAID

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**Version 10.0
2 February 2016**

IMPAACT P1026s PROTOCOL TEAM ROSTER

All questions concerning this protocol should be sent via e-mail to impaact.teamp1026s@fstrf.org. Remember to include the participant's PID when applicable. A response should generally be received within 24 hours (Monday - Friday). For protocol registration questions, e-mail protocol@tech-res.com or call 301-897-1707. Protocol registration material can be sent electronically to epr@tech-res.com or via fax at 1-800-418-3544 or 301-897-1701. For EAE questions, e-mail DAIDSRSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709, or fax 1-800-275-7619 or 301-897-1710. For enrollment questions, contact the Data Management Center at (716) 834-0900 or by e-mail sdac.random.desk@fstrf.org.

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IMPAACT P1026s PROTOCOL TEAM ROSTER

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IMPAACT P1026s PROTOCOL TEAM ROSTER

TABLE OF CONTENTS

GLOSSARY	8
SCHEMA	10
1.0 INTRODUCTION	13
1.1 Background and Rationale.....	13
1.2 Clinical Pharmacology in Pregnancy.....	13
1.3 Pharmacokinetics of Approved Antiretroviral Drugs in Pregnancy.....	14
1.4 Use of Tuberculosis (TB) and Antiretroviral (ARV) Medicines during Pregnancy ..	16
1.5 Contraceptives and Antiretrovirals.....	18
1.6 Genital Tract HIV and Antiretroviral Concentrations	19
1.7 Pharmacogenetics	20
1.8 History of Versions 1.0 - 9.0	21
2.0 OBJECTIVES	22
2.1 Primary Objectives	22
2.2 Secondary Objectives	22
3.0 STUDY DESIGN.....	22
3.1 Enrollment Procedures.....	23
3.2 Maternal Antepartum and Postpartum Pharmacokinetic Sampling.....	24
3.3 Reporting of Pharmacokinetic Results	25
3.4 Intrapartum Pharmacokinetic Sampling	25
3.5 Infant Pharmacokinetic Sampling.....	26
4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS.....	26
4.1 Maternal Inclusion Criteria.....	26
4.2 Maternal Exclusion Criteria.....	29
4.3 Infant Enrollment Criteria.....	29
4.4 Infant Requirements for Washout Pharmacokinetic Sampling	29
4.5 Enrollment Procedures.....	29
4.6 Co-Enrollment Procedures.....	30
4.7 Study Drug Formulations	30
5.0 TOXICITY MANAGEMENT.....	31
5.1 Toxicity Monitoring.....	31
5.2 Bilirubin Toxicity Monitoring for Postpartum Women Receiving Atazanavir.....	33
5.3 Criteria for Discontinuation.....	33
6.0 EXPEDITED ADVERSE EVENT REPORTING.....	33
6.1 Adverse Event Reporting to DAIDS	33
6.2 Reporting Requirements for this Study	33
6.3 Grading Severity of Events.....	34
6.4 Expedited AE Reporting Period	34
7.0 DISALLOWED MEDICINES.....	34
7.1 NRTIs	34
7.2 NNRTIs.....	34
7.3 PIs	35
7.4 Integrase Inhibitors	36
7.5 Tuberculosis (TB) drugs	36

7.6	Combined Oral Contraceptives (COCs) and Etonogestrel Implant.....	37
8.0	STATISTICAL CONSIDERATIONS.....	38
8.1	General Design Issues.....	38
8.2	Outcome Measures	38
8.3	Randomization and Stratification	39
8.4	Sample Size and Accrual	39
8.5	Monitoring	43
8.6	Analysis	44
9.0	CLINICAL PHARMACOLOGY PLAN.....	46
9.1	Objectives	46
9.2	Primary and Secondary Data to be Accessioned	47
9.3	Study Design, Modeling and Data Analysis.....	48
10.0	DATA COLLECTION REQUIREMENTS	51
11.0	HUMAN SUBJECTS	53
11.1	Institutional Review Board (IRB) Review and Informed Consent.....	53
11.2	Subject Confidentiality	54
11.3	Study Discontinuation	54
12.0	PUBLICATION OF RESEARCH FINDINGS	54
13.0	BIOHAZARD CONTAINMENT.....	54
14.0	REFERENCES	55
	TABLE A: Guidelines for Using Schedule of Evaluations and Sample Informed Consents	60
	APPENDIX I-A: Schedule of Evaluations for Women on ARV Medicines without Tuberculosis Treatment	61
	APPENDIX I-B: Schedule of Evaluations for Women on ARV Medicines with Tuberculosis Treatment	63
	APPENDIX I-AMR: Additional Monitoring Requirements for Women on DRV and LPV	65
	APPENDIX I-C: Schedule of Evaluations for HIV-Uninfected Women with Tuberculosis Treatment	66
	APPENDIX I-D: Schedule of Evaluations for Postpartum Women on ARV Medicines and Hormonal Contraceptives	68
	APPENDIX II: Schedule of Evaluations for Infants	70
	APPENDIX III: Maternal Intensive Pk Sampling Schedule for ARV Medicines, Tuberculosis Treatment and Hormonal Contraceptives	72
	APPENDIX IV: Dietary Recommendations for Antiretroviral Medicines, Tuberculosis Medicines and Hormonal Contraceptives.....	74
	APPENDIX V: Maternal Pharmacokinetic Parameter Targets	75
	APPENDIX VI-A: Sample Consent Form for Women on ARV Medicines without Tuberculosis Treatment	81

APPENDIX VI-B: Sample Consent Form for Women on ARV Medicines with Tuberculosis Treatment (First Line and Second Line).....	86
APPENDIX VI-C: Sample Consent Form for HIV-Uninfected Pregnant Women on No ARV Medicines with Tuberculosis Treatment.....	93
APPENDIX VI-D: Sample Consent Form for Postpartum Women on Antiretroviral Medicines and Hormonal Contraceptives.....	99
APPENDIX VII: History of Version 1.0 to Version 9.0	104

GLOSSARY

3TC	Lamivudine
AAG	Alpha-1 Acid Glycoprotein
ABC	Abacavir
AE	Adverse Event
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV	Atazanavir
ATV/Cobi	Atazanavir/ cobicistat
ATV/r	Atazanavir/ritonavir
AUC	Area Under the Curve
b.i.d	Twice A Day
CBC	Complete Blood Count
CID	Case Identification Number
CVL	Cervical-vaginal Lavage
COCs	Combined Oral Contraceptives
CRF	Case Report Form
C _{min}	Plasma Concentration at the End of the 24 Hour Dosing Interval
CYP	Cytochrome
d4T	Stavudine
DAIDS	(United States) Division of AIDS
ddI	Didanosine delayed release (Videx [®] EC)
DMC	Data Management Center
DTG	Dolutegravir
DRV	Darunavir
DRV/Cobi	Darunavir/cobicistat
DRV/r	Darunavir/ritonavir
EAE	Expedited Adverse Event
EC	Ethics Committee, Enteric Coated
EFV	Efavirenz
ELV/Cobi	Elvitegravir/cobicistat
EMB	Ethambutol
ENG	Etonogestrel
EVA	Ethylene vinylacetate
FDA	(United States) Food and Drug Administration
FTC	Emtricitabine
HIV	Human Immunodeficiency Virus
IMPAACT	International Maternal, Pediatric, Adolescent AIDS Clinical Trials Network
IND	Investigational New Drug
INH	Isoniazid
IRB	Institutional Review Board
LDMS	Laboratory Data Management System
LPC	Laboratory Processing Chart
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir (Kaletra [®] or Alluvia [®])
NFV	Nelfinavir
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NICHD	(United States) National Institute of Child Health and Human Development
NIH	(United States) National Institutes of Health

NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OHRP	(United States) Office for Human Research Protections
P1022	Randomized Trial of Protease Inhibitor Including Vs. Protease Inhibitor Sparing Regimens for Women who Initiate Therapy for HIV Infection During Pregnancy
P1070	Dose-Finding and Pharmacogenetic Study of Efavirenz in HIV-Infected and HIV/TB Co-Infected Infants and Children ≥ 3 Months to < 36 Months of Age
P1078	A Phase IV Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety of Immediate (Antepartum-initiated) Versus Deferred (Postpartum-initiated) Isoniazid Preventive Therapy among HIV-Infected Women in High TB Incidence Settings
PI	Protease Inhibitor
PID	Patient Identification Number
PK	Pharmacokinetic
PZA	Pyrazinamide
q.d.	Every day
RIF	Rifampicin
RSC	(United States) Regulatory Support Center
RTV	Ritonavir
SAE	Serious Adverse Event
SIP	Site Implementation Plan
TAF	Tenofovir Alafenamide Fumarate
TB	Tuberculosis
TDF	Tenofovir
t.i.w.	Three Times a Week
ULN	Upper Limit of Normal
U.S.	United States of America
VQA	Virology Quality Assurance
WHO	World Health Organization
WITS	Women and Infants Transmission Study
ZDV	Zidovudine

SCHEMA

IMPAACT P1026s PHARMACOKINETIC PROPERTIES OF ANTIRETROVIRAL AND RELATED DRUGS DURING PREGNANCY AND POSTPARTUM

DESIGN: Phase IV, prospective pharmacokinetic (PK) study

SAMPLE SIZE: Each study arm will enroll a minimum of 12 women and have a target enrollment of 25 women with evaluable 3rd trimester PK data for antiretroviral (ARV) and tuberculosis (TB) arms, or evaluable postpartum PK data for hormonal contraceptive arms. Women who do not have evaluable PK data will be replaced. Enrollment may be restricted to the second trimester and/or increased above 25 so that evaluable 2nd trimester PK data are obtained from at least 12 women. Enrollment may also be increased above 25 to obtain additional second line TB drug data or infant washout PK data.

POPULATIONS: Pregnant and postpartum women receiving the following medicines as part of clinical care and infants born to those women enrolled during pregnancy.

STUDY ARMS:

Antiretrovirals (ARVs) without tuberculosis (TB) Treatment (10 Arms): HIV-infected pregnant women ≥ 20 weeks gestation NOT on tuberculosis treatment receiving one or more of the following ARV drugs/drug combinations:

- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 800/100 mg b.i.d. until 30 weeks gestation; then 800/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 900/100 mg b.i.d. until 30 weeks gestation; then 900/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn
- dolutegravir 50 mg q.d.
- tenofovir alafenamide fumarate (TAF) 25 mg q.d. without cobicistat or ritonavir boosting
- tenofovir alafenamide fumarate (TAF) 10 mg q.d. with cobicistat
- tenofovir alafenamide fumarate (TAF) 10 mg q.d. with ritonavir
- elvitegravir/cobicistat 150/150 mg q.d.
- darunavir/cobicistat 800/150 mg q.d.
- atazanavir/cobicistat 300/150 mg q.d.
- Participants outside of Thailand only: efavirenz 600 mg q.d.

Antiretrovirals with First Line Tuberculosis Treatment (2 Arms - one for each ARV drug): HIV-infected pregnant women ≥ 20 weeks gestation receiving one of the following ARV drugs/drug combinations and TB treatment with at least one of the following TB drugs at study entry:

ARVs:

- efavirenz 600 mg q.d.
- lopinavir/ritonavir 800/200 mg b.i.d.

TB drugs:

- rifampicin 8-12 mg/kg (max 600 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
- ethambutol 15-20 mg/kg q.d., 25-35 mg/kg t.i.w.
- isoniazid 4-6 mg/kg (max 300 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
- pyrazinamide 20-30mg/kg q.d.; 30-40mg/kg t.i.w.

No Antiretrovirals with First Line Tuberculosis Treatment (1 Arm): HIV-uninfected pregnant women ≥ 20 weeks gestation receiving at least two of the following first line TB drugs at study entry:

- rifampicin 8-12 mg/kg (max 600 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
- ethambutol 15-20 mg/kg q.d., 25-35 mg/kg t.i.w.
- isoniazid 4-6 mg/kg (max 300 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
- pyrazinamide 20-30mg/kg q.d.; 30-40mg/kg t.i.w.

Second Line Tuberculosis Treatment for Drug-Resistant Tuberculosis with or without Antiretrovirals (1 Arm): HIV-infected and HIV-uninfected pregnant women ≥ 20 weeks gestation receiving at least two of the following second line TB drugs at study entry:

Injectable agents:

- kanamycin
- amikacin
- capreomycin

Fluoroquinolones:

- moxifloxacin
- levofloxacin
- ofloxacin

Oral bacteriostatic second-line agents:

- ethionamide/prothionamide
- terizidone/cycloserine
- para-aminosalicylic acid (PAS)

Other agents:

- high dose INH
- bedaquiline
- clofazamine
- delamanid
- linezolid
- pretomanid

Antiretrovirals with Postpartum Contraceptives (4 Arms): HIV-infected women 2-12 weeks (14-84 days) post-delivery receiving one of the following ARV drug combinations AND starting postpartum contraceptives as listed below:

- darunavir/cobicistat 800/150 mg q.d. or atazanavir/cobicistat 300/150 mg q.d. postpartum and starting combined oral contraceptives formulated with 30-35 μ g ethinyl estradiol
- darunavir/cobicistat 800/150 mg q.d. or atazanavir/cobicistat 300/150 mg q.d. postpartum and starting etonogestrel implant
- efavirenz 600mg q.d. postpartum and starting combined oral contraceptives formulated with 30-35 μ g ethinyl estradiol
- atazanavir/ritonavir/tenofovir 300/100/300 mg q.d. postpartum and starting combined oral contraceptives formulated with 30-35 μ g ethinyl estradiol

REGIMEN: Pregnant women will continue on ARV and TB medications as prescribed by their clinician. Women enrolled into the postpartum contraception arms will have their ARV and contraception medications prescribed by their clinician. The timing of antepartum and postpartum pharmacokinetic evaluations will vary by drug. If ARV drug concentrations are not adequate, dose adjustments may be made at the discretion of the care provider. The new dose may be different than the current United States Food and Drug Administration (FDA) approved dose.

STUDY DURATION: HIV-infected pregnant women without tuberculosis (TB) will be followed for 6 – 12 weeks after delivery with the exception of women on DRV/r who will be followed for 2 – 3 weeks after delivery.

HIV-infected and non-infected women receiving TB treatment (first or second line) will be followed for 2 – 8 weeks after delivery.

Postpartum women will be followed until 6 – 7 weeks after the initiation of hormonal contraceptives.

Infants will be followed for 16 – 24 weeks of life.

PRIMARY OBJECTIVES:

1. To describe the pharmacokinetic parameters during pregnancy of selected ARV drugs currently used in the clinical care of HIV-infected pregnant women, and to compare these parameters to a) historical pharmacokinetic data from non-pregnant women and b) postpartum pharmacokinetic data from the same women in the study cohorts.
2. To describe the pharmacokinetic parameters during pregnancy and postpartum of selected ARV drugs (efavirenz, lopinavir/ritonavir) and first line TB drugs when co-administered as part of clinical care of HIV-infected pregnant women and of first line TB drugs when used in HIV-uninfected pregnant women.
3. To describe the pharmacokinetic parameters during pregnancy and postpartum of second line TB drugs administered as part of clinical care to HIV-infected and HIV-uninfected pregnant women.
4. To describe the pharmacokinetic parameters of ARV drugs in postpartum women before and after starting hormonal contraceptives.
5. To describe the concentrations of ethinyl estradiol, etonogestrel and other progestins in women using hormonal contraceptives and selected ARV drugs as compared to historical controls not using those ARV drugs.

SECONDARY OBJECTIVES:

1. To compare ARV and TB drug concentrations in plasma from cord blood with those in maternal plasma at the time of delivery.
2. To assess plasma protein binding of highly bound ARV drugs during pregnancy and postpartum.
3. To assess ARV concentrations and HIV RNA/DNA concentrations in vaginal secretions among pregnant and postpartum and compare to simultaneous plasma concentrations.
4. To explore genetic sources for variability in ARV and TB drug exposure in pregnant women and their infants.
5. To describe maternal and infant safety and clinical outcomes.
6. To describe the neonatal elimination of selected ARV and TB drugs acquired across the placenta after maternal dosing during pregnancy.
7. To describe pharmacokinetics of ARV drug combinations in HIV-infected women on second line TB treatment.

1.0 INTRODUCTION

1.1 Background and Rationale

Clinical trials to study the pharmacokinetics of antiretroviral (ARV), tuberculosis (TB) and contraceptive drugs in pregnant and postpartum women are limited. The development of appropriate dosing regimens for ARV and TB drugs in the pregnant woman is critical to the health of both mother and fetus. Overdosing may lead to maternal adverse events and increased risk of fetal toxicity. Under dosing may lead to inadequate virologic or mycobacterial control, increased risk of development of drug resistance mutations and a higher rate of perinatal HIV and TB transmission. Both increased metabolism and suppressed immunologic response during pregnancy can leave the mother at risk for viral/mycobacterial breakthrough and progression of disease. Independent of pharmacologic factors, pregnant women may be at particular risk for progression of HIV and TB disease. Pregnancy produces a temporary physiologic and immunologic homeostasis between tissues that are antigenically different. In order to accommodate the fetus, the maternal immune system is at least partially suppressed with an elevation of glucocorticoids (implicated in inducing hepatic metabolism) as one component of this response (1).

Clinical trials studying the drug interactions between ARVs and TB drugs or postpartum contraceptives are also lacking. An understanding of these drug interactions is necessary to ensure safe and effective use of ARVs, TB drugs and contraceptives in pregnant and postpartum women. While pharmaceutical companies rarely undertake clinical trials in pregnant women, it remains a priority for the IMPAACT network to obtain data on how pregnancy affects drug exposure so that safe and effective doses of ARVs and anti-tuberculin medications for pregnant women can be prescribed. Data on use of these drugs within the context of contraceptive use are also much needed and are a priority for the network and its sites. The network and its stakeholders would also support the use of P1026s data for any possible label modification for use of a drug during pregnancy or in the context of contraceptive usage, should that become a feasible possibility. Labels can and should include data about dosing in pregnancy, even if the dose is not changed. ARV drug pharmacology in neonates is different from that in older infants and children due to immaturity and the physiologic changes experienced by the neonate during the adaptation to the extrauterine environment in the first days of life. ARV drugs may be used in the neonate to prevent or treat HIV infection. Clinical trials studying the neonatal elimination of ARV drugs acquired across the placenta after maternal dosing during pregnancy are critical first steps in understanding the pharmacology of ARV drugs in neonates and establishing safe and effective neonatal dosing regimens.

1.2 Clinical Pharmacology in Pregnancy

Historically, women have been underrepresented in clinical drug trials (2). Recent investigations demonstrate that pharmacokinetic (PK) parameters may differ in men and women, and that women may display distinct therapeutic and toxic responses to specific compounds. One area of active investigation is the impact of gender on hepatic drug metabolism. Women demonstrate increased clearance of various drugs (e.g. verapamil, diazepam, and midazolam) when compared to men owing to enhanced cytochrome (CYP) P450 isozyme activity (3, 4). Many antiretroviral agents, including protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized by cytochrome P450 pathways. An understanding of the impact of gender differences on the metabolism of these drugs is needed in order to maximize efficacy and minimize toxicity of these agents when used in women (5-7).

Pregnancy may have an additional profound effect on drug disposition. Pregnant women experience unique physiological changes that may result in clinically significant alterations in drug pharmacokinetics and pharmacodynamics. These changes begin early in gestation and include: (a) increased gastrointestinal transit time that can alter the rate and extent of drug absorption; (b) large changes in total

body water and fat, increasing drug distribution volume; (c) decreased albumin and increased alpha acid glycoprotein (AAG) concentrations that may cause clinically relevant changes in drug protein binding; (d) increased cardiac output, ventilation, and hepatic and renal blood flow which may impact drug metabolism and elimination; (e) increased concentrations of endogenous glucocorticoids that may affect the activity of hepatic enzyme systems that regulate drug metabolism (1, 8-12).

Placental drug transport is another critical aspect of perinatal pharmacology for which few data exist for many antiretrovirals. Transport of antiretroviral agents from mother to fetus may provide protection of the fetus against HIV infection across the placenta and at the time of birth, but may also expose the fetus to the risk of toxicity. Placental drug transfer may be studied by several techniques, all of which have advantages and disadvantages. *In vitro* methods, such as isolated perfused placenta preparations, are convenient but may not accurately reflect *in vivo* conditions. Chronically catheterized non-human animal models allow complete characterization of the relationship between maternal and fetal concentrations, but interspecies differences limit the extrapolation of these findings to humans. Human studies are limited to comparisons of the ratio of maternal drug concentrations, at the time of delivery, to those in cord blood. While this ratio provides information about only a single point in time, it is the only technique currently available for human subjects and, for now, is the most useful.

Another tool, post-partum wash-out pharmacokinetic sampling in babies of mothers who are on the ARVs under study in P1026s and who are already exposed to the ARVs *in utero* can help set the stage for future studies of the ARVs in newborns and infants. By pairing the short term safety data, with limited sampling to characterize drug elimination in infants who have already received the ARV *in utero*, design of further studies including dose finding and pharmacokinetic/pharmacodynamic studies in newborns can be better informed.

1.3 Pharmacokinetics of Approved Antiretroviral Drugs in Pregnancy

Pharmacokinetic evaluations during pregnancy of many approved antiretroviral drugs have traditionally been lacking or inadequate. For the past decade, P1026s has helped to address some of these gaps in scientific data for ARV exposure during pregnancy. Data are briefly summarized below for currently approved antiretroviral drug classes.

1.31 Nucleoside/tide Reverse Transcriptase Inhibitors (NRTIs)

The pharmacokinetics of nucleoside reverse transcriptase inhibitors, including zidovudine (ZDV), lamivudine (3TC), and stavudine (d4T) during pregnancy are similar overall to pharmacokinetics in non-pregnant women (13, 14). While pregnancy does seem to alter pharmacokinetics for some drugs, such as abacavir (ABC), emtricitabine (FTC) and tenofovir (TDF), those changes are small in magnitude and likely not clinically significant (15, 16). Placental passage for nucleoside agents with chronic dosing is high, with approximately equal concentrations in cord blood and maternal blood paired samples. No dose adjustments are recommended for these nucleoside agents during pregnancy.

Tenofovir PK in pregnancy when administered as the prodrug tenofovir disoproxil fumarate (TDF) was studied in earlier versions of P1026s. (17) A new tenofovir prodrug, tenofovir alafenamide fumarate (TAF), with improved cellular uptake and lower toxicity will soon be approved for use in the US. (18) The PK of TAF in pregnant women will be studied in Version 10.0 of P1026s.

1.32 Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

For nevirapine (NVP), the physiologic changes associated with labor and delivery have a significant impact on pharmacokinetic parameters seen with initial doses given during labor, including increases in

volume, clearance, and half-life and decreases in maximum concentrations and area under the curve (AUC). Since NVP autoinduces its own clearance during the first weeks of chronic therapy, initial dose data cannot be extrapolated to chronic dosing. Nevirapine pharmacokinetics with chronic dosing during pregnancy were studied in P1022, Randomized Trial of Protease Including vs. Protease Sparing Regimens for Women to Initiate Therapy for HIV Infection During Pregnancy and Version 2.0 of P1026s. A combined analysis of the NVP PK data from these 2 studies show no significant differences in pharmacokinetic parameters during pregnancy compared to postpartum (19).

Although severe teratogenic effects were observed with EFV use in pregnant primates, similar effects have not been seen in observational studies in humans and its use throughout pregnancy is becoming more popular (20). Clinicians are encouraged to refer to the Perinatal Guidelines for updated information about the use of EFV during pregnancy (available at <http://aidsinfo.nih.gov/guidelines/>) (21). Our prior study of EFV PK in primarily Thai women showed increased clearance and lower trough concentrations during pregnancy, but the magnitude of changes were small and not likely clinically significant. Efavirenz PK in HIV-infected women outside of Thailand have not been adequately described, and will continue to be studied in version 10 of P1026s.

Etravirine and rilpivirine are newer NNRTI's whose pharmacokinetics have been studied in previous versions of P1026s.

1.33 Protease Inhibitors (PIs)

Prior versions of P1026s have shown that plasma concentrations of protease inhibitors, including lopinavir (LPV), atazanavir (ATV), nelfinavir (NFV), saquinavir (SQV), indinavir (IDV), fosamprenavir (fAPV) and darunavir/ritonavir (DRV/r), are significantly decreased when standard adult doses are used in pregnancy compared to postpartum women (22-28). The largest decreases have been seen in the third trimester, while second trimester concentrations are generally decreased to a lesser extent. Cord blood to maternal concentration ratios of PIs are generally less than 20%. Higher than standard doses of lopinavir/ritonavir (LPV/r) and atazanavir/ritonavir (ATV/r) have been studied in previous P1026s arms. These increased doses during the third trimester raise the PI concentrations back to typical concentrations seen in non-pregnant women on standard doses for LPV/r (29, 30). P1026s Version 9.0 included arms studying increased doses of darunavir with ritonavir during pregnancy. These arms have not fully accrued and will continue in Version 10.0.

Many of the completed protease inhibitor arms of P1026s involved protease inhibitors boosted with ritonavir. Recently cobicistat, a new antiretroviral pharmacoenhancer, has been licensed for use in boosting the PI's atazanavir and darunavir, but no PK data are available for these drug combinations during pregnancy. P1026s Version 10 will include arms studying these protease inhibitor/cobicistat combinations.

1.34 Integrase Inhibitors

Raltegravir was the first human immunodeficiency virus integrase strand transfer inhibitor (HIV-1 INSTI), commonly referred to as an integrase inhibitor, licensed for use in the US. Raltegravir was studied in earlier versions of P1026s. (31) Two newer integrase inhibitors, elvitegravir, administered with the booster cobicistat, and dolutegravir, will be studied in this version of P1026s.

1.35 Entry Inhibitors

An arm to study maraviroc pharmacokinetics was included in previous versions of P1026s.

1.4 Use of Tuberculosis (TB) and Antiretroviral (ARV) Medicines during Pregnancy

1.41 First Line TB Drugs

Tuberculosis and HIV co-infection is becoming increasingly common and requires treatment for both diseases, including during pregnancy. There are currently no data describing the PK during pregnancy of medicines used to treat TB. *P1078, A Phase IV Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Safety of Immediate (Antepartum-initiated) Versus Deferred (Postpartum-initiated) Isoniazid Preventive Therapy among HIV-Infected Women in High TB Incidence Settings* will address isoniazid (INH) therapy in pregnancy but not as part of standard multi-drug TB therapy. Rifampicin (RIF), used in first line TB regimens, is a potent inducer of CYP P450 enzymes and has significant drug interactions with ARVs (32). Nevirapine and EFV drug exposure are reduced when dosed concurrently with RIF, and an increase of the EFV dose to 800 mg may be recommended (33). These factors are further complicated in the setting of pregnancy. Genetic polymorphisms will also play a role – individuals with the 2B6 516TT phenotype have slow EFV metabolism and paradoxically increased EFV concentrations with RIF (34). Lopinavir metabolism is also significantly increased by RIF, and the recommendation is to either double the LPV/r dose or give additional RTV when LPV/r and RIF are administered together (32). The standard approach at IMPAACT network African sites is to use double doses of LPV/r in pregnant women on RIF-based TB therapy. This version of P1026s will continue to study the combination of TB drugs with the ARVs EFV and LPV/r.

1.42 Second Line TB Drugs

Globally, the burden of multi-drug resistant TB (MDR-TB, i.e. *Mycobacterium tuberculosis* resistant to rifampicin and isoniazid) is increasing, against a background of increasing HIV prevalence. In 2013, 3.5% of all incident TB cases reported were resistant to *M. tuberculosis*, with only 48% of adult MDR-TB patients having favorable TB treatment outcomes (35). Many of these drug-resistant TB (DR-TB) cases occur in women of childbearing age of whom a proportion are or will become pregnant, and who are frequently also HIV co-infected. Current recommendations for MDR-TB treatment call for an intensive phase with at least 4 second-line TB drugs (Table 1) likely to be effective, including a second line injectable drug for at least 8 months duration. Treatment should also routinely include a fluoroquinolone and pyrazinamide, and the total duration of treatment should be at least 20 months.

There are currently limited data available on the PK and safety during pregnancy of these second line TB drugs used to treat MDR-TB. The only PK data on fluoroquinolone use during pregnancy is provided by 3 small studies, which include only short-term data and have conflicting results. Two separate studies showed low peak serum concentrations for moxifloxacin (36) and ofloxacin (37); however, another study reported peak serum concentrations comparable to non-pregnant adult target levels for moxifloxacin and levofloxacin in caesarean-sectioned women (38). PK data on the other second line TB drugs during pregnancy are limited to one pharmacokinetic study on the use of amikacin reported in 1977, where 11 pregnant women achieved a peak concentration of 24.23 ug/ml, following a single dose of intramuscular amikacin (39).

A paucity of data also exists for potential drug/drug interactions between second line TB medicines and ARVs. Moxifloxacin concentrations may potentially be reduced by ritonavir, and clofazimine, a weak inhibitor of CYP3A4, may potentially increase protease inhibitor concentrations (40); however the presence and magnitude of these interactions have not been well described. Efavirenz increases para-

aminosalicylic acid (PAS) clearance, resulting in lower PAS exposure (41). The novel TB drug bedaquiline, metabolized by cytochrome P450 (CYP) 3A, has a number of important drug/drug interactions with ARVs (42). (43).

There are limited safety data available for the currently used second line TB drugs during pregnancy. Most of these drugs are classified by the FDA as safety class C, with the exception of amikacin and kanamycin, categorized as safety class D (Table 1). In nonpregnant adults, use of injectable TB drugs has been associated with hearing deficits and of ethionamide and para-aminosalicylic acid with thyroid function abnormalities, but there are no data on these specific toxicities in pregnant women. Capreomycin, a cyclic polypeptide, is the injectable agent of choice for use in pregnancy (44), although the evidence base regarding potential reduced ototoxicity compared to kanamycin and streptomycin, is limited (45, 46). No human pregnancy data are available for the newly licensed drugs bedaquiline (safety class B) and delamanid, used to treat adult MDR and more extensively drug-resistant TB, however these important drugs are becoming increasingly available.

In summary, PK and safety data on the use of second line TB medicines are needed to address a large existing knowledge gap preventing optimal clinical care of MDR TB infected pregnant women and their infants. This version of P1026s will therefore study the PK and safety of second line TB medicines, with or without ARVs, during pregnancy. Table 1 lists the drug groups currently considered for the treatment of DR-TB during pregnancy, with key drugs to be prioritized for pharmacokinetic (PK) study highlighted, based on frequency of use. Samples for other TB drugs (e.g. those used for pre-XDR and XDR-TB, and ARVs) will be stored and analysed based on feasibility.

Table 1. Drug groups considered for the routine treatment of MDR-TB during pregnancy, along with current FDA Safety Class.

Group	Group Name	Drugs	Pregnancy Safety Class#
1	First-line oral agents	Ethambutol Pyrazinamide	C C
2	Injectable agents	Kanamycin* Amikacin Capreomycin	D D C
3	Fluoroquinolones	Moxifloxacin* Levofloxacin* Ofloxacin	C C C
4	Oral bacteriostatic second-line agents	Ethionamide* / Prothionamide Terizidone */ Cycloserine Para-aminosalicylic acid*	C C C
5	Agents with unclear efficacy or concerns regarding usage	High-dose isoniazid Clofazimine Linezolid Bedaquiline Delamanid Pretomanid (previously PA-824)	C C C B (not yet classified) (not yet classified)

*Second-line anti-tuberculosis drugs to be prioritized for PK study; samples will be stored for all other TB drugs and ARVs as used and will be analyzed as feasible (i.e. when reasonable numbers accrue)

FDA category definitions: A: No risk to human fetus in first trimester, B: No risk to fetus in animal studies, C: Adverse effects to fetus shown in animal studies, D: Risk for human adverse events in fetus

1.5 Contraceptives and Antiretrovirals

Limited data from small, mostly unpublished studies suggest that some ARV therapies might alter the pharmacokinetics of combined oral contraceptives (COCs). Few studies have measured clinical outcomes. However, contraceptive steroid levels in the blood decrease substantially with ritonavir-boosted protease inhibitors (47). Such decreases have the potential to compromise contraceptive effectiveness. Conversely, contraceptives may lead to increased ARV exposure and potential toxicity or decreased ARV levels and inadequate viral suppression and resistance (48). Etonogestrel implant (Implanon/Nexplanon) is a long-acting (up to 3 years), reversible, contraceptive method. The contraceptive effect of etonogestrel implant is achieved by several mechanisms that include suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.

Implanon, one of the commercially available etonogestrel implants is an off-white, non-biodegradable, etonogestrel containing a single sterile rod for subdermal use. Each rod consists of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel (ENG), surrounded by an EVA copolymer skin. The release rate is 60-70 µg/day in week 5-6 and decreases to approximately 35-45 µg/day at the end of the first year, to approximately 30-40 µg/day at the end of the second year, and then to approximately 25-30 µg/day at the end of the third year. After subdermal insertion of Implanon, ENG is released into the circulation and is approximately 100% bioavailable. The mean peak serum concentrations in 3PK studies ranged between 781 and 894 pg/mL and were reached within the first few weeks after insertion (49, 50). The mean serum ENG concentration decreases gradually over time declining to 192 - 261 pg/mL at 12 months (n=41), and 154 - 194 pg/mL at 24 months. *In vitro* data shows that ENG is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. The elimination half-life of ENG is approximately 25 hours. Excretion of ENG and its metabolites, either as free steroid or as conjugates, is mainly in urine and to a lesser extent in feces.

In clinical use among women aged 18 to 35 years who received Implanon, 6 pregnancies during 20,648 cycles of use were reported. Two pregnancies occurred in each of Years 1, 2, and 3. Each conception was likely to have occurred shortly before or within 2 weeks after Implanon removal. With these 6 pregnancies, the cumulative Pearl Index was 0.38 pregnancies per 100 women-years of use (51, 52). Postmarketing experience in Australia evaluated 127 cases of pregnancy when using Implanon classified as product/method failures once other reasons had been excluded. Using the 204,486 Implanon devices subsidized in this period to estimate the population exposed and the 218 pregnancies reported, the approximate failure rate in postmarketing use was 1 in 1000 insertions (53).

The acceptability, safety and efficacy of Implanon in HIV infected women was confirmed in 79 women followed in the public health setting in Brazil. Fifty-six of the women were taking antiretrovirals; 31 were taking a PI-based regimen and 25 were taking an NNRTI-based regimen. Women were followed for 3 years after Implanon insertion. No pregnancies occurred in the 79 women. Two women required implant removal before three years after insertion due to excessive menstrual bleeding (54). There are no data describing drug/drug PK interactions between etonogestrel implants and ARV drugs.

Few studies have evaluated interactions between COCs and the currently most commonly used ARVs such as LPV/r, ATV/r and EFV. Ethinyl estradiol concentration was reduced 42%, but no effect on norethindrone was observed with the use of LPV/r (55). In one study TDF was administered to 20 women and no interaction was observed with the concomitant use of COCs (56). Atazanavir/ritonavir was administered to 20 healthy women and significant increases in ethinyl estradiol (37%) and norgestimate (102%) concentrations were observed (57). There are no data evaluating the effect of COCs on LPV/r, ATV/r or tenofovir concentrations.

Recent cases of contraceptive failure have been reported in HIV infected women on efavirenz with both implanted etonogestrel (Implanon) and levonorgestrel (Jadelle) contraception. (58-61) While two PK studies have shown a marked reduction in levonorgestrel concentrations in women receiving Jadelle implants, no data are available for the interaction between efavirenz and etonogestrel implants, which are the preferred contraceptive implants used at many IMPAACT P1026s sites. (62, 63) Given the current WHO guidelines encouraging use of EFV/FTC/TDF as the first line cART regimen across populations, it is critical to examine possible drug/drug interactions between EFV and contraceptives in postpartum women as soon as possible. Version 10 of P1026s will continue to study the drug/drug PK interactions between EFV and both oral and implanted (etonogestrel) contraception in postpartum women, and will add arms studying the interactions between the new darunavir/cobicistat and atazanavir/cobicistat formulations with both oral and implanted (etonogestrel) contraception.

1.6 Genital Tract HIV and Antiretroviral Concentrations

Genital tract levels of HIV are independently associated with the risk of maternal-to-child transmission of HIV. In a sub-study of a randomized trial of breast versus formula feeding in Kenya, both cervical and vaginal HIV DNA levels were associated with the risk of infant HIV infection, after adjustment for CD4+ cell count, prematurity, genital ulcers, exposure to breast milk, and mastitis (64). None of the women in this study received ARV therapy. In a study from Thailand, genital tract HIV RNA levels were significantly reduced among women receiving ZDV compared to placebo (65). In both treatment groups, the risk of transmission to the infant was significantly associated with detectable HIV RNA in the cervical-vaginal lavage (CVL), in both high ($> 10,000$ copies/mL) and low ($< 10,000$ copies/mL) plasma HIV RNA groups. This study clearly showed the ability of antiretroviral drugs to reduce genital tract RNA levels and the association of genital tract HIV levels with transmission. In a case-control analysis of a subset of women enrolled in the *Women and Infants Transmission Study* (WITS), the level of HIV DNA detected in CVL, but not the level of HIV RNA, was associated with the risk of vertical transmission of HIV among women not delivering by cesarean section before the onset of labor, suggesting exposure of the infant to cell associated HIV in the genital tract plays a role in HIV transmission (66). The adjusted risk of transmission increased by a factor of 2.28 (1.09-4.78) for each one log increase in CVL HIV DNA level. In this study, the majority of women were receiving ARVs, predominantly ZDV monotherapy. Thus, data are consistent in showing an association between genital tract HIV levels and risk of vertical transmission, independent of plasma HIV RNA levels, but it is still not clear whether cell-free (RNA) or cell-associated (DNA) HIV is more important for transmission. In addition, the data available to date on genital HIV and transmission are from untreated women or women receiving ZDV monotherapy. Triple ARV regimens may suppress genital tract viral load to a greater extent. This suppression may help to account for lower transmission rates among women on triple ARV regimens.

The majority of studies have shown a correlation between plasma HIV RNA levels and genital tract HIV RNA levels or DNA detection. However, many studies demonstrate some women with persistently detectable genital tract HIV despite undetectable plasma HIV RNA. In studies done before the triple ARV era, plasma HIV RNA levels and CD4+ cell count depletion were consistently associated with detection of HIV RNA or DNA in the female genital tract (67). In one study of women on various antiretroviral regimens, HIV RNA was detectable in the genital tract from CVL among 25% of women with undetectable plasma HIV RNA. This finding was more frequent among women on less intensive ARV regimens (68). However, even among women on triple ARV regimens, 8 (28.6%) of 28 had detectable HIV RNA, most with detectable plasma HIV RNA. In another study that evaluated plasma and genital tract RNA levels before and for 28 weeks after triple ARV initiation, 98% of women had undetectable plasma RNA and 95% had undetectable genital tract RNA after 18 weeks of therapy. With repeated sampling, 47% of women had at least one episode of genital tract HIV detection despite consistently undetectable plasma HIV RNA levels (69). In a study of plasma and genital tract RNA levels among 38 pregnant women, two (22%) of the nine women with undetectable plasma HIV RNA levels had detectable

vaginal HIV RNA (70). A study of 268 women from the WITS detected genital tract HIV shedding in 57% of women overall, including among 130 (80%) of 163 women with detectable plasma RNA and among 27 (33%) of 83 women with plasma HIV RNA under 500 copies/mL (71). Seventy-four percent of these 27 women were on ARV therapy, including 14 (52%) on a protease inhibitor. Other studies have confirmed the strong association between plasma HIV RNA levels and detection of HIV in the genital tract, and a small proportion of women with persistently detectable genital tract HIV even with undetectable plasma HIV RNA (72, 73). In a subsequent study from WITS of 290 women with undetectable plasma HIV RNA, 44 (15%) had detectable HIV RNA in cervical swab specimens (74). In a multivariable analysis of factors associated with genital tract HIV detection, only NNRTI use (compared to PI use, odds ratio 2.24, 95% confidence interval 1.13-4.45) and illicit drug use (OR 2.41, 0.96-5.69) were found to be associated with genital tract detection of HIV RNA. Thus, plasma HIV RNA level is not an adequate predictor of genital tract HIV detection, and the risk of genital tract HIV shedding may vary by the ARV regimen used.

The levels of ARVs in the genital tract and potential effects on genital tract HIV levels vary by drug and class. An early study found that the detection of HIV RNA in CVL specimens was inversely related to the number of ARV drugs the woman was taking, while detection of HIV DNA in the genital tract occurred in similar proportions of women in various therapy groups (75). A study of LPV and IDV plasma and genital tract levels in non-pregnant women found markedly different penetration of the drugs into CVL. Lopinavir was detected in 7 (37%) of 19 samples at peak plasma time and in 4 (21%) at trough times. The median CVL/plasma ratio for LPV was 0.076 at peak and 0.070 at trough times. Indinavir was detected among 14 (93%) of CVL samples at peak and 12 (92%) of 13 at trough times, with the peak CVL/plasma ratio of 1.32 at peak and 3.8 at trough times (76). In two studies using aspiration of vaginal pool fluid for drug level determinations, genital tract/plasma concentration ratios were 4.11 for 3TC, 3.95 for emtricitabine (FTC), 2.35 for ZDV, 0.75 for TDF, < 0.08-0.26 for RTV, 0.21 for ddI, 0.18 for ATV, 0.08-0.21 for LPV, 0.08 for ABC, 0.05 for d4T, 0.83-1.17 for NVP, 0.40-4.64 for IDV, and 0.004-0.25 for EFV (77, 78). Similarly, in another study, pre-dose genital tract/plasma ratios were above one for 3TC, TDF, ZDV, ddI and FTC, while levels of ABC, RTV, and ATV were between 0.33-0.81, and levels of EFV, NVP, LPV, NFV and FPV were below 0.10 (79). Ratios three to four hours after oral dosing were lower but followed a similar pattern. In a study of pregnant women using the same aspiration technique and laboratory methods as the studies by Dumond and Min, genital tract/plasma ratios for ZDV and LPV were significantly lower than those in nonpregnant women, suggesting that genital tract drug levels from nonpregnant women cannot be extrapolated to pregnant women (80).

Version 10 of P1026s will continue to include collection of vaginal secretions samples to allow assessment of antiretroviral concentrations in genital tract secretions and vaginal swab sampling to measure HIV levels that would be encountered by the infant during labor and vaginal delivery.

1.7 Pharmacogenetics

Considerable variability exists in the pharmacokinetics of ARVs in both adults and children. In addition to the changes in drug disposition due to pregnancy, variations in genes that affect drug transport and metabolism creates variability in ARV exposure. The commonly used non-nucleosides all exhibit genetic polymorphisms that impact drug metabolism. CYP 2B6 is responsible for a significant portion of NVP and EFV and the CYP 2B6 TT genotype at position 516 is associated with impaired metabolism of CYP2B6 substrates (81, 82). This genotype has been reported to be more common in African-Americans (20%) than in European-Americans (3%). The CYP 2B6 516 T/T is associated with more than double the EFV AUC in adults (83) and similar increases were observed by Saitoh et al in children (82). More recently other CYP2B6 genetic variations have been identified with functional increases and decreases in EFV metabolism (84). NVP is metabolized by both CYP 3A4 and CYP 2B6. Polymorphisms in CYP 2B6 affect NVP exposure but these influences are not as large as for EFV. The most recently approved NNRTI,

etravirine, is not a substrate for CYP 2B6 but is metabolized by CYP 3A4, CYP 2C9 and CYP 2C19 (85). Both CYP 2C9 and CYP 2C19 have well described genetic variations associated with impaired drug metabolism (86) and thus etravirine exposure will likely be increased in patients with CYP 2C9 and/or CYP 2C19 poor metabolizer genotypes.

There are also potential pharmacogenomic influences on protease inhibitor (PI) absorption and metabolism. Although currently available PIs are pharmacologically boosted by the CYP 3A inhibitor, RTV, making patients on RTV-boosted PIs phenotypically poor metabolizers, pharmacogenomic influences on PI exposure still exist. Genetic variants in ORM1 (ORM1*F1, ORM1*F2 and ORM1*S resulting from A to G transition at codons for aa position 20 in exon 1 and 156 in exon 5), SLCO1B1 (rs4149056 and rs4149032), CYP3A5 and PXR (rs2472677) have been identified to alter LPV or ATV pharmacokinetics (87-90).

The identification of genetic influences on the pharmacokinetics of ARVs is rapidly increasing; however, the interplay between pharmacogenomics and other key factors are poorly understood. Preliminary pharmacokinetic results from infants receiving EFV in *P1070, Dose Finding and Pharmacokinetic Study of Efavirenz in HIV-infected and HIV/TB co-infected Infants and Children ≥3 Months to <36 Months of Age*, suggest that that genotype may have a more profound impact than in older populations with infant poor metabolizers having much higher EFV AUCs. Similar interactions between pregnancy and pharmacogenomics on ARV PK may exist and are in need of investigation. In addition to pharmacokinetic-pregnancy interactions, genetic differences in drug metabolism may also alter toxicity. Hepatotoxicity from TB therapy has been linked to drug metabolizing activity of N-acetyl-transferases-2 (NAT-2) and CYP 2E1 (91). More recently elevation of liver enzymes has been linked to the drug transporter MDR1 (also known as p-glycoprotein) (92).

Among mothers and infants participating in washout PK sampling in this version of P1026s, informed consent will be sought for collection and testing of specimens to determine common single nucleotide polymorphisms (SNPs) associated with ARV transporters and drug metabolizing enzymes. These assays will allow exploratory analyses of pregnancy and pharmacogenomic influences on ARV disposition. In addition, having pharmacogenomic information collected in P1026s participants will help expand the mechanistic understanding of extreme drug exposures or response during pregnancy. Whether a mother agrees to genetic testing for herself and/or her infant will otherwise not affect their participation in this study. It is entirely optional.

1.8 History of Versions 1.0 - 9.0

See Appendix VII for a history of study arms included in protocol Versions 1.0 – 9.0.

2.0 OBJECTIVES

2.1 Primary Objectives

- 2.11 To describe the pharmacokinetic parameters during pregnancy of selected ARV drugs currently used in the clinical care of HIV-infected pregnant women, and to compare these parameters to a) historical pharmacokinetic data from non-pregnant women and b) postpartum pharmacokinetic data from the same women in the study cohorts.
- 2.12 To describe the pharmacokinetic parameters during pregnancy and postpartum of selected ARV drugs (efavirenz, lopinavir/ritonavir) and first line TB drugs when co-administered as part of clinical care of HIV-infected pregnant women and of first line TB drugs when used in HIV-uninfected pregnant women.
- 2.13 To describe the pharmacokinetic parameters during pregnancy and postpartum of second line TB drugs administered as part of clinical care to HIV-infected and HIV-uninfected pregnant women.
- 2.14 To describe the pharmacokinetic parameters of ARV drugs in postpartum women before and after starting hormonal contraceptives.
- 2.15 To describe the concentrations of ethinyl estradiol, etonogestrel and other progestins in women using hormonal contraceptives and selected ARV drugs as compared to historical controls not using those ARV drugs.

2.2 Secondary Objectives

- 2.21 To compare ARV and TB drug concentrations in plasma from cord blood with those in maternal plasma at the time of delivery.
- 2.22 To assess plasma protein binding of highly bound ARV drugs during pregnancy and postpartum.
- 2.23 To assess ARV concentrations and HIV RNA/DNA concentrations in vaginal secretions among pregnant and postpartum and compare to simultaneous plasma concentrations.
- 2.24 To explore genetic sources for variability in ARV and TB drug exposure in pregnant women and their infants.
- 2.25 To describe maternal and infant safety and clinical outcomes
- 2.26 To describe the neonatal elimination of selected ARV and TB drugs acquired across the placenta after maternal dosing during pregnancy.
- 2.27 To describe pharmacokinetics of ARV drug combinations in HIV-infected women on second line TB treatment.

3.0 STUDY DESIGN

This is a Phase IV prospective study to evaluate the pharmacokinetics of selected currently prescribed antiretroviral (ARV) medicines when used alone or with tuberculosis (TB) medicines during pregnancy or with postpartum hormonal contraceptives in HIV-infected pregnant and postpartum women. The washout PK of transplacentally acquired ARV and TB drugs will be studied in the infants born to study mothers who enter the study during pregnancy. HIV-uninfected pregnant women receiving TB treatment (first line or second line) will also be enrolled to serve as a control group to evaluate the interaction between TB and ARV drugs in pregnant women. Eligible women can enroll between 20 0/7 – 37 6/7 weeks gestation or 2-12 weeks postpartum, depending on study arm. All infants of mothers enrolled during pregnancy will be enrolled in-utero, after maternal enrollment. Enrolled infants who meet the requirements for washout PK sampling, as specified in Section 4.4, will undergo PK sampling.

Women must be currently receiving one of the ARV, TB drug, or hormonal contraceptives at the specified doses listed in the Schema. The drug/drug combinations selected for study are among those lacking PK data during pregnancy and postpartum and are most commonly used or are likely to be commonly used in the near future. If a woman is receiving two or more of the ARVs being studied she may be sampled for each drug/drug combination and be included in the enrollment for each arm. Maternal clinical and laboratory toxicities will be assessed through medical histories and physical examinations, and laboratory testing on each PK sampling day and at delivery. Women will continue to take their prescribed medicines throughout the course of their pregnancy. Medicines may be changed for toxicity or lack of efficacy by the clinical providers, but the protocol team should be notified of any medicine changes.

Each study arm will enroll a minimum of 12 women and have a target enrollment of 25 women with evaluable 3rd trimester PK data in the ARV and TB arms, or evaluable postpartum PK data in the contraception arms. Enrollment may be restricted or adjusted so that 2nd trimester PK data are collected from at least 12 women. When combined enrollment in the increased dose darunavir arms reach 25 participants, the PK data will be evaluated to determine if the data for these arms can be combined and whether enrollment of additional participants in these arms should continue. Sample size for an ARV or TB drug arm may be increased if additional infants need to be enrolled to collect infant washout PK data. The sample size of the second line TB drug arm may be increased above 25 to obtain additional data for less commonly used second line TB drugs.

3.1 Enrollment Procedures

3.11 Maternal Antepartum Enrollment (during pregnancy)

Pregnant women who meet the eligibility criteria, as specified, in Section 4.1 will enroll in P1026s prior to or at the time of pharmacokinetic sampling. The initial PK sampling visit must occur within 5 days of participant enrollment. *See Appendix I-A through I-C for a complete description of the procedures to be performed for each study arm, and Section 10 Data Collection Requirements, for a description of data to be collected.*

3.12 Maternal Postpartum Enrollment (after delivery)

Women receiving antiretroviral drugs and contraceptives, and who meet the eligibility criteria as specified in Section 4.1, will enroll in P1026s at 2-12 weeks after delivery. *See Appendix I-D, Schedule of Evaluations for Postpartum Women on Antiretroviral Medicines and Hormonal Contraceptives, for a complete description of the procedures to be performed, and Section 10.0 Data Collection Requirements, for a description of data to be collected.*

3.13 Infant Enrollment

All infants of mothers enrolled during pregnancy (antepartum) should be enrolled in utero, immediately after the maternal enrollment, and followed in P1026s. Enrolled infants who meet the requirements specified in Section 4.4 will undergo washout PK sampling. *See Appendix II, Schedule of Evaluations for Infants, for a complete description of the procedures to be performed.*

Note: Infants, born to women enrolling postpartum (ARVs with postpartum contraceptives arms), will not be enrolled in P1026s.

3.2 Maternal Antepartum and Postpartum Pharmacokinetic Sampling

Intensive PK sampling will be performed to determine plasma concentrations of ARVs, TB medicines and hormonal contraceptives. Plasma alpha-1 acid glycoprotein (AAG) concentration and protein binding of highly bound ARV drugs will also be determined, as will ARV concentrations and HIV viral load in vaginal secretion samples. Women must be stable on the ARV and/or TB drug(s) being studied for at least two weeks prior to PK sampling. The timing of dosing for the three days prior to and the day of the PK evaluation must be the same, and must be the same for the PK evaluation(s) done during pregnancy and postpartum. Women are expected to revert back to standard dosing after discharge; if not, the study pharmacologist should be consulted prior to PK sampling.

A woman receiving two of the ARV drugs/drug combinations being studied may be sampled for each ARV drug/drug combination, but the enrollment site will receive credit for enrollment of a single participant.

The schedule of antepartum and postpartum pharmacokinetic sampling time points varies by drug and is described in *Appendix III, Maternal Intensive Pharmacokinetic Sampling Schedule for Antiretroviral Medicines, Tuberculosis Treatment and Hormonal Contraceptives*.

On each PK sampling day, the study visit should be scheduled to start at the point in time that coincides with the end of the previous dosing interval. The dose(s) of the study drug(s) will be administered on site after the pre-dose sample is drawn. An intravenous catheter will be placed in an arm vein for serial blood collection. Participants having 12 hour sampling should remain in the clinic until the completion of PK sampling. Participants having 24 hour sampling may leave the clinic following the 12 hour time point, and return for the 24 hour time point.

All women will be asked to report the time and a description of their two most recent meals and to carefully note the day and time of their previous two doses prior to the start of PK sampling. In addition, the Perinatal Adherence Questionnaire will be administered on each PK sampling day to HIV-infected women. See *Appendix IV, Dietary Recommendations for Antiretroviral Medicines, Tuberculosis Medicines and Hormonal Contraceptives*, for dietary recommendations.

3.21 Genital Tract Viral Load and Drug Concentrations

HIV-infected pregnant women not on TB drugs will have vaginal samples for ARV concentrations obtained at the second and third trimester and the 6-12 postpartum PK sampling visits. Samples will be obtained pre-dose and at 1, 2, and 4 hours after dosing. Samples for drug concentrations will be obtained with the soft plastic aspirator without speculum placement or by another appropriate technique and can be collected by the participant or by a clinician. Samples will be stored and batch shipped for testing. Since target drug concentrations for vaginal samples have not been determined, real time testing and reporting of vaginal specimen results to the sites will not be done. A single vaginal swab will also be obtained without speculum placement for viral load testing once during each PK visit. No vaginal specimens will be collected if contraindicated by a pregnancy complication such as placenta previa or premature rupture of membranes.

3.22 Hormonal Contraceptive PK Sampling

Women taking either darunavir/cobicistat or atazanavir/cobicistat or EFV after delivery and starting on combined oral contraceptives with ethinyl estradiol and any progestin or etonogestrel implant prior to 12 weeks postpartum will have intensive PK sampling performed at 2-12 weeks postpartum (prior to contraceptive initiation) and again 6-7 weeks after contraceptive initiation. Oral contraceptives and the ARV being studied should be taken at the same time of day three days prior to PK sampling and on the day of PK sampling.

3.3 Reporting of Pharmacokinetic Results

ARV plasma drug assays and pharmacokinetic calculations during pregnancy will be performed in real time during pregnancy and the results will be reported to the participant and her clinical caregiver. The participant and the clinical caregiver will also be informed if the estimated pharmacokinetic exposure parameter for an individual participant is less than the pharmacokinetic exposure target as described in *Appendix V, Maternal Pharmacokinetic Parameter Targets*, generally the 10th percentile for non-pregnant women. Based on the results of the ARV plasma drug assays, the participant's clinical status and laboratory values, and the study pharmacologist recommendations (if any), the participant and clinical caregiver may decide to modify dosing. The new dose may not have been approved by the FDA. If dosing is modified, the clinical caregiver may elect to have repeat pharmacokinetic sampling performed during pregnancy after at least one week on the new dose. If the new dose meets the drug exposure target, the participant will remain on that dose until delivery. Dosing will revert to standard adult dosing at discharge from the hospital after delivery and pharmacokinetic sampling will be performed again at either 2-3 weeks or 6-12 weeks postpartum, depending on study arm. If the new dose does not meet the drug exposure target, an alternative therapy should be considered, as no further dose adjustments will be allowed. Sampling will only be repeated once for participants who have dose adjustments, because pregnancy is a time limited condition and it is unlikely that there would be sufficient time for a third dose adjustment and pharmacokinetic assessment to be completed prior to delivery. If a woman remains on a dose postpartum for which evaluable antepartum PK parameters exist, postpartum PK sampling will be performed. If at least 12 women are enrolled in an arm and the estimated 3rd trimester pharmacokinetic exposure parameter (AUC or C_{min}) for 6 or more of them falls below the pharmacokinetic exposure target, the protocol team will evaluate the pharmacokinetic data and with agreement of the Medical Officers, will determine whether enrollment in that cohort should be continued.

TB plasma samples will be stored at the site and shipped when requested by the protocol team for batch testing. Results of TB drug concentration assays and pharmacokinetic calculations may be reported back to the participant and her clinical caregiver after the assays have been completed. A study pharmacologist will be available to assist with the interpretation of these results at the request of the clinical caregiver.

Hormonal contraceptive samples will be stored at the site and shipped when requested by the protocol team for batch testing. Since target concentrations have not been clearly defined, hormonal contraceptive assay results will not be reported to the participant or her clinical caregiver.

3.4 Intrapartum Pharmacokinetic Sampling

Transplacental passage of the ARV and TB drugs of interest will be assessed by measurement of drug concentrations in maternal plasma at the time of delivery and cord blood. A single maternal specimen will be drawn at the time the cord is clamped. A single specimen will also be obtained from the umbilical cord.

3.5 Infant Pharmacokinetic Sampling

Infants who meet the requirements criteria specified in Section 4.4 will have 4 blood samples collected in the first days of life. The timing of collection of these samples is described in Appendix II. Infant pharmacokinetic samples will be stored at the site until the maternal postpartum pharmacokinetic samples have been collected and then both sets of samples will be shipped to the appropriate pharmacology laboratory.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Maternal Inclusion Criteria

4.11 Eligible participants must belong to one of the 5 groups described below:

4.111 HIV-infected pregnant women ≥ 20 weeks gestation NOT on tuberculosis treatment receiving one or more of the following ARV drugs/drug combinations:

- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 800/100 mg b.i.d. until 30 weeks gestation; then 800/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn.
- darunavir/ritonavir twice daily 600/100 mg b.i.d. or 900/100 mg b.i.d. until 30 weeks gestation; then 900/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn.
- dolutegravir 50 mg q.d.
- tenofovir alafenamide fumarate (TAF) 25 mg q.d. without cobicistat or ritonavir boosting
- tenofovir alafenamide fumarate (TAF) 10 mg q.d. with cobicistat
- tenofovir alafenamide fumarate (TAF) 10 mg q.d. with ritonavir
- elvitegravir/cobicistat 150/150 mg q.d.
- darunavir/cobicistat 800/150 mg q.d.
- atazanavir/cobicistat 300/150 mg q.d.
- Participants outside of Thailand only: efavirenz 600 mg q.d.

4.112 HIV-infected pregnant women ≥ 20 weeks gestation receiving one of the following ARV drugs/drug combinations and TB treatment with at least one of the following TB drugs at study entry:

ARV's:

- efavirenz 600 mg q.d.
- lopinavir/ritonavir 800/200 mg b.i.d.

TB drugs:

- rifampicin 8-12 mg/kg (max 600 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
- ethambutol 15-20 mg/kg q.d., 25-35 mg/kg t.i.w.
- isoniazid 4-6 mg/kg (max 300 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
- pyrazinamide 20-30mg/kg q.d.; 30-40mg/kg t.i.w.

4.113 HIV-uninfected pregnant women ≥ 20 weeks gestation receiving at least two of the following first line TB drugs at study entry:

- rifampicin 8-12 mg/kg (max 600 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
- ethambutol 15-20 mg/kg q.d., 25-35 mg/kg t.i.w.
- isoniazid 4-6 mg/kg (max 300 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
- pyrazinamide 20-30mg/kg q.d.; 30-40mg/kg t.i.w.

4.114 HIV-infected and HIV-uninfected pregnant women ≥ 20 weeks gestation receiving at least two of the following second line TB drugs at study entry:

Injectable agents:

- kanamycin
- amikacin
- capreomycin

Fluoroquinolones:

- moxifloxacin
- levofloxacin
- ofloxacin

Oral bacteriostatic second-line agents:

- ethionamide/prothionamide
- terizidone/cycloserine
- para-aminosalicylic acid (PAS)

Other agents:

- high dose INH
- bedaquiline
- clofazamine
- delamanid
- linezolid
- pretomanid

Note: Infants of mothers enrolled during pregnancy (meeting criteria 4.111, 4.112, 4.113 and 4.114 specified above) should be enrolled, in utero, immediately after maternal enrollment.

4.115 HIV-infected women 2-12 weeks (14-84 days) post-delivery receiving one of the following ARV drug combinations AND starting postpartum contraceptives as listed below:

- darunavir/cobicistat 800/150 mg q.d. or atazanavir/cobicistat 300/150 mg q.d. . postpartum and starting combined oral contraceptives formulated with 30-35 μ g ethinyl estradiol
- darunavir/cobicistat 800/150 mg q.d. or atazanavir/cobicistat 300/150 mg q.d. . postpartum and starting etonogestrel implant
- efavirenz 600mg q.d. postpartum and starting combined oral contraceptives formulated with 30-35 μ g ethinyl estradiol
- atazanavir/ritonavir/tenofovir 300/100/300 mg q.d. postpartum and starting combined oral contraceptives formulated with 30-35 μ g ethinyl estradiol

4.12 The woman must be stable on the ARV drug/drug combination and/or TB drug combination for at least two weeks prior to PK sampling.

- 4.13 If a woman is receiving a specific generic ARV formulation, the team has approved this formulation.
- 4.14 HIV-infected pregnant women must be planning to continue on current ARV regimen until postpartum PK sampling is completed. HIV-infected postpartum women on hormonal contraceptives must be planning to continue on ARV and contraceptive regimens until final PK sampling is completed.
- 4.15 For HIV-infected women:

Confirmed HIV infection, documented by positive results from two samples collected at different time points prior to study entry. All samples tested must be whole blood, serum or plasma. All test methods should be FDA-approved if available. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT central laboratory

Sample #1 may be tested in a non-study laboratory (e.g., laboratories used by participant's non-study medical providers and/or by PEPFAR and other public health programs). However, adequate source documentation, including the date of specimen collection, date of testing, test performed, and test result, must be available for filing in the participant's study chart. If such documentation is not available, Sample #1 should be tested in a CAP/CLIA approved laboratory (for US sites) or a laboratory that operates according to good clinical laboratory practice (GCLP) guidelines, participates in appropriate external quality assurance programs, and is approved by the IMPAACT Central Laboratory (for non-US sites).

Sample #1 may be tested using any of the following:

- Two rapid antibody tests from different manufacturers or based on different principles and epitopes
- One EIA OR WB OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One HIV RNA PCR (above the limit of detection)
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid

Sample #2 must be tested in a CAP/CLIA approved laboratory (for US sites) or a laboratory that operates according to GCLP guidelines, participates in appropriate external quality assurance programs, and is approved by the IMPAACT Central Laboratory.

Sample#2 may be tested using any of the following:

- Rapid antibody test. If this option is used in combination with two rapid tests for Sample #1, at least one of the three rapid tests must be FDA-approved and the third rapid test must be from a third manufacturer or based on a third principle or epitope.
- One EIA OR WB OR immunofluorescence OR chemiluminescence
- One HIV DNA PCR
- One HIV RNA PCR (above the limit of detection)
- One HIV culture (prior to August 2009)
- One total HIV nucleic acid

- 4.16 HIV-uninfected pregnant women must have documented negative HIV antibody test during current pregnancy.

Note: adequate source documentation, including the date of specimen collection, date of testing, test performed, and test result, must be available.

- 4.17 Participants enrolling in the 3rd trimester must enroll by 37 6/7 weeks gestation.
- 4.18 Participant can provide legal informed consent per local regulations.
- 4.19 If a woman has completed P1026s and becomes pregnant again, she may re-enroll in P1026s only if she is enrolled in a different arm than that studied during her initial enrollment.

4.2 Maternal Exclusion Criteria

- 4.21 Women on medicines known to interfere with absorption, metabolism, or clearance of the drug being evaluated (See Section 7.0). (rifampicin is permitted for women being evaluated for TB and ARV drug interactions).
- 4.22 Women if pregnant, carrying multiple fetuses.
- 4.23 Clinical or laboratory toxicity that, in the opinion of the site investigator, would be likely to require a change in the medicine regimen during the period of study.

4.3 Infant Enrollment Criteria

All infants of mothers enrolled during pregnancy (meeting criteria 4.111, 4.112, 4.113, and 4.114 specified above) are enrolled, in utero, immediately after maternal enrollment.

4.4 Infant Requirements for Washout Pharmacokinetic Sampling

Enrolled infants who meet the criteria specified below are eligible for Washout Pharmacokinetic Sampling

- 4.41 Born to HIV infected mother enrolled during pregnancy in an ARV arm (does not include infants born to HIV uninfected mothers receiving TB drugs).
- 4.42 Birth weight > 1000 grams
- 4.43 NOT receiving disallowed medications described in Section 7
- 4.44 Does not have any severe congenital malformation or other medical condition not compatible with life or that would interfere with study participation or interpretation, as judged by the site investigator.
- 4.45 Born after singleton delivery (not after multiple birth)

4.5 Enrollment Procedures

This protocol is open to IMPAACT US and non-US sites that have been approved to participate by the IMPAACT network. Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed 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 approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) for an amended version of the protocol *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.

A Site Implementation Plan (SIP) is required from each international site participating in the study. The plan must be submitted to the Protocol Team for review and approval before protocol registration can occur.

Written informed consent for study participation must be obtained before any study related procedures are performed.

If a woman has completed P1026s and becomes pregnant again, she may re-enroll in P1026s only if she is enrolling on a different arm than that studied during her initial enrollment. In this case, she may be re-registered to the protocol using a case identification (CID) number. The site must contact the DMC Randomization Desk to register women who become eligible for re-enrollment. The Randomization Desk will re-register the mother using the site's next available PID as the mother's CID. The site will then use the CID to identify the mother when filling out the forms for the second pregnancy.

4.6 Co-Enrollment Procedures

Co-enrollment into other protocols requires the approval of the protocol chairs of P1026s and the co-enrollment protocol.

4.7 Study Drug Formulations

No ARV drugs/drug combinations, TB drugs or contraceptive agents are supplied as part of this study. All drugs, including those being studied at non-standard doses, must be provided by participants' clinical care providers by prescription.

Participants may receive innovator (i.e., brand name or non-generic) or generic formulations of ARVs, TB drugs and contraceptives being studied in this version of the protocol. Unless stipulated in the protocol, generic ARV formulations must be a similar formulation, with similar expected bioavailability and drug release characteristics to the standard name-brand innovator formulation. Sites must contact the

protocol team prior to enrollment of participants receiving a specific generic ARV formulation to obtain approval for enrollment of participants receiving that specific formulation. All efforts should be made to ensure that participants receive the same product from the same manufacturer prior to all PK sampling periods. Protocol CRFs will record the name and manufacturer of each generic product used.

For pregnant women on DRV/r or LPV/r: Some women on these drugs/drug combinations may be receiving non-standard (increased) doses during pregnancy and therefore additional monitoring is warranted for the duration of the study. Women who change dosing of other drugs to non-standard doses due to PK results will also have additional monitoring. Additional monitoring guidelines are outlined in Appendix I-AMR.

Participants are expected to revert back to standard dosing after discharge; if not, the study pharmacologist should be consulted prior to PK sampling.

5.0 TOXICITY MANAGEMENT

5.1 Toxicity Monitoring

For women receiving DRV/r, LPV/r or other non-standard doses of ARVs or TB drugs, toxicity monitoring is as follows. In the event of treatment-limiting toxicity, other ARVs may be substituted for the drug thought to be responsible for the toxicity. It is critical to maintain good virologic control during pregnancy to decrease the risk of vertical transmission. Alternate explanations for Grade 3 toxicities must be sought prior to study drug discontinuation. For Grade 4 toxicities, study drug should be discontinued, the laboratory value should be repeated, and alternate explanations for the toxicity should be considered. Toxicities caused by underlying infections or processes or by drugs other than the study regimen will not necessarily result in dose interruptions. Abnormal clinical findings and laboratory values should be followed at least every 2 weeks until the toxicity resolves to a Grade 2 and below.

The general toxicity management schema is presented below, followed by specific guidelines for management of amylase, creatinine, proteinuria, gestational diabetes, and nausea/vomiting.

- Grade 1 and 2 Toxicity:

Continue the study regimen

- Grade 3 Toxicity:

Repeat laboratory evaluations within 72 hours to confirm. If the toxicity resolves to $\leq$ Grade 2, continue the study regimen.

Participants with confirmed drug-related $>$ Grade 3 toxicity should stop the study regimen and will be observed for resolution of the toxicity.

- If the toxicity does not resolve to $<$ Grade 2 within 14 days, the participant may switch to another antiretroviral regimen (or resume using standard adult doses if in the LPV/r or DRV/r study arm).
- If the toxicity resolves to $<$ Grade 2 within 14 days, restart the study regimen. If the toxicity recurs at $>$ Grade 3 after restarting the study regimen, the participant may switch to another antiretroviral regimen or resume standard adult doses if in the LPV/r or DRV/r study arm. Participants with persistent drug-related Grade $>$ 3 toxicity will stop the study regimen and will be observed for

resolution of the toxicity. Participants will continue to be followed on study but off study drug for routine safety/toxicity monitoring.

- Grade 4 Toxicity:

Stop the study regimen. Repeat laboratory evaluations within 72 hours to confirm. If the toxicity is life-threatening, the study regimen will not be restarted and the participant will be observed for resolution of the toxicity.

If the toxicity is non-life-threatening, the study regimen will be stopped, and the participant will be observed for resolution of the toxicity.

- If the toxicity does not resolve to $\leq$ Grade 2+ within 14 days, the participant will be off the study regimen and observed for resolution of the toxicity.
- If the toxicity resolves to $<$ Grade 2 within 14 days, restart the study regimen. If the toxicity recurs at $>$ Grade 3 after restarting the study regimen, the participant will discontinue the study regimen and be observed for resolution of the toxicity.

Specific Guidelines:

- Elevated Amylase
 - For Grade 3 elevations of total amylase, the participant should be evaluated for symptoms of pancreatitis, and lipase should be checked. If asymptomatic and lipase $< 2 \times$ ULN, the study regimen may be continued at the discretion of the site investigator, with notification to the team.
 - For Grade 4 elevations of total amylase, obtain fractionated values. If found to be mostly pancreatic, or if the participant is symptomatic or has a lipase $> 2 \times$ ULN, the study regimen will be held until the toxicity resolves to Grade ≤ 2 . If resolution occurs within 14 days and the initial episode was not life-threatening, restart the study regimen at the full dose. If symptomatic, lipase $> 2 \times$ ULN or Grade 4 elevations in fractionated pancreatic amylase recur, the study regimen should be stopped and the participant will be observed for resolution of the toxicity.
 - For $\geq$ Grade 3 elevations of pancreatic amylase, lipase should be checked.
- Creatinine
 - If $>$ Grade 1, evaluate for possible pre-eclampsia. The participant will be allowed to continue on the study regimen whether or not pre-eclampsia is present.
- Proteinuria
 - Proteinuria with pre-eclampsia: If Grade 2-4 proteinuria is confirmed and pre-eclampsia is present, the participant may continue the study regimen.
 - Proteinuria without pre-eclampsia: Follow routine toxicity management as specified in Section 5.1.
- Gestational Diabetes
 - The participant will be allowed to continue on the study and study regimen whether or not gestational diabetes is present.
- Nausea/Vomiting
 - If $>$ Grade 3 nausea/vomiting persists for more than 3 days, antiemetics should be used as needed. If the nausea/vomiting is thought to be drug-related and not pregnancy-related, and symptoms do not return to $<$ Grade 2 or to baseline within 14 days, stop the study regimen. If symptoms improve within 14 days, restart study regimen.

5.2 Bilirubin Toxicity Monitoring for Postpartum Women Receiving Atazanavir

If maternal total bilirubin ≤ 7.5 mg/dl and maternal direct bilirubin ≤ 2.5 mg/dl, no additional monitoring is required. If maternal total bilirubin > 7.5 mg/dl and/or maternal direct bilirubin > 2.5 mg/dl, follow toxicity monitoring guidelines according to grade as described above.

5.3 Criteria for Discontinuation

Participants must be discontinued from the study if:

- The participant or the participant's mother or legal guardian refuses further participation.
- The participant requires treatment with disallowed medications.
- The participant discontinues all medications being studied for the arm on which they enrolled and is not being monitored for safety/toxicity outcomes.
- The investigator determines further participation would be detrimental to the participant's health or well-being.
- The participant fails to comply with P1026s requirements, so as to cause harm to self or seriously interfere with the validity of the study results.
- The study is cancelled at the discretion of IMPAACT, the Food and Drug Administration (FDA), NIAID, the Office for Human Research Protections (OHRP), or the local and/or national IRB or EC.

6.0 EXPEDITED ADVERSE EVENT REPORTING

6.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (referred to as the DAIDS EAE Reporting Manual), dated January 2010, which is available on the RSC website at <http://rsc.tech-res.com>.

The 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 NIAID Clinical Research Management System at CRMSsupport@niaid.nih.gov. Questions may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites 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/expeditedreportingdaers.aspx>. For questions about EAE reporting, please contact the RSC (DAIDS RSCSafetyOffice@tech-res.com).

6.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Reporting Manual, will be used for this study. Reporting requirements apply to both study mothers and their infants.

The study agents for which relationship assessments are required are the drugs (and their boost counterparts) for which pharmacokinetic data is being obtained.

In addition to reporting all SAEs as defined above, other events that sites must report in an expedited fashion include fetal demises and Grade 4 hepatotoxicities whether or not symptomatic or related to study drug.

The death of any participant after enrollment or within 30 days of study completion, regardless of the cause, must be reported immediately and no later than 3 reporting days of first becoming aware of the death. After the 30-day period, deaths need to be reported only as part of long-term follow-up studies. If an autopsy is performed, the report must be provided. Reports of all deaths must be communicated as soon as possible to the appropriate IRB or EC and/or reported in accordance with local law and regulations.

For all SAE's submitted to RSC, sites must file an updated SAE report to RSC with the final or stable outcome (Status Code p. 5 of the EAE form) unless the SAE reported in the initial EAE form already had a final or stable outcome.

6.3 Grading Severity of Events

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, dated November 2014, (which can be at the following website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>) must be followed.

6.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is the entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).

After the protocol-defined AE reporting period, unless otherwise noted, only Suspected Adverse Events as defined in Version 2.0 of the EAE Reporting Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.0 DISALLOWED MEDICINES

Since some medicines interfere with the pharmacokinetic profile of an antiretroviral drug, the following medicines are disallowed for two weeks prior to PK sampling of that drug.

7.1 NRTIs

For tenofovir alafenamide fumarate, no medicines are disallowed.

7.2 NNRTIs

For efavirenz, the following medicines are disallowed:

- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Antifungal: voriconazole
- Antihistamines: astemizole, cisapride
- Calcium channel blocker: bepridil
- Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine
- Herbal products: St. John's wort (*Hypericum perforatum*)

- Neuroleptic: pimozide
- Protease Inhibitors: atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, telaprevir, tipranavir
- Sedative hypnotics: midazolam, triazolam

7.3 PIs

For *ALL* protease inhibitors, which includes atazanavir (Reyataz®), darunavir (Prezista®), lopinavir + ritonavir (Alluvia®), ritonavir (Norvir®) and the pharmacoenhancer cobicistat (Tybost®) the following medicines are disallowed:

- Alpha-1 adrenoceptor antagonist: alfuzosin
- Antiarrhythmics: amiodarone, flecanide, propafenone, quinidine
- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Antihistamines: astemizole, cisapride, terfenadine
- Antimycobacterial: rifampin [disallowed for ARV-only study arms, but allowed for women enrolled on the ARV/TB study arms]
- Calcium channel blocker: bepridil
- Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine
- Herbal products: St. John's wort (*Hypericum perforatum*)
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- Neuroleptic: pimozide
- Non-nucleosides: delavirdine, efavirenz, nevirapine
- Phosphodiesterase-5 inhibitor: sildenafil for the treatment of pulmonary arterial hypertension
- Sedative hypnotics: triazolam, orally administered midazolam

7.31 Atazanavir

For atazanavir, the following medicines are disallowed in addition to those listed above:

- Antineoplastic: irinotecan
- Protease inhibitor: indinavir
- Proton pump inhibitors: esomeprazole, lansoprazole, omeprazole, rabeprazole

7.32 Darunavir

For darunavir, the following medicines are disallowed in addition to those listed above:

- Antiarrhythmic: dronedarone
- Anti-gout: colchicine
- Anti-anginal: ranolazine

7.33 Ritonavir

For all ritonavir containing regimens, the following medicines are disallowed in addition to those listed in section 7.5:

- Antialcoholics: disulfiram, metronidazole
- Synthetic corticosteroid: fluticasone

7.34 Cobicistat

For cobicistat with either atazanavir or darunavir, the following medicines are disallowed in addition to those listed above:

- Antiarrhythmic: dronedarone
- Antineoplastics: irinotecan

7.4 Integrase Inhibitors

For dolutegravir, the following medicines are disallowed:

- Antiarrhythmic: dofetilide
- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Herbal products: St. John's wort (*Hypericum perforatum*)
- Non-nucleosides: delavirdine, efavirenz, etravirine, nevirapine
- Protease Inhibitors: atazanavir, darunavir, ritonavir, telaprevir, tipranavir

For elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, the following medicines are disallowed:

- Alpha-1 adrenoceptor antagonist: alfuzosin
- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Antifungals: ketoconazole, itraconazole, voriconazole
- Antimycobacterial: rifampin
- Ergot derivatives: dihydroergotamine, ergotamine, ergonovine, methylergonovine
- GI motility agents: cisapride
- Glucocorticoids: systemic dexamethasone
- Herbal products: St. John's wort (*Hypericum perforatum*)
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- Neuroleptic: pimozide
- Phosphodiesterase-5 inhibitor: sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension
- Protease Inhibitors: atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, ritonavir, tipranavir
- Sedative hypnotics: triazolam, orally administered midazolam

7.5 Tuberculosis (TB) drugs

For amikacin, the following medicine is disallowed:

- cidofovir

For bedaquiline, the following medicine is disallowed:

- moxifloxacin

For capreomycin, no medicines are disallowed.

For clofazimine, no medicines are disallowed.

For delamanid, the following medicines are disallowed:

- Strong CYP 3A4 inducers: carbamazepine, oxcarbazepine, phenobarbital, phenytoin

For ethambutol, no medicines are disallowed.

For ethionamide/prothionamide, no medicines are disallowed.

For isoniazid, the following medicines are disallowed:

- Anti-anginals: ranolazine
- Antiarrhythmics: dronedarone
- Antibiotics: furazolidone, linezolid
- Antineoplastic: procarbazine
- Anti-Parkinsonian: levodopa, selegiline
- Monoamine oxidase inhibitors: isocarboxazid, phenelzine, tranylcypromine
- Selective norepinephrine reuptake inhibitors: atomoxetine

For kanamycin, the following medicine is disallowed:

- cidofovir

For linezolid, the following medicines are disallowed:

- Monoamine oxidase inhibitors: isocarboxazid, phenelzine, tranylcypromine

For moxifloxacin, the following medicine is disallowed:

- Bedaquiline

For levofloxacin, no medicines are disallowed.

For ofloxacin, no medicines are disallowed.

For para-aminosalicylic acid (PAS), no medicines are disallowed.

For pretomanid, no medicines are disallowed.

For pyrazinamide, no medicines are disallowed.

For rifampicin, the following medicines are disallowed:

- Antifungals: voriconazole
- Calcium channel blocker: nifedipine
- Non-nucleosides: delavirdine, etravirine

For terizidone/cycloserine, no medicines are disallowed.

7.6 Combined Oral Contraceptives (COCs) and Etonogestrel Implant

For combined oral contraceptives or for etonogestrel implant, the following medicines are disallowed:

- Anticonvulsants: barbiturates, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate
- Antibiotics: rifampin, ampicillin, tetracyclines
- Anti-inflammatories: phenylbutazone
- Antifungal: griseofulvin, itraconazole, ketoconazole
- Herbal products: St. John's wort (*Hypericum perforatum*)
- Psychostimulants; modafinil

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This is a Phase IV prospective study to evaluate the pharmacokinetics of currently prescribed ARVs and TB drugs in pregnant women and ARVs and postpartum contraceptive agents prescribed in postpartum women. The washout PK of transplacentally acquired antiretroviral drugs will also be studied in infants born to mothers who enter the study during pregnancy.

The primary objectives are to describe the maternal pharmacokinetic parameters of the study drugs and compare these parameters to those from a suitable control group. The control group data to be used for these comparisons will vary according to the type of study drug (ARV, TB drug, or contraceptive) and may include (i) historical pharmacokinetic data reported in the literature or from previously-evaluated arms of P1026s, (ii) postpartum pharmacokinetic data from the same women who were sampled during pregnancy, (iii) pharmacokinetic data from pregnant HIV-uninfected women receiving the TB drugs of interest (but not the ARV drugs), and/or (iv) ARV pharmacokinetic data after initiation of contraceptives from the same women who were sampled before starting contraceptives (Please see Section 8.6 for details on the control groups to be used and comparisons to be made for each type of drug). The secondary objectives are to compare ARV and TB drug concentrations in plasma from cord blood with those in maternal plasma at the time of delivery, to assess plasma protein binding of selected ARVs, to assess ARV and HIV RNA concentrations in vaginal secretions and compare to simultaneous plasma concentrations, to explore genetic sources of variability in ARV exposure, to describe maternal and infant safety and clinical outcomes, to describe the neonatal elimination of selected ARV drugs acquired across the placenta after maternal dosing during pregnancy, and to describe the pharmacokinetics of ARV drug combinations in HIV-infected women on second line TB treatment.

The P1026s study design is opportunistic in that it enrolls women who are already receiving the study drugs as part of clinical care, but this design has one major limitation, namely that the results may be overly optimistic. Since participants must have been stable on the ARV drug/drug combination and/or TB drug combination for at least two weeks prior to PK sampling in order to enroll in the study, the study population will not include women who started the study drug and discontinued it within two weeks due to toxicity, intolerance, virologic failure, or any other reason. Thus, this study will not be able to identify pharmacokinetic, safety, or tolerance issues that occur very soon after drug initiation and estimates of the frequency of outcomes such as virologic response and mother-to-child HIV transmission may be overly optimistic. The fact that the results of this study will generalize only to the population of women who are able to stay on the study drugs for at least two weeks will be discussed as a limitation of the study in presentations and publications of results. The protocol team acknowledges this limitation, but feels that the PK data obtained using the current design will still be quite valuable nonetheless.

8.2 Outcome Measures

8.21 Primary Outcome Measures

8.211 For ARVs and first-line TB drugs: The target pharmacokinetic parameter specified in Appendix V and other pharmacokinetic parameters listed in Section 9.24

8.212 For second-line TB drugs: Pharmacokinetic parameters listed in Section 9.24

8.213 For contraceptives: Concentration in plasma

8.22 Secondary Outcome Measures

- 8.221 Ratio of cord blood concentration to maternal blood concentration
- 8.222 Ratio of unbound/total drug concentrations for the highly bound ARVs specified in section 9.0
- 8.223 Rate of detection of study drugs in vaginal secretions; ratio of vaginal drug concentrations to simultaneous blood concentrations; rate of detection of HIV RNA/DNA in vaginal secretions and comparison to level in blood
- 8.224 ARV and TB drug exposure (as measured by area under the curve or other PK parameters) during pregnancy and postpartum according to genotype
- 8.225 Maternal and infant safety and clinical outcomes, including adverse events of grade 3 or higher and infant neurological events of grade 1 or higher, according the DAIDS toxicity grading table; adverse pregnancy outcomes including preterm birth, low birth weight, and fetal demise; congenital anomalies; and infant HIV infection status as defined according to the most current IMPAACT definition.
- 8.226 Infant washout pharmacokinetics parameters listed in Section 9.24
- 8.227 ARV exposure (as measured by area under the curve or other PK parameters) during pregnancy and postpartum.

8.3 Randomization and Stratification

None.

8.4 Sample Size and Accrual

8.41 Sample Size

The sample size calculations will be based on assessing whether therapeutic dosing regimens for the study drugs produce adequate drug exposure during pregnancy as compared to historical data from non-pregnant adults. Such observations will be assessed to determine, if possible, whether the level of exposure to these drugs during pregnancy is adequate, or inadequate, based upon current knowledge.

The PK exposure parameter of primary interest for sample size calculations will be the area under the curve (AUC), as determined from 12 hour sampling or 24 hour sampling (Refer to Appendix III for the sampling schedule for each drug). The AUC is commonly treated as following a log-normal distribution.

Each study arm will enroll a minimum of 12 women and have a target enrollment of 25 women with evaluable 3rd trimester PK data for ARV and TB arms, or evaluable postpartum PK data for oral contraceptive arms. Women who do not have evaluable data will be replaced. Enrollment may be restricted or adjusted so that evaluable 2nd trimester PK data are obtained from at least 12 women. The sample size for an arm may also be increased if additional mothers and infants need to be enrolled to obtain evaluable infant washout PK data. Thus, the total number of participants enrolled per arm may be larger than 25 if women need to be replaced due to non-evaluable data, if additional women need to be enrolled to obtain 2nd trimester PK data, if additional mothers and infants need to be enrolled to obtain infant washout PK data and/or if additional women need to be enrolled to obtain enough second line TB

drug data. When combined enrollment in the increased dose darunavir arms reaches 25 participants, the PK data will be evaluated to determine if the data for these arms can be combined and whether enrollment of additional participants in these arms should continue. Geometric means and 90% confidence intervals for oral clearance and key dose-adjusted parameters such as AUC, $C_{\max}$ and C_{trough} from both groups will be compared and enrollment will be stopped if these data are dose-proportional over this small dose range.

The actual sample size will be based on the determination of PK exposure parameters, and whether or not the current dose provides adequate drug exposure to pregnant women. Based on data regarding drugs presently under study, the major concern is that the drug exposure in pregnant women might be lower than that seen in the non-pregnant population. Interim pharmacokinetic exposure monitoring will be implemented which compares each pregnant woman's values to the distribution from a non-pregnant population, so that the question of whether the dose is too low will be tested by comparison to historic controls. Adequate exposure will be defined as fewer than 6 out of 25 pregnant women having PK exposure parameters below the 10th percentile for the non-pregnant population, because the team considers that having more than 20% of the women below the 10th percentile would be unacceptable. Consequently, if 6 or more of the pregnant women have PK exposure parameters below the 10th percentile, it will be concluded that the PK exposure in the pregnant population is lower than that of non-pregnant population. Given the discrete nature of the data, if 6 or more participants have low PK exposure parameters, the lowest sample probability that can be achieved is 24%, 6 out of 25, and the exact 80% confidence limits are (13%, 38%). These confidence limits exclude the tenth percentile and indicate that the team is at least 90% confident that the true percentage of pregnant women having PK parameters below the 10th percentile for the non-pregnant population is > 10%. Note that the 10th percentile from the non-pregnant historic controls is being treated as a constant.

Table 2 provides the probability of finding the exposure of the pregnant population to be lower than that of the non-pregnant population given the current dose with a sample size of 25 evaluable women. Consider four possible true cumulative probabilities in the pregnant population for the value of the 10th percentile from the non-pregnant population. If the true cumulative probability corresponds to .10 in the pregnant population the probability of finding the populations different is small (< 4%). If the true cumulative probability reaches .30 then the probability of finding a difference goes to .81. Finally, if it reaches .40 then the probability of finding a difference is .97, indicating that 3% of the time a difference will not be found.

Table 2: Probabilities of finding the exposure of the pregnant population to be lower than that of the non-pregnant population with a sample size of 25 evaluable women

True cumulative probability associated with the value for the 10 th percentile from the non-pregnant population in the pregnant population	Probability of finding the exposure of the pregnant population to be lower than the non-pregnant population
.10	.033
.20	.38
.30	.81
.40	.97

Antiretroviral and TB drugs will also be studied in a repeated measures design, in which each woman will be measured during pregnancy and postpartum, or in the second and third trimester, or before and after starting contraceptives, depending on the specific drug being studied. The comparisons will be made at the within participant level, using the Wilcoxon signed-rank test and 90% confidence limits for the geometric mean ratio of the PK exposure parameter in the two conditions (pregnant versus non-pregnant,

or second versus third trimester, or before versus after starting contraceptives). At this stage of the analysis, the test and confidence interval are assessing whether the drug exposure differs in the two conditions.

Table 3 illustrates the width of the confidence limits and whether they would exclude the value of 1.0 according to the standard deviation and observed point estimate, assuming that 12 participants have both antepartum and postpartum (or both second and third trimester or both pre- and post-contraceptive initiation) PK parameter measurements. If the confidence limits exclude 1.0, this would indicate that the PK exposure parameter is significantly lower (or higher) in one condition than in the other, with one-sided p-value <0.05 (two-sided p-value <0.10). The dark shaded areas represent cases where the confidence limits exclude the value 1.0. For example, if the geometric mean of the observed ratios is 1.0 and the standard deviation (SD) of the natural log observed ratio is 0.3, then the 90% confidence interval would be 0.86 to 1.17 so the true ratio of the geometric mean PK exposure parameter is likely to be close to one with high confidence. These results would indicate that no statistically significant difference between the pregnant and non-pregnant conditions was observed. For a SD of 0.3, the ratio would need to be as large as 1.25 (or as small as 0.80 to indicate a detectable difference between the two conditions (that is for the confidence limits to exclude the value 1.0). If the SD is 0.5 or 0.7, a ratio of 1.5 or greater (or 0.67 or smaller) would be required to indicate a detectable difference. If the SD is 0.9 or higher, a ratio of 2 or greater (or 0.5 or smaller) would be required to indicate a detectable difference. When there are more than 12 participants in a study arm who have both antepartum and postpartum (or both second and third trimester or both pre- and post-contraceptive initiation) PK parameter measurements, the confidence intervals will be narrower than those given in Table 3, and we will have a higher power to detect any difference in the ratio.

Note: The above examples are provided to give the reader a sense for the magnitude of the differences that will be detectable, based on the information in the following table. During the study, confidence limits will be calculated for the actual observed ratios and standard deviations.

Table 3: 90% Confidence Limits for the Geometric Mean Ratio of the PK Exposure Parameter (n=12)

SD	OBS_RATIO	Lower Confidence Limit (LCL)	Upper Confidence Limit (UCL)
0.3	0.25	0.21	0.29
	0.5	0.43	0.58
	0.67	0.57	0.78
	0.80	0.68	0.94
	1	0.86	1.17
	1.25	1.07	1.46
	1.5	1.28	1.75
	2	1.71	2.34
0.5	4	3.42	4.68
	0.25	0.19	0.32
	0.5	0.39	0.65
	0.67	0.52	0.87
	0.80	0.62	1.04
	1	0.77	1.30
	1.25	0.96	1.62
	1.5	1.16	1.94
0.7	2	1.54	2.59
	4	3.09	5.18
	0.25	0.17	0.36
	0.5	0.35	0.72
	0.67	0.47	0.96
	0.80	0.56	1.15
	1	0.70	1.44
	1.25	0.87	1.80

SD	OBS_RATIO	Lower Confidence Limit (LCL)	Upper Confidence Limit (UCL)
	1.5	1.04	2.16
	2	1.39	2.88
	4	2.78	5.75
0.9	0.25	0.16	0.40
	0.5	0.31	0.80
	0.67	0.42	1.07
	0.80	0.50	1.28
	1	0.63	1.60
	1.25	0.78	1.99
	1.5	0.94	2.39
	2	1.25	3.19
	4	2.51	6.38
1.1	0.25	0.14	0.44
	0.5	0.28	0.88
	0.67	0.38	1.18
	0.80	0.45	1.41
	1	0.57	1.77
	1.25	0.71	2.21
	1.5	0.85	2.65
	2	1.13	3.54
	4	2.26	7.07

OBS_RATIO is the anti-log of the mean of the log ratios of the PK exposure parameters for the pregnant versus non-pregnant conditions (or 2nd vs. 3rd trimester, or pre- vs. post-contraceptive initiation).

SD represents SD of the natural log of the observed ratio (OBS_RATIO).

LCL and UCL are the lower and upper confidence limits, respectively, assuming a Student's t distribution with n=12.

The dark-shaded rows represent cases where the CI excludes the value 1.0, indicating that the PK exposure differs significantly in the pregnant vs. non-pregnant conditions (or 2nd vs. 3rd trimester, or pre- vs. post-contraceptive initiation).

Based on past experience, standard deviations on the log scale of the order of 0.5 to 1.1 are likely for PI-containing regimens, whereas regimens containing only NRTIs tend to have smaller values. For the completed LPV/r arm, the standard deviation of 12 participants having both antepartum and postpartum AUC measurements was 0.68. For the completed ABC arm, the standard deviation of 17 participants was 0.31.

8.42 Accrual

As of October 8, 2015, a cumulative total of 766 women and 316 children had been enrolled under P1026s protocol Versions 2.0-5.0 and 7.0-9.0 (Versions 1.0 and 6.0 did not open to enrollment). Over the preceding 12 months, the monthly accrual ranged from 14-17 women and 1-12 infants. In Version 10.0, 8 new treatment arms have been opened and 10 treatment arms from Version 9.0 have been retained. The total number of new enrollments to be expected under Version 10.0 is very difficult to determine, because the actual enrollment to each arm and total enrollment to P1026s will depend on several factors:

- Each study arm will have a target enrollment of 25 women with evaluable 3rd trimester PK data for ARV and TB arms, or evaluable postpartum PK data for oral contraceptive arms;
- When combined enrollment in the increased dose darunavir arms reaches 25 participants, the PK data will be evaluated to determine if the data for these arms can be combined and whether enrollment of additional participants in these arms should continue;
- Women who do not have evaluable data will be replaced, but will still be counted in the enrollment for that arm (which may therefore exceed 25);
- Enrollment to an arm may be restricted or adjusted upward (above 25) so that evaluable 2nd trimester PK data are obtained from at least 12 women;

- All infants of women enrolled in the antepartum arms of P1026s will be enrolled in utero (immediately after maternal enrollment) and counted in the total enrollment to P1026s;
- Enrollment to an arm may be adjusted upward (above 25) to obtain additional evaluable infant washout PK data;
- Enrollment to an arm may be adjusted upward (above 25) to obtain additional second line TB drug data;
- An arm may be closed early due to slow accrual;
- An arm may be closed early if PK targets are not met in 6 women, at any time after at least 12 women have been enrolled.

Thus, although the total number of participants actually enrolled in a given arm may be more or less than 25, if the 10 retained arms in Version 9.0 were to complete enrollment of 25 evaluable women per arm (which would require enrollment of at least 136 additional women and 113 additional infants), the 8 new arms were to enroll 25 evaluable women per arm (which would require enrollment of at least 200 women and 150 infants), 15% of women (and their infants) need to be replaced due to lack of evaluable PK data, one would expect approximately 395 new maternal enrollments and 309 new infant enrollments to P1026s Version 10.0.

8.5 Monitoring

8.51 Interim PK Exposure Monitoring During Pregnancy (for ARVs only)

Based on data regarding the ARV drugs presently under study, the major concern is that the ARV drug exposure in pregnant women will be lower than that of the non-pregnant population, and the interim PK exposure monitoring rules are designed to detect this scenario quickly. In each study arm, at any time after a minimum of 12 participants have been enrolled, if six or more pregnant women have the third-trimester PK exposure parameter below the 10th percentile for the non-pregnant population, the study team will evaluate the adequacy of drug exposure in that arm, and with the agreement of the medical officers, determine whether enrollment to that arm should continue. The exact 80% confidence limits for 6 participants with low drug exposure out of a total of 25 are (0.13, 0.38), which exclude 10% and indicate strong evidence that the distribution of the PK parameter of interest for the pregnant women is different from that for the non-pregnant women. If a statistical difference appears to be clinically important, then enrollment into that study arm will stop and a new study arm at a higher dose will be developed, if feasible.

8.52 Replacement

Participants will be replaced if their antepartum ARV or TB pharmacokinetic data are deemed unevaluable. A participant's antepartum pharmacokinetic data will be deemed unevaluable for the Stage 1 analysis (described in Section 8.6), if they do not have adequate pharmacokinetic evaluations to determine the PK exposure parameter.

Additional participants will be enrolled to any arm in which fewer than 12 participants have evaluable postpartum pharmacokinetic data. A participant's data will be deemed unevaluable for the Stage 2 analysis (described in Section 8.6), if (a) they do not have adequate pharmacokinetic evaluations to determine the PK parameters of interest under both the pregnant and non-pregnant conditions (or both 2nd and 3rd trimester, or both pre- and post-contraceptive initiation), or (b) the patients' dosing regimen changed between the pregnant and non-pregnant conditions (or between the 2nd and 3rd trimester evaluation, or between the pre- and post-contraceptive initiation evaluation) in a way that was not specified in the protocol, or (c) there is a change in the underlying treatment during that time period (e.g.,

no longer receiving study drug, or receiving a disallowed medication). Changes in underlying treatment as well as data completeness will be monitored in order to replace unevaluable patients in a timely fashion

An integral part of this protocol is reporting ARV drug assay results to the clinical caregivers of the participants. Knowledge of these results may impact which patients complete the sampling protocol without an ARV dosing change and which patients receive an ARV dosing change and need to be replaced. In this way the replacement of unevaluable patients may introduce a selection bias into the population available for the within patient comparison of the pregnant and non-pregnant condition. This potential bias is an inescapable consequence of the study design, but is outweighed by the ethical imperative to provide all potentially valuable clinical information to study participants.

8.6 Analysis

The data analyses to address the primary objectives for each study arm will include descriptive statistics and the comparisons below. The mean as a measure of location and the standard deviation as a measure of dispersion as well as other descriptive statistics of interest will be calculated, along with confidence intervals. Within-participant comparisons (e.g., between pregnant versus non-pregnant conditions, second versus third trimester, or before versus after starting contraception) will be performed for continuous outcome measures using the Wilcoxon signed-rank test and for dichotomous outcome measures using McNemar's test. Between-participant comparisons will be performed for continuous outcome measures using the Wilcoxon rank-sum test and for dichotomous outcome measures using the chi-square or Fisher exact test. 90% confidence limits for the geometric mean ratio of the PK exposure parameter in the pregnant versus non-pregnant conditions (or before versus after starting contraception) will also be calculated to describe the range of values that are consistent with the observed data and help the protocol team assess whether there is a clinically important difference in exposure in the two conditions. The confidence coefficient will be 90% rather than 95% to match the usual practice in the pharmacokinetic literature. For infant washout PK data, ARV taken with second-line TB drugs, and other secondary objectives, descriptive statistics will be summarized.

As noted in Section 8.1, the comparisons to be performed to address the primary objectives will vary according to type of drug and timing of sampling. Table 4 summarizes these comparisons. The analysis of ARV drug PK parameters during pregnancy will follow a two or three stage approach. In Stage I, an individual woman's PK exposure parameter during pregnancy will be compared in real time to the 10th percentile for that PK exposure parameter for that drug from a non-pregnant population, and the woman and her clinical provider will be notified if the woman's value is below the 10th percentile. If there is strong evidence that the true percentage of pregnant women having the PK exposure parameter below the 10th percentile for the non-pregnant population is greater than 10%, the study team will evaluate whether to stop enrollment early and whether to recommend that additional study of the drug/drug combination is necessary. (See Interim Exposure Monitoring in Section 8.51.)

Table 4: Pharmacokinetic Parameter Comparisons to be Performed for Each Type of Drug for the Primary Objectives

Type of Drug	Analysis Stage	Description of Pharmacokinetic Parameter Comparison	Type of Comparison
ARV without TB Drugs	Stage 1	Antepartum PK parameter vs. 10 th percentile from external, non-pregnant population	Between-participant
	Stage 2	Antepartum vs. postpartum PK parameters	Within-participant
ARV with First Line TB Drugs	Stage 1	Antepartum ARV PK parameter vs. 10 th percentile from non-pregnant population	Between-participant
	Stage 2	Antepartum vs. postpartum ARV PK parameters	Within-participant

	Stage 3	ARV PK parameter with TB drugs vs. ARV PK parameter without TB drugs in previous P1026s arm	Between-participant
First Line TB drugs with ARVs (HIV+) and First Line TB drugs without ARVs (HIV-)	Stage 1*	Antepartum TB drug PK parameter vs. 10 th percentile from non-pregnant population	Between-participant
	Stage 2	Antepartum vs. postpartum TB drug PK parameter, separately for HIV+ and HIV-	Within-participant**
	Stage 3	TB drug PK parameter with ARV (HIV+) vs. TB drug PK parameter without ARV (HIV-)	Between-participant
Second Line TB drugs with or without ARVs	Stage 2	Antepartum vs. postpartum TB drug PK parameters	Within-participant**
ARV with Contraceptives [#]	Stage 2	Postpartum ARV PK parameter before vs. after starting contraceptives	Within-participant
Contraceptives with ARVs	Stage 3	Postpartum contraceptive concentration with ARV vs. external historical controls not receiving ARV	Between-participant
*Stage 1 analysis for the TB drugs will not be done in real time and will only be done when batched PK data are available (unlike the Stage 1 analysis for ARVs). **This comparison may have a smaller sample size than 25 because some women may complete their TB treatment before the postpartum PK visit. [#]Interim AUC monitoring (Stage 1 analysis) is not done for these arms (only done during pregnancy).			

Stage 2 for the ARV drugs taken during pregnancy will implement a repeated measures design, in which antepartum and postpartum measurements from each woman will be compared. This stage requires a minimum of 12 participants in each arm to have postpartum PK measurements. If less than 12 participants out of the 25 in any arm have postpartum measurements, more participants will be enrolled in that arm until the minimum postpartum measurement number of 12 is reached. The comparisons will be made at the within participant level, using the Wilcoxon signed-rank test to assess whether there is a statistically significant difference in the PK exposure parameter in the pregnant versus non-pregnant conditions. 90% confidence limits for the geometric mean ratio of the PK exposure parameter in the pregnant versus non-pregnant conditions will also be calculated to describe the range of values that are consistent with the observed data and help the protocol team assess whether there is a clinically important difference in exposure in the pregnant versus non-pregnant conditions.

For the ARV drugs being taken with first-line TB drugs, in addition to Stages 1 and 2, a third stage of analysis (Stage 3) will be performed which will compare the ARV PK exposure with first-line TB drugs to the PK exposure for these ARVs without first-line TB drugs in previously evaluated arms of the P1026s study. This analysis will involve a between-participants comparison of PK exposure parameters using the two-sample Wilcoxon rank sum test. 90% confidence limits for the geometric mean ratio of the PK exposure parameters in the two groups of women will also be calculated.

For the first-line TB drugs, a Stage 1 analysis similar to that described above will be performed but only after completion of the concentration assays following batch shipment (refer to Section 3.3). Since the TB drug samples will not be shipped and assayed in real time and the duration of TB drug treatment is time limited, the participant may no longer be receiving the TB drug being studied when the TB drug assay results become available. The PK analysis for the first-line TB drugs will also include the Stage 2 approach described above, in which a within-participants comparison of TB drug PK exposure during pregnancy and postpartum will be performed, separately for HIV-infected and HIV-uninfected women in

each study arm. Note that the sample size for this comparison may be less than the desired 25 evaluable women if some women complete their TB medication course before the postpartum visit where the PK sampling will be done. In addition, a Stage 3 between-participants comparison of first-line TB drug PK exposure in HIV-infected versus HIV-uninfected women will be performed (using the two-sample Wilcoxon rank sum test) to assess whether exposure to first-line TB drugs differs with vs. without concomitant ARV drug use and presence of HIV-infection. Note that if a significant difference is observed in the between-participants analysis, it will not be possible to determine whether this difference is due to ARV use or HIV infection.

For the second-line TB drugs, the PK analysis will use the Stage 2 approach described above, in which a within-participants comparison of TB drug PK exposure during pregnancy and postpartum will be performed. Note that the sample size for these comparisons may be less than the desired 25 evaluable women per drug because the inclusion criteria for this study arm only require that women are receiving at least two of the specified second-line TB drugs, and because some women may complete their TB medication course before the postpartum visit where the PK sampling will be done. It may or may not be possible to perform a Stage 3 between-participants comparison of second-line TB drug PK exposure in HIV-infected versus HIV-uninfected women; depending on the number of women receiving each TB drug, it may be necessary to combine data from HIV-infected and HIV-uninfected women.

For the ARV drugs being taken with postpartum contraceptives, the Stage 1 analysis above will not be performed (the Stage 1 analysis will only be done for ARV during pregnancy). A within-participants analysis similar to the Stage 2 analysis described above will be performed, except that the ARV PK exposure parameters before versus after starting contraceptives will be compared (instead of during pregnancy versus postpartum).

For the contraceptives, a stage 3 analysis will be performed that will compare the contraceptive concentrations observed in P1026s women receiving a protease inhibitor to data from historical controls not receiving ARVs, as reported in the available literature.

9.0 CLINICAL PHARMACOLOGY PLAN

9.1 Objectives

This study's primary objectives are to 1) determine the PK of antiretroviral drugs used as part of the management of pregnant HIV-infected women and to compare drug exposure among pregnant women with that of a) historical data in non-pregnant women and b) the same women postpartum; 2) describe and compare the concentrations of selected ARV and first line TB drugs in HIV-infected and first line TB drugs in HIV-uninfected pregnant women; 3) describe and compare the concentrations of selected second line TB drugs in HIV-infected and HIV-uninfected pregnant women; 4) determine ARV concentrations in postpartum women before and after starting the use of hormonal contraceptives (combined oral contraceptives (COCs) and etonogestrel implants); and 5) determine hormone concentrations in women using hormonal contraceptives and selected ARV drugs. Such observations will be assessed to determine, if possible, that the level of exposure to these drugs during pregnancy or postpartum is adequate, or inadequate, based upon current knowledge. This study has 7 secondary objectives: a) to compare ARV and TB drug concentrations in plasma from cord blood with those in maternal plasma at the time of delivery, b) to determine plasma protein binding of highly bound ARVs (>85% bound) during pregnancy and postpartum, c) to describe and compare ARV concentrations and HIV RNA/DNA concentrations in maternal blood and genital secretions, d) to explore genetic sources of ARV and TB drug exposure variability in pregnancy and postpartum, e) to describe maternal and infant safety and clinical outcomes f) to describe the neonatal elimination of selected ARV and TB drugs acquired across the placenta after

maternal dosing during pregnancy and g) to describe the pharmacokinetics of ARV drug combinations in HIV-infected women on second line TB treatment.

There are few clinical trials describing the pharmacokinetics of ARV, antituberculosis and/or hormonal contraceptives in pregnant and postpartum women, limiting our ability to design appropriate dosing schedules for these agents in HIV-infected pregnant and postpartum woman. Overdosing may lead to maternal and/or fetal toxicity. Under dosing may lead to inadequate efficacy. An understanding of the pharmacokinetics of ARV and antituberculosis drugs during pregnancy and hormonal contraceptives postpartum is necessary for the safety and well-being of both HIV-infected mothers and their infants.

9.2 Primary and Secondary Data to be Accessioned

9.21 Pharmacokinetic sampling data

- 9.211 Dosing history (date, time and amount of last two doses of study drug prior to study dose and of study dose)
- 9.212 Last two maternal meals to include dates, times, description
- 9.213 Pre-pregnancy weight and height at initial PK sampling, and weight at subsequent PK sampling visits and at or within 2 weeks before delivery
- 9.214 Date and time PK samples drawn
- 9.215 Ratio of unbound/total drug concentrations, if unbound drug measured
- 9.216 Date and time of vaginal PK sampling
- 9.217 Date and time when COC were started and the last dose was taken
- 9.218 Date of etonogestrel implant insertion
- 9.219 Genotype of drug metabolizing enzymes (CYP P450)

9.22 Delivery data

- 9.221 Date, time and amount of last doses before delivery of all ARV agents
- 9.222 Date and time of delivery
- 9.223 Date and time of maternal blood drawing
- 9.224 Date and time cord blood obtained

9.23 Demographic and historical data

- 9.231 Maternal age and ethnicity
- 9.232 Infant gestational age, birth length and weight
- 9.233 Date, time and amount of last doses of all other medicines taken in last 7 days

- 9.234 Maternal laboratory studies: liver function tests (ALT, AST, bilirubin), renal function tests (creatinine, BUN), albumin, Hgb, total amylase, lipase, genotype, phenotype

9.24 Pharmacokinetic Parameters

- 9.241 Maternal limited sampling schedule: Pre-dose concentration, T_{max}, C_{max}, AUC for all drugs. C_i/F, V/F, t_{1/2} if data sufficient or population analysis undertaken.
- 9.242 Maternal full sampling schedule: Pre-dose concentration, C_{min} (end of sampling interval), T_{max}, C_{max}, AUC, C_i/F, V/F, t_{1/2}.
- 9.243 Infant washout sampling: t ¹/₂, drug concentrations
- 9.244 Genital secretions: ARV concentrations in vaginal secretions and plasma

9.25 Infant HIV infection status

9.3 Study Design, Modeling and Data Analysis

This study will determine the pharmacokinetics of ARV drugs, antituberculosis drugs and hormonal contraceptives in pregnant and postpartum women receiving standard and non-standard adult doses of these drugs as part of routine clinical care and the washout pharmacokinetics of transplacentally acquired antiretroviral and TB drugs in infants born to mothers receiving antiretroviral drugs during pregnancy. In some arms, pregnant women will be enrolled who are receiving increased doses of the antiretroviral drug of interest. If so, dose reduction to the standard adult dose will occur upon postpartum discharge from the hospital. Pregnant participants may enroll in the second or third trimester. Pharmacokinetic sampling will be performed during the third trimester and postpartum for all pregnant participants and in the second trimester as well for those pregnant participants enrolling in the second trimester. Eligible women will be those HIV- infected or uninfected pregnant or postpartum women receiving treatment as part of clinical care with any of the specified ARV drugs, antituberculosis drugs or contraceptive agents, for which adequate pregnancy pharmacokinetic data are lacking. Pharmacokinetic parameters will be compared during pregnancy and postpartum or prior to and after 6-7 weeks of postpartum contraceptive treatment and the potential influence of concomitant medications and drug metabolizing genotype will be assessed. For pregnant participants, samples of maternal blood at delivery and of cord blood will be obtained in order to allow comparison of maternal and fetal plasma ARV concentrations at birth. Genital secretion samples will also be obtained from pregnant participants and compared to simultaneous plasma concentrations for ARV during pregnancy. Washout pharmacokinetics of transplacentally acquired drug will be determined in infants born to mothers receiving ARV and TB drugs during pregnancy.

9.31 Laboratory Analysis and Reporting

Site: All PK samples will be registered in the Lab Data Management System (LDMS) database. The study database will be kept up to date by close tracking of samples. Plasma samples will be sent to the UCSD Pediatric Clinical Pharmacology Laboratory (PCPL) or other specified pharmacology laboratories participating in an ACTG QA/QC Pharmacology program. Such laboratories include but are not limited to the IMPAACT Chiang Mai Pharmacology Laboratory and the Pharmacology Laboratory of the University of Cape Town. Plasma samples will be assayed for concentrations of ARV drugs, antituberculosis drugs and/or hormonal contraceptives. All samples will be destroyed after the primary assays have been completed for the pharmacokinetic and protein-binding studies.

Methods to be used: All methods will be standardized with a filed Methods Report, under Good Laboratory Practice (GLP) conditions such as those currently used in the UCSD PCPL, the Chiang Mai laboratory and the Pharmacology Laboratory of the University of Cape Town, or will be derived from published methods.

Reporting of Assay Data: For ARVs during pregnancy, assays will be batched by participant PK visits aggregated in sufficient participant numbers to provide a routine assay group [n=25-30 samples]. These will be performed during each week, and in a reasonable time frame to achieve reporting every week, in order of receipt of samples from sites within a week of sample receipt into the laboratory. Participant assay data will be reported to the site investigator and to the DMC from the pharmacologist. Initial data reports will include estimated AUC and a comparison with a concentration-time profile for the appropriate drug derived from non-pregnant adult data for all regimens, which will be reported to the site investigator regardless of plasma level. In cases where the PK parameter of interest (AUC or C_{min}) is below the 10th percentile for that drug, compared to non-pregnant adult values, the assay report will enclose a notice to the site investigator that this level may be lower than expected therapeutic levels. This notice will advise the site investigator advice may be solicited from a study pharmacologist regarding a change in dosing regimen of the drug reported. If so, request is made to the study pharmacologist and DAIDS medical officer by e-mail. If any change in the dose of the drug is made to such participants, the site investigator may request that a second series of PK plasma samples be analyzed and reported on a schedule arranged between the assay laboratory and pharmacologist. The team should be notified by e-mail of any changes made to the participant's regimen. These changes will also be recorded on the appropriate CRF.

Samples to be assayed for TB drug or hormonal contraceptive assays will be batch shipped to the appropriate laboratory at the request of the protocol team. TB drug assay results and initial pharmacokinetic interpretation will be reported back to the DMC, the participant and her clinical caregiver shortly after completion of the assays. Hormonal contraceptive assay data will not be reported back to the participant and her clinical caregiver.

Aggregated data reports for each individual drug will be constructed by the UCSD PCPL and periodically reported out to the protocol team and the data management center.

9.32 PK sampling schedules and analysis

- 9.321 A limited maternal sampling schedule of 5-6 samples collected over the first half of a dosing interval will be used for drugs that have demonstrated linear pharmacokinetics, predictable absorption and no significant circadian variability in pre-existing pharmacokinetic data from non-pregnant individuals. The concentration data collected for these drugs will be analyzed by inspection to determine pre-dose concentration, T_{max}, C_{max} and by Bayesian modeling to estimate AUC. Additional pharmacokinetic parameters (Cl/F, V/F, t_{1/2}) will be determined by traditional or population pharmacokinetic techniques if there are pre-existing pharmacokinetic data to support the analytic approach and if there are sufficient data points available to make the effort potentially valuable. Population analysis will be performed using the computer program NONMEM.
- 9.322 A full maternal sampling schedule of 7-8 samples collected throughout an entire dosing interval will be used for drugs with known or suspected non-linear pharmacokinetics, erratic absorption and/or significant circadian variability. All of the currently available protease inhibitors fall into this category. Standard pharmacokinetic analyses using model dependent and independent pharmacokinetic approaches will be used to analyze the full

sampling schedule drug concentration data. These analyses will be carried out by the team pharmacologists, or by other IMPAACT pharmacologists, as decided by the protocol team.

- 9.323 Infant washout sampling will be collected as specified in Appendix II. Pharmacokinetic analysis will include descriptive statistics of drug concentrations and estimation of elimination $t_{1/2}$.
- 9.324 Aggregate PK Analysis: Analysis of PK data for all drugs will be performed in the UCSD Section on Pediatric pharmacology routinely. Aggregated PK analytical data will be reported to the pharmacologists and the data management center routinely. Aggregated files of analyzed PK data will be kept at the UCSD laboratory for regular additions and management. Reports will be written and distributed as necessary for presentations and publications.
- Standard pharmacokinetic analyses will be performed when sufficient data are accumulated in the aggregate data reports on all drugs studied. Model dependent and independent traditional pharmacokinetic approaches will be used to analyze drug concentration data on those drugs for which sampling is conducted over the entire dosing interval. These analyses will be carried out by the team pharmacologists, or by other pharmacologists decided by the protocol team.
 - Population and physiologic based pharmacokinetic techniques may be used to analyze data for those drugs for which sample collections are not gathered over the entire dosing interval, if there are sufficient data points available to make this effort potentially valuable and if this effort is necessary, at all, in support of other pharmacokinetic data in a given drug group. This will be accomplished using Mixed Effects Modeling with a computer program such as NONMEM [NONlinear Mixed Effects Modeling version VI or later] analyzing data comprised of repeated measurements in non-linear systems. Individual variation in drug clearance may be explained by individual differences in fixed effects, such as age, weight, pregnancy status and pharmacogenics as well as random error. This combination of "fixed" and "random" effects makes up the "mixed" effects used in the models. By describing these fixed effects, the relationships among the PK parameters and participant clinical attributes may be determined. Model development will be performed in 3 steps, as described by Mandema, et al. (93), with oversight by Dr. Edmund Capparelli of the UCSD Pharmacology Laboratory.

Typical concentration-time profiles for each drug will be constructed with Monte Carlo simulations of study participants and the final population model, parameters and variability. Final parameter estimates and simulations will be compared within participants and/or with those from non-pregnant adult populations.

- 9.325 Statistical approach - See Section 8.0
- 9.326 Anticipated Outcomes - The data from this study will describe maternal ARV PK assessments during and after pregnancy, after starting hormonal contraception postpartum, and in the context of TB drugs. Pharmacokinetic parameters during pregnancy will be compared to a) historical PK data from non-pregnant adults and b) PK data from the same women in these cohorts during the postpartum period. If significantly low ARV drug exposure is observed among participants antepartum, these results will be reported

to the principal investigator of that study site, and if a dosing modification for that participant is acted upon, the IMPAACT laboratory will offer post-dosing change PK assessments. Such participants will be excluded from the antenatal/postpartum ARV comparisons. Based upon comparative data assessments dosing modifications for future research studies may be recommended.

The study will also compare antiretroviral and TB drug concentrations of cord blood with maternal plasma at delivery and describe the pharmacokinetics of washout elimination of transplacentally acquired drugs.

The ratio of unbound to total drug concentrations for selected highly bound ARVs will be compared to assess the impact of pregnancy on protein binding.

This study will provide data to compare ARV concentrations in genital tract secretions versus plasma in pregnant HIV-infected women. These data should advance our knowledge on drug penetration into the female genital tract during pregnancy.

10.0 DATA COLLECTION REQUIREMENTS

Note: For Infants see Appendix II for data collection requirements.

Maternal Medications History:

Prophylaxis and/or treatment of HIV related complications, TB treatment, blood products and transfusions, antibiotics, hormonal contraceptives, and other prescription medications are to be recorded on the CRFs. Over the counter medications or nutritional and herbal supplements, with the exception of prenatal vitamins, should not be recorded. Labor and delivery anesthesia/epidurals and other prescription medications given in the intrapartum/postpartum period are to be recorded on the CRFs. Over the counter medications given in the intrapartum/postpartum period should not be recorded.

At Entry, all current ARV medications as well as any ARV medications received in the 12 months prior to the estimated date of confinement are to be recorded on the CRFs. After study entry, all modifications to ARV medications including treatment initiations, modifications, and permanent discontinuation of treatment are to be recorded on the CRFs at each visit including antiretroviral medications given in the intrapartum period.

Medications that meet the above criteria are to be recorded on CRFs, based on the study arm the participant is enrolled, as follows:

- HIV-infected pregnant women: At Entry, all medications including ARVs taken during the current pregnancy must be recorded. For women on TB treatment, a complete history of TB medications taken during the current pregnancy must be recorded. After entry, medications taken since the last study visit are to be recorded on the CRFs.
- HIV-uninfected pregnant women on no ARV medications with tuberculosis treatment: At Entry, all medications taken during the current pregnancy including a complete history of TB medications must be recorded. After entry, medications taken since the last study visit are to be recorded on the CRFs.
- HIV-infected postpartum women on ARV medications and hormonal contraceptives: At Entry, all medications that have been taken or administered within 30 days prior to registration to the protocol must be recorded. After entry, medications taken since the last study visit are to be recorded on the CRFs.

Maternal Signs and Symptoms:

All $\geq$ Grade 3 nausea, constipation, headache, fatigue, reflux/heartburn must be recorded on the CRFs. In addition, all* other $\geq$ Grade 2 events should be recorded. History of hypertension and proteinuria of $\geq$ Grade 2, during the current pregnancy, should be recorded on the CRFs for all occurrences prior to 20 weeks gestation. After 20 weeks gestation, record only if it is clear that the diagnosis of preeclampsia has been excluded. If the complete date of sign/symptom is not known, then the date should be estimated according to date conventions.

*Note: It is not necessary to record signs and symptoms that are associated with a diagnosis that has been recorded on the Diagnoses CRF. All Grade 3 or 4 events and deaths, and any events that met EAE reporting requirements or lead to a change in the treatment for which they are on this study, must be further evaluated on the study Event Evaluation Form.

Signs and symptoms that meet the above criteria are to be recorded on the CRFs, based on the study arm the participant is enrolled, as follows:

- HIV-Infected pregnant women on DRV/r and LPV/r: In addition to other sign and symptom history, history of headache, abdominal pain, nausea, diarrhea and other gastrointestinal symptoms $\geq$ Grade 2 are to be recorded on the CRFs.
- HIV-infected pregnant women: At Entry, signs and symptoms during the current pregnancy are to be recorded on the CRFs. After entry, all signs and symptoms identified since the last visit are to be recorded on the CRFs.
- HIV-uninfected pregnant women on no ARV medications with tuberculosis treatment: At Entry, signs and symptoms during the current pregnancy are to be recorded on the CRFs. After entry, all signs and symptoms identified since the last study visit are to be recorded on the CRFs.
- HIV-infected postpartum women on ARV medications and hormonal contraceptives: At Entry, signs and symptoms within 30 days prior to registration to the protocol are to be recorded on the CRFs. After entry, all signs and symptoms identified since the last study visit are to be recorded on the CRFs.

Diagnosis History:

- HIV-infected pregnant women: At Entry, a history of any ongoing major HIV related diagnoses and lifetime history of major obstetrical related diagnoses, including diagnoses during the current pregnancy are to be recorded on the CRFs. After entry, all diagnoses, based on the current Diagnoses Appendix (available at fstrf.org), and identified since the last visit are to be recorded on the CRFs.
- Pregnant women receiving tuberculosis treatment: At Entry, a history of any ongoing major TB related diagnoses and lifetime history of major obstetrical related diagnoses including during the current pregnancy are to be recorded on the CRFs. After entry, all diagnoses, based on the current Diagnoses Appendix (available at fstrf.org), and identified since the last visit are to be recorded on the CRFs.
- HIV-infected postpartum women on ARV medications and hormonal contraceptives: At Entry, HIV related and obstetrical related diagnosis within 30 days prior to registration to the protocol are to be recorded on the CRFs. After entry, all diagnoses based on the current Diagnoses Appendix (available at fstrf.org), and identified since the last visit are to be recorded on the CRFs.

Hematology and Chemistry history in addition to protocol-required labs listed in Appendix I-A through I-D and I-AMR:

- HIV-infected pregnant women:

Hematology: All $\geq$ Grade 2 results for CBC with differential and platelets; first and last test results at each reportable grade and first normal result afterwards are to be recorded on the CRFs. All HIV-1 RNA results and Lymphocyte subsets during the current pregnancy and postpartum are to be recorded on the CRFs.

Chemistries: All $\geq$ Grade 2 results for AST, ALT, albumin, BUN, creatinine, and total bilirubin during the current pregnancy are to be recorded on CRFs, including during postpartum follow up.

- HIV-uninfected pregnant women on no ARV medications with tuberculosis treatment:

Hematology: All $\geq$ Grade 2 results for CBC with differential and platelets; first and last test results at each reportable grade and first normal result afterwards.

Chemistries: All $\geq$ Grade 2 during the current pregnancy are to be recorded on CRFs, including during postpartum follow up. After delivery, all $\geq$ Grade 2 results for AST, ALT, and lactate are to be recorded on the CRFs.

- HIV-infected postpartum women on ARV medications and hormonal contraceptives:

Hematology: All $\geq$ Grade 2 results for CBC with differential and platelets, first and last test results at each reportable grade and first normal result afterwards.

Chemistries: All $\geq$ Grade 2 results for AST, ALT, and lactate are to be recorded on the CRFs. At entry, results obtained within 30 days prior to registration to the protocol are to be recorded on the CRFs. After entry, all results since the last study visit are to be recorded on the CRFs.

11.0 HUMAN SUBJECTS

The Division of AIDS has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in clinical trials and should NOT be considered by local IRBs for the recruitment of prisoners.

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent documents (*Appendices VI-A through VI-D*), and any subsequent modifications must be reviewed and approved by the IRB or Ethics Committee (EC) responsible for oversight of the study. The mother must give written informed consent for her participation in the study and for that of her infant. The informed consent 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 mother.

Each site which receives US HHS funding and follows the United States Code of Federal Regulations Title 45 – Public Welfare, Part 46 – Protection of Human Subjects (also known as the Common Rule) should have on record at the site a plan that detects and addresses any change in guardianship occurring in pediatric subjects and determines when a study subject must have a consent process which involves a legally authorized representative (LAR) other than a family member with guardianship. The plan will include how the site determines when a LAR is initially or no longer needed and how frequently the LAR

resigns the consent. The plan should follow all IRB, local, and state guidelines. Confirmation of such a plan at a site should be placed in the site's regulatory file where it is available for review by site monitors.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified only by a coded number to maintain subject confidentiality. All records will be kept in a secured area. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary, for monitoring by the FDA, OHRP, the NIAID, or the local or national IRB or Ethics Committee.

11.3 Study Discontinuation

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

12.0 PUBLICATION OF RESEARCH FINDINGS

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

13.0 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.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations – Packing Instruction 602. Refer to individual carrier guidelines (e.g., Federal Express or Airborne) as well as specific requirements of the host country for specific instructions required for ground transportation within that country.

14.0

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TABLE A
GUIDELINES FOR USING SCHEDULE OF EVALUATIONS AND SAMPLE INFORMED CONSENTS

Participant criteria	Regimen(s) being studied	Use this Schedule of Evaluations	Use this Consent Form
HIV-infected pregnant women and their infants	ARVs without TB Treatment	Appendix I-A and I-AMR (Maternal) Appendix II (Infant)	Appendix VI-A
HIV-infected pregnant women and their infants	ARVs with TB Treatment (First and Second Line TB Treatment)	Appendix I-B and I-AMR (Maternal) Appendix II (Infant)	Appendix VI-B
HIV-uninfected pregnant women and their infants	No ARVs with TB Treatment (First and Second Line TB Treatment)	Appendix I-C (Maternal) Appendix II (Infant)	Appendix VI-C
HIV-infected postpartum women	ARVs with Contraceptives	Appendix I-D (Maternal)	Appendix VI-D

APPENDIX I-A

SCHEDULE OF EVALUATIONS FOR WOMEN ON ARV MEDICINES WITHOUT TUBERCULOSIS TREATMENT

NOTE: ADDITIONAL CLINICAL MONITORING IS REQUIRED FOR WOMEN ON DRV/r. SEE APPENDIX I-AMR FOR SPECIFIC REQUIREMENTS

EVALUATION	2 nd Trimester (20-26 weeks) ⁹	3 rd Trimester (30-38 weeks) ⁹	Delivery (+/- 4 days) ¹⁴	2-3 weeks Postpartum	6-12 weeks Postpartum ¹⁵
ARMS ¹⁶	All	All	All	DRV/r	EFV, DTG, ELV/Cobi, DRV/Cobi, ATV/Cobi, TAF(all TAF arms)
CLINICAL					
Informed Consent	X	X			
Documentation of HIV Infection ¹	[3 mL]	[3 mL]			
History/Concomitant Medicines ²	X	X	X	X	X
Physical Exam ³	X	X	X	X	X
Perinatal Adherence Questionnaire ⁴	X	X		X	X
Report to ARV Pregnancy Registry	X		X		
LABORATORY					
Albumin ⁵	5 mL	5 mL		5 mL	5 mL
BUN/creatinine/bilirubin ⁵	X	X	2.5 mL	X	X
AST/ALT ⁵	X	X	2.5 mL	X	X
Hgb ⁵	1 mL	1 mL	1 mL	1 mL	1 mL
Alpha-1 acid glycoprotein ⁶	X	X		X	X
IMMUNOLOGY					
CD4 cell count	1 mL	1 mL	1 mL	1 mL	1 mL
VIROLOGY					
HIV RNA	6 mL	6 mL	6 mL	6 mL	6 mL
Vaginal Swab ⁷	X	X			X
PHARMACOLOGY					
Intensive PK sampling ^{7,8}	17-19 mL ⁹	17-19 mL ⁹		17-19 mL	17-19 mL
Vaginal secretions ^{7,10}	X	X			X
PHARMACOGENETICS					
Genotyping ⁷	X ¹¹	X ¹¹			
OTHER					
Cord Blood ¹²			X		
Maternal Delivery Sample ¹³			5 mL		
TOTAL BLOOD VOLUME	30-35 mL	30-35 mL	18 mL	30-32 mL	30-32 mL

APPENDIX I-A FOOTNOTES

1. If there is insufficient documentation of HIV status, as specified in Section 4.15, HIV diagnostic testing is to be done according to the protocol definition.
2. See Section 10, Data Collection Requirements, for history requirements.
3. Physical exam to include at a minimum weight, height (entry), vital signs, signs and symptoms and diagnoses.
4. Administer on same days as intensive PK sampling.
5. Draw at time of PK sampling in second and third trimesters and postpartum. BUN/creatinine/bilirubin and AST/ALT can be assayed from the albumin sample if drawn at the same time.
6. Measured from PK sample; an extra tube is not required.
7. See the Laboratory Processing Chart (LPC) on the P1026 Protocol Specific Webpage on the IMPAACT Website (<http://www.impaactnetwork.org>) for collection, processing and shipping instructions.
8. See Appendix III for 12-hour or 24-hour sampling time points depending on the ARV drug evaluated.
9. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System.
10. Collect vaginal secretions for drug levels at pre-dose, and 1, 2, and 4 hours after dosing for all drugs.
11. Obtain at first PK evaluation.
12. Draw immediately after the cord is clamped.
13. Draw at the time the cord is clamped.
14. Evaluations can be done four days prior to delivery through four days after delivery; day of delivery = day 0 for determining the target dates for postpartum evaluations.
15. Abstract data from participants chart if available within the window for the visit.

APPENDIX I-B

SCHEDULE OF EVALUATIONS FOR WOMEN ON ARV MEDICINES WITH TUBERCULOSIS TREATMENT

NOTE: ADDITIONAL CLINICAL MONITORING IS REQUIRED FOR WOMEN ON LPV/r. SEE APPENDIX I-AMR FOR SPECIFIC REQUIREMENTS.

EVALUATION	Second Trimester (20-26 weeks) ⁸	Third Trimester (30-38 weeks) ⁸	Delivery (+/- 4 days) ¹³	2-8 weeks Postpartum ¹⁶
ARMS	ARVs with First or Second Line Tuberculosis Treatment			
CLINICAL				
Informed Consent	X	X		
Documentation of HIV Infection ¹	[3 mL]	[3 mL]		
History/Concomitant Medicines ²	X	X	X	X
Physical Exam ²	X	X	X	X
Perinatal Adherence Questionnaire ³	X	X		X
Report to ARV Pregnancy Registry	X		X	
Audiology assessment ¹⁴			X	
LABORATORY				
Albumin ⁴	5 mL	5 mL		5 mL
BUN/creatinine/bilirubin ⁴	X	X	2.5 mL	X
AST/ALT ⁴	X	X	2.5 mL	X
Hgb ⁴	1 mL	1 mL	1 mL	1 mL
Alpha-1 acid glycoprotein ⁵	X	X		X
TSH/ft4 ¹⁵	6 mL	6 mL		6 mL
IMMUNOLOGY				
CD4 cell count	1 mL	1 mL	1 mL	1 mL
VIROLOGY				
HIV RNA	6 mL	6 mL	6 mL	6 mL
PHARMACOLOGY				
Intensive PK Sampling ^{6,7}	31-35 mL ⁸	31-35 mL ⁸		31-35 mL ⁹
PHARMACOGENETICS				
Genotyping ⁶	X ¹⁰	X ¹⁰		
OTHER				
Cord Blood ¹¹			X	
Maternal Delivery Sample ¹²			5 mL	
TOTAL BLOOD VOLUME	44-57 mL	44-57 mL	18 mL	13-54 mL

APPENDIX I-B FOOTNOTES

1. If there is insufficient documentation of HIV status, as specified in Section 4.15, HIV diagnostic testing is to be done according to the protocol definition.
2. Physical exam to include at a minimum weight, height (entry), vital signs, signs and symptoms and diagnoses. See Section 10, Data Collection Requirements, for history requirements.
3. Administer on same days as intensive PK sampling.
4. Draw at time of PK sampling in second and third trimesters and postpartum. BUN/creatinine/bilirubin and AST/ALT can be assayed from the albumin sample if drawn at the same time.
5. Measured from PK sample; an extra tube is not required.
6. See the Laboratory Processing Chart (LPC) on the P1026 Protocol Specific Webpage on the IMPAACT Website (<http://www.impaactnetwork.org>) for collection, processing and shipping instructions.
7. See Appendix III for the number of samples and timing of specimens will vary depending on the ARV/TB drug being evaluated.
8. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System.
9. Obtain PK sampling *only* if participant is still taking TB drugs.
10. Obtain at first PK evaluation.
11. Draw immediately after the cord is clamped. For this arm, collection of cord blood can be omitted if there are circumstances that prohibit collection (i.e. delivery at non-study facility, delivery during non-business hours).
12. Draw at time the cord is clamped. For this arm, collection of maternal delivery sample can be omitted if there are circumstances that prohibit collection (i.e. delivery at non-study facility, delivery during non-business hours).
13. Evaluations can be done four days prior to delivery through four days after delivery; day of delivery = day 0 for determining the target dates for postpartum evaluations.
14. For participants treated with any injectable TB medication the audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the LPC for additional information.
15. For participants treated with ethionamide and/or para-aminosalicylic acid. Refer to the LPC for additional information; follow the assay requirements of your testing lab.
16. Abstract data from participants chart if available within the window for the visit.

APPENDIX I-AMR
ADDITIONAL MONITORING REQUIREMENTS FOR WOMEN ON DRV AND LPV

NOTE: THESE REQUIREMENTS ARE IN ADDITION TO THOSE SPECIFIED IN APPENDIX IA AND IB. ONLY PERFORM ONCE IN THE EVENT OF OVERLAP WITH APPENDIX I-A AND I-B.

EVALUATION	Antepartum			2-3 weeks Postpartum
	Entry ¹	From Entry to 30 weeks gestation	From 30 weeks gestation to delivery ⁹	
CLINICAL				
History ²	X	q4 weeks	q2 weeks	X
Physical Exam ³	X	q4 weeks	q2 weeks	X
Targeted OB Exam (fundal height; fetal heart tones)	X	q4 weeks	q2 weeks	
Electrocardiogram	X ⁴		X ⁵	
LABORATORY				
Chemistries ⁶	5 mL	5 mL q4 weeks	5 mL q4 weeks	5 mL
CBC ⁷	1 mL	1 mL q4 weeks	1 mL q4 weeks	1 mL
Gestational Diabetes Screening ⁸		X	X	
TOTAL BLOOD VOLUME	6 mL	6 mL	6 mL	6 mL

APPENDIX I-AMR FOOTNOTES

- Entry visit may occur on the same day as initial PK sampling.
- History will include assessment of headache, abdominal pain, nausea, diarrhea and other gastrointestinal symptoms $\geq$ Grade 2.
- Physical exam to include at a minimum weight, height (entry), vital signs, signs and symptoms and diagnoses.
- It is acceptable to do the EKG within +/- 2 weeks of entry.
- EKG should be done after 30 weeks gestation but prior to delivery.
- Chemistries will include ALT, AST, bilirubin, electrolytes, glucose, BUN, creatinine, pancreatic amylase. Lipase is required if pancreatic amylase is $\geq$ Grade 3. If pancreatic amylase is not available, use total amylase.
- CBC will include cell differential and platelet count.
- Diabetes screening must be done once while on increased dose DRV or LPV/r, between 24 weeks gestation and delivery. May obtain from chart abstraction. If not done as part of clinical care, perform gestational diabetes screening, typically using 1-hour 50 gram or 2-hour 75 gram glucose test, or using local standard of care test. If results are abnormal, follow-up as per local standard of care.
 Note: if diabetes or gestational diabetes diagnosis has already been made, do not perform above tests.
- Non-stress test and amniotic fluid index are recommended starting at 34 weeks gestation but are not reported.

APPENDIX I-C
SCHEDULE OF EVALUATIONS FOR HIV-UNINFECTED WOMEN WITH TUBERCULOSIS TREATMENT

EVALUATION	Second Trimester (20-26 weeks) ⁵	Third Trimester (30-38 weeks) ⁵	Delivery (+/- 4 days) ⁹	2-8 weeks Postpartum ¹¹
ARMS	EMB, INH, PZA, RIF, or Second Line TB Treatment			
CLINICAL				
Informed Consent	X	X		
History/Concomitant Medicines ¹	X	X	X	X
Physical Exam (weight) ¹	X	X	X	X
Audiology assessment ¹⁰			X	
LABORATORY				
Albumin ²	5 mL	5 mL		5 mL
BUN/creatinine/bilirubin ²	X	X	2.5 mL	X
AST/ALT ²	X	X	2.5 mL	X
Hgb ²	1 mL	1 mL	1 mL	1 mL
Alpha-1 acid glycoprotein ³	X	X		X
TSH/ft4 ¹²	6 mL	6 mL		6 mL
PHARMACOLOGY ⁴				
Intensive PK sampling ⁵	17 mL ⁶	17 mL ⁶		17 mL ⁷
PHARMACOGENETICS ⁴				
Genotyping	X ⁸	X ⁸		
TOTAL BLOOD VOLUME	23-29 mL	23-29 mL	6 mL	6-29 mL

APPENDIX I-C FOOTNOTES

1. Physical exam to include at a minimum weight, height (entry), vital signs, signs and symptoms and diagnoses. See Section 10, Data Collection Requirements, for history requirements.
2. Draw at time of PK sampling in second and third trimesters and postpartum. BUN/creatinine/bilirubin and AST/ALT can be assayed from the albumin sample if drawn at the same time.
3. Measured from PK sample; an extra tube is not required.
4. See the Laboratory Processing Chart (LPC) on the P1026 Protocol Specific Webpage on the IMPAACT Website (<http://www.impaactnetwork.org>) for collection, processing and shipping instructions.
5. See Appendix III for 12-hour sampling time points; collect at pre-dose, and at 1, 2, 4, 6, 8, and 12 hours post-dose.
6. Entry may occur at the second or third trimester visit. The participant must be on the medicine of interest for at least 2 weeks prior to PK sampling. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System.
7. Obtain PK sampling *only* if participant is still taking TB drugs.
8. Obtain at first PK evaluation.
9. Evaluations can be done four days prior to delivery through four days after delivery; day of delivery = day 0 for determining the target dates for postpartum evaluations.
10. For participants treated with any injectable TB medication the audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the LPC for additional information.
11. Abstract data from participants chart if available within the window for the visit.
12. For participants treated with ethionamide and/or para-aminosalicylic acid. Refer to the LPC for additional information; follow the assay requirements of your testing lab.

APPENDIX I-D
SCHEDULE OF EVALUATIONS FOR POSTPARTUM WOMEN ON ARV MEDICINES AND HORMONAL CONTRACEPTIVES

EVALUATION	2-12 weeks Postpartum ¹²	6-7 weeks after Contraceptive Initiation ¹³
ARMS	EFV or DRV/COBISISTAT or ATV/COBISISTAT WITH ETHINYL ESTRADIOL or ETONOGESTREL IMPLANT	
CLINICAL		
Informed Consent	X	
Documentation of HIV Infection ¹	[3mL]	
History/Concomitant Medicines ²	X	X
Physical Exam (weight) ²	X	X
Perinatal Adherence Questionnaire ³	X	X
LABORATORY		
Hematology ⁴	1 mL	1 mL
Chemistries ⁵	5 mL	5 mL
Pregnancy Test (serum or urine)		X
Alpha-1 acid glycoprotein ⁶	X	X
IMMUNOLOGY		
CD4 Cell Count	1 mL	1 mL
VIROLOGY		
HIV RNA	6 mL	6mL
PHARMACOLOGY ⁷		
ARV Intensive PK sampling ⁸	17-19 mL	17-19 mL
Contraceptive Intensive PK sampling (ethinyl estradiol and progestin) ⁹		[16 mL]
Etonogestrel PK ¹⁰		[4 mL]
Progesterone		1 mL
PHARMACOGENETICS ⁷		
Genotyping	X ¹¹	
TOTAL BLOOD VOLUME	30-35 mL	35 – 49 mL

APPENDIX I-D FOOTNOTES

1. If there is insufficient documentation of HIV status, as specified in Section 4.15, HIV diagnostic testing is to be done according to the protocol definition.
2. Physical exam to include at a minimum weight, height (entry), vital signs, signs and symptoms and diagnoses. See Section 10, Data Collection Requirements, for history requirements.
3. Administer on same day as intensive PK sampling.
4. Hematology includes CBC with cell differential and platelet count.
5. Chemistries include ALT, AST, bilirubin, electrolytes, glucose, BUN, creatinine, total amylase. Lipase is required if total amylase is $\geq$ Grade 3.
6. Measured from PK sample; an extra tube is not required.
7. See the Laboratory Processing Chart (LPC) on the P1026 Protocol Specific Webpage on the IMPAACT Website (<http://www.impaactnetwork.org>) for collection, processing and shipping instructions.
8. See Appendix III for 12-hour or 24-hour sampling time points depending on ARV being evaluated.
9. See Appendix III for 24-hour sampling time point. Collect 2 mL at pre-dose, 1, 2, 4, 6, 8, 12 and 24 hours post-dose only on women on oral contraceptives.
10. Collect one 4mL sample only on women with etonogestrel implant.
11. Obtain at first PK evaluation
12. The participant must be on the ARV of interest for at least 2 weeks prior to the initial PK sampling and not using any hormonal contraceptive method during that time. PK sampling visit should occur within 5 days after enrollment using the Subject Enrollment System.
13. ARVs and the combined oral contraceptives should be taken at the same time of day on the day of PK sampling and three days before PK sampling.

APPENDIX II SCHEDULE OF EVALUATIONS FOR INFANTS

EVALUATION	Birth ⁸ (through day 3 of life)	5-9 days of life (infants undergoing washout PK only, see Section 4.4)	16 – 24 weeks of life ¹⁰
CLINICAL			
Physical Exam ¹	X	X	X
HIV Infection Status ²	X	X	X
History/Chart abstraction ³	X	X	X
Audiology assessment ⁹	X		
PHARMACOLOGY ⁴			
Washout PK Sampling Plasma	2.25 mL ⁵	0.75 mL ⁶	
Dried Blood Spot (for pharmacogenetics)	0.25 mL ⁷	0.25 mL ⁷	
TOTAL BLOOD VOLUME	0 to 2.5 mL	0 to 1 mL	

- Physical exam should include measurement of length and weight.
- Record all HIV test results available.
- At birth, record the following results/events that are available since birth. After the birth visit, record all available results/events since the last visit.
 Infant feeding status, if available
 Hematology: All $\geq$ Grade 2 results for CBC with differential and platelets; first and last results at each reportable grade and first normal result afterwards.
 Chemistries: All $\geq$ Grade 2 results for glucose, AST, ALT for all infants. For HIV-infected infants, also record $\geq$ Grade 2 electrolytes, BUN, creatinine, total and direct bilirubin, lipase, albumin, total protein, triglycerides, cholesterol, CPK, and amylase.
 Signs/Symptoms: All $\geq$ Grade 1 neurologic events, and all other $\geq$ Grade 2 events.
 Diagnoses: Any diagnoses as defined in the Diagnoses Appendix (which can be found at www.fstrf.org), including congenital anomalies and mitochondrial disorders.
 Note that all Grade 3 or 4 events and deaths, and all $\geq$ Grade 1 neurologic events must be further evaluated on the study Event Evaluation Form.
 Record any concomitant prescription medicines since birth. After the birth visit, record any concomitant prescription medicines taken since the last visit.
- Collection of PK samples can be omitted, with approval of the protocol team, if there are circumstances that prohibit collection (i.e. delivery at non-study facility). Only infants who meet the requirements for infant washout PK will undergo pharmacology evaluations; see protocol Section 4.4 for infant requirements for washout PK sampling.
- Blood samples to be collected at 2-10, 18-28 and 36-72 hours after birth. See Laboratory Processing Chart (LPC) for collection, processing and shipping instructions.
- Single blood sample to be collected between 5 – 9 days of life. See Laboratory Processing Chart (LPC) for collection, processing and shipping instructions.
- For infants for which informed consent has been obtained for genetic testing: Obtain once, at any collection, at either the Birth (through day 3 of life) Visit OR at the 5 - 9 days of life visit (if washout

PK to be collected). See Laboratory Processing Chart (LPC) for collection, processing and shipping instructions.

8. Evaluations can be done from birth through day 3 of life; day of birth = day 0
9. Only for infant of mothers treated with any injectable TB medication. The audiology assessment can be from chart abstraction or otherwise can be performed at any time during follow-up; refer to the LPC for additional information.
10. Abstract data from the participants chart if available within the window for the visit.

APPENDIX III
MATERNAL INTENSIVE PK SAMPLING SCHEDULE FOR ARV MEDICINES,
TUBERCULOSIS TREATMENT AND HORMONAL CONTRACEPTIVES

REGIMEN(S) BEING STUDIED	PHARMACOKINETIC (PK) SAMPLING SCHEDULE
ARVS WITHOUT TB TREATMENT	
darunavir/ritonavir twice daily	12 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum. If therapy begins prior to 30 weeks gestation, women will receive 600/100 mg b.i.d. or 800/100 mg b.i.d. or 900/100 mg b.i.d. Dose may be adjusted based on results of optional individual 2 nd trimester sampling. Dose will be increased to 800/100 mg b.i.d. or 900/100 mg b.i.d. at 30 weeks gestation regardless of 2 nd trimester results. PK sampling will be done no sooner than two weeks after the dose increase. After delivery, 800/100 mg b.i.d. or 900/100 mg b.i.d. will continue until discharge from the hospital or 3 days postpartum whichever is earlier. Postpartum PK sampling will be done 2-3 weeks postpartum on 600/100 mg b.i.d. dose.
dolutegravir	24 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum
elvitegravir/cobicistat	24 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum
darunavir/cobicistat	24 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum
atazanavir/cobicistat	24 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum
tenofovir alafenamide fumarate 25 mg q.d. without cobicistat or ritonavir	24 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum
tenofovir alafenamide fumarate/ 10 mg q.d. with cobicistat	24 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum
tenofovir alafenamide fumarate 10 mg q.d. with ritonavir	24 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum
efavirenz	24 hour sampling during optional 2 nd trimester, during 3 rd trimester and 6-12 weeks postpartum
ARVs WITH TB TREATMENT	
efavirenz with TB drugs (ethambutol, isoniazid, pyrazinamide, rifampicin)	24 hour sampling during 2 nd trimester (if enrolled), during 3 rd trimester and 2-8 weeks postpartum if still taking TB drugs.
lopinavir/ritonavir with TB drugs (ethambutol, isoniazid, pyrazinamide, rifampicin)	12 hour sampling during 2 nd trimester (if enrolled), during 3 rd trimester and 2-8 weeks postpartum if still taking TB drugs.
kanamycin, amikacin, capreomycin, moxifloxacin, levofloxacin, bedaquiline, clofazamine, pretomanid, ofloxacin, ethionamide/	12 hour sampling during 2 nd trimester (if enrolled), during 3 rd trimester and 2-8 weeks postpartum if still taking TB drugs.

REGIMEN(S) BEING STUDIED	PHARMACOKINETIC (PK) SAMPLING SCHEDULE
prothionamide, terizidone/cycloserine, high dose INH, delamanid, linezolid, para-aminosalicylic acid (PAS)	
NO ARVS WITH TB TREATMENT	
ethambutol, isoniazid, pyrazinamide, rifampicin	12 hour sampling during 2 nd trimester (if enrolled), during 3 rd trimester and 2-8 weeks postpartum if still taking TB drugs.
ARVS WITH CONTRACEPTIVES	
darunavir/cobicistat or atazanavir/cobicistat with ethinyl estradiol containing contraceptives	24 hour sampling 2-12 weeks postpartum for ARVs and 24 hour sampling 6-7 weeks after contraceptive initiation for both ARVs and oral contraceptives
darunavir/cobicistat or atazanavir/cobicistat with etonogestrel implant	24 hour sampling 2-12 weeks postpartum for ARVs and 24 hour sampling 6-7 weeks after contraceptive initiation for ARVs and a single sample for etonogestrel implant PK.
efavirenz with ethinyl estradiol containing contraceptives	24 hour sampling 2-12 weeks postpartum for ARVs and 24 hour sampling 6-7 weeks after contraceptive initiation for both ARVs and oral contraceptives
atazanavir/ritonavir/tenofovir with ethinyl estradiol containing contraceptives	24 hour sampling 2-12 weeks postpartum for ARVs and 24 hour sampling 6-7 weeks after contraceptive initiation for both ARVs and oral contraceptives

12 hour sampling time points: Pre-dose, and at 1, 2, 4, 6, 8 and 12 hours post-dose

24 hour sampling time points: Pre-dose, and at 1, 2, 4, 6, 8, 12, and 24 hours post-dose

For women who are on multiple arms of P1026s, doses of medicines should be administered at the same time OR additional samples must be drawn to complete the PK evaluation for EACH drug (i.e., samples need to be drawn at 1, 2, 4, etc. hours post-dose for each study drug if doses are staggered). In addition, single samples will be obtained at delivery from the mother and from the umbilical cord after being clamped.

APPENDIX IV

DIETARY RECOMMENDATIONS FOR ANTIRETROVIRAL MEDICINES, TUBERCULOSIS MEDICINES AND HORMONAL CONTRACEPTIVES

NRTIs

- Tenofovir alafenamide fumarate (TAF): Take with food.

PIS/COMBINATIONS

- Darunavir/ritonavir twice daily: Take with food to enhance bioavailability. Studied with meals ranging from 240 Kcal (12 grams of fat) to 928 Kcal (56 grams of fat).
- Lopinavir/ritonavir (Alluvia®): Take with a high fat meal to enhance bioavailability and minimize pharmacokinetic variability. (Studied with meals of ~850 Kcal, ~55% from fat.)
- Atazanavir/ritonavir/tenofovir: For tenofovir, avoid high fat meals two hours before and two hours after taking dose. For atazanavir/ritonavir, take with a light meal to enhance bioavailability and minimize pharmacokinetic variability. Take at least two hours before or one hour after administration of an antacid.
- Atazanavir/cobicistat and darunavir/cobicistat: Take with food.

NNRTIs

- Efavirenz: Take on an empty stomach (at least one hour before or two hours after a meal).

Integrase Inhibitors

- Dolutegravir: May be taken without regard to meals.
- Elvitegravir/cobicistat: Take with food.

First Line Tuberculosis Medicines:

If a combination product is used, then it should be administered with food. If administered as separate medications:

- Ethambutol: Take with food to minimize stomach upset if needed.
- Isoniazid: Take on an empty stomach (at least one hour before or two hours after a meal)
- Pyrazinamide: May be administered without regard to meals.
- Rifampicin: Take on an empty stomach (at least one hour before or two hours after a meal).

Second Line Tuberculosis Medicines:

Second Line TB drugs can be given without regards for meals, with the exception of delamanid and bedaquiline which should be administered with meals.

Hormonal Contraceptives:

- May be taken without regard to meals.

APPENDIX V
MATERNAL PHARMACOKINETIC PARAMETER TARGETS
Current Open Study Arms:

ARV Study Drug	PK Parameter	Non-pregnant Typical Value (mcg*hr/mL)	Estimated 10th percentile (mcg*hr/mL)	Reference
Atazanavir/cobicistat	AUC ₀₋₂₄	46.1	28.4	Evotaz™ [package insert] Princeton, NJ; Bristol-Myers Squibb Company; 2015.
Darunavir/cobicistat	AUC ₀₋₂₄	100.6	70.4*	Tashima K, Crofoot G, Tomaka FL, Kakuda TN, Brochot A, Van de Casteele T, et al. Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. AIDS Res Ther. 2014 Dec 1;11:39.
Elvitegravir/cobicistat	AUC ₀₋₂₄	23	16.1*	Stribild™ [package insert] Foster City, CA; Gilead Sciences; 2013
Darunavir/ritonavir twice daily (800/100 mg b.i.d.)	AUC ₀₋₁₂	62.3	43.6*	Prezista™ [package insert] Titusville, NJ; Janssen; 2012
Dolutegravir	AUC ₀₋₂₄	53.6	37.5*	Tivicay™ [package insert] Research Triangle Park, NC; ViiV Healthcare; 2014
Efavirenz	AUC ₀₋₂₄	58.1	40	Sustiva™ [package insert] Princeton, NJ; Bristol-Myers Squibb Company; 2004.
Lopinavir/ritonavir	AUC ₀₋₁₂	80	52	Murphy R, Brun S, Hicks C, Eron J, Gulick R, King M, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results. AIDS 2001;15: 1-9.
Tenofovir alafenamide fumarate (TAF) without cobicistat or ritonavir	AUC ₀₋₂₄			To be updated once drug is FDA-approved.
TAF/cobicistat	AUC ₀₋₂₄			To be updated once drug is FDA-approved.
TAF/ritonavir	AUC ₀₋₂₄			To be updated once drug is FDA-approved.

TB Study Drug	PK Parameter	Minimum Cut-off Value	Reference
Ethambutol	C _{max}	Once Daily: < 2 mcg/mL Thrice Weekly: < 4 mcg/mL	Chideya S, et al. CID 2009;48:1685-94. Tappero JW, et al. CID 2005;41:461-9. Peloquin CA. Drugs 2002;62(15):2169-83.
Isoniazid	C _{max}	Once Daily: < 3 mcg/mL Thrice Weekly: 8 mcg/mL	Chideya S, et al. CID 2009;48:1685-94. Tappero JW, et al. CID 2005;41:461-9. Peloquin CA. Drugs 2002;62(15):2169-83.
Pyrazinamide	C _{max}	Once Daily: < 20 mcg/mL Thrice Weekly: < 40 mcg/mL	Chideya S, et al. CID 2009;48:1685-94. Tappero JW, et al. CID 2005;41:461-9. Peloquin CA. Drugs 2002;62(15):2169-83.
Rifampicin	C _{max}	Once Daily or Thrice Weekly: < 8 mcg/mL	Chideya S, et al. CID 2009;48:1685-94. Tappero JW, et al. CID 2005;41:461-9. Peloquin CA. Drugs 2002;62(15):2169-83.

* There are inadequate data for this combination to estimate the 10th percentile. Therefore, a 30% reduction from typical exposure will be used as the minimal acceptable exposure.

Closed Study Arms:

ARV Study Drug	PK Parameter	Non-pregnant Typical Value (mcg*hr/mL)	Estimated 10 th percentile (mcg*hr/mL)	Reference
Abacavir	AUC ₀₋₁₂	5.8	4.1	McDowell JA, Lou Y, Symonds WS, Stein DS. Multiple-dose pharmacokinetics and pharmacodynamics of abacavir alone and in combination with zidovudine in HIV infected adults. Antimicrob Agents Chemother. 2000;44:2061-2067.
Amprenavir	AUC ₀₋₁₂	23.9	13.2	Falloon J, Piscitelli S, Vogel S, Sadler B, Mitsuya H, Kavlick MF, et al. Combination therapy with amprenavir, abacavir, and efavirenz in human immunodeficiency virus (HIV)-infected patients failing a protease-inhibitor regimen: pharmacokinetic drug interactions and antiviral activity. Clin Infect Dis 2000;30:313-318.
Atazanavir/ritonavir	AUC ₀₋₂₄	57	29.4	Reyataz TM [package insert] Princeton, NJ; BMS Virology; 2003.
Darunavir/ritonavir once daily (800/100 mg. q.d.)	AUC ₀₋₂₄	87.854	56.486	Prezista TM [package insert] Titusville, NJ; Janssen, 2012
Didanosine delayed release EC	AUC ₀₋₂₄	3.10	2.04	WangY, Livingston E, Patil S, McKinney RE, Bardeguez AD, Gandia J, O'Sullivan MJ, Clax P, Huang S, Unadkat JD. J Infect Dis 1999;180:1536-41.
Etravirine	AU ₀₋₁₂	4.2	2.5	Boffito M, Winston A, Jackson A, Fletcher C, Pozniak A, Nelson M, et al. Pharmacokinetics and antiretroviral response to darunavir/ritonavir and etravirine combination in patients with high-level resistance. AIDS 2007;21:1449-1455.
Fosamprenavir/ritonavir	AUC ₀₋₁₂	39.6	27.7*	Lexiva TM [package insert] Cambridge, MA: Vertex Pharma; 2003
Indinavir/ritonavir	AUC ₀₋₁₂	19.1	12.9	Cressey T, Leenasirimakul P, Jourdain G, Tod M, Sukrakanchana P, Kunkeaw S, Puttimit C, Lallemand M. Low doses of indinavir-boosted with ritonavir in HIV-infected Thai patients: pharmacokinetics, efficacy and tolerability. J Antimicrob Chemother 2005;55:1041-44.
Maraviroc	AUC ₀₋₁₂	2.5	1.75*	Selzentry TM [package insert] New York; Pfizer; 2011
Nelfinavir	AUC ₀₋₁₂	26	18.5	Viracept TM [package insert] Agouron Pharmaceuticals; 2004.
Raltegravir	C _{min}	55 ng/mL	1.9 ng/mL	Isentress TM [package insert] Whitehouse Station, NJ; Merck; 2012
Rilpivirine	AUC ₀₋₂₄	2396 ng*hr/mL	1609 ng*hr/mL	Edurant TM [package insert] Raritan, NJ; Tibotec; 2011
Tenofovir	C _{pre-dose}	3.7	2.5	Havliir D, Cheeseman S, McLaughlin M, Murphy R, Erice A, Spector S. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. JID 1995;171:537-45.

ARV Study Drug	PK Parameter	Non-pregnant Typical Value (mcg*hr/mL)	Estimated 10 th percentile (mcg*hr/mL)	Reference
Tipranavir/Ritonavir	AUC0-12	476	333*	Yong C, Sabo J, Oksala C, MacGregor T, Kohlbrenner V, McCallister S, et al. Population pharmacokinetic assessment of systemic steady-state tipranavir concentrations for adults administered tipranavir/ritonavir 500/200 mg twice daily. 12th Conference on Retroviruses and Opportunistic Infections 2005; 654 (abstract).

**APPENDIX VI-A
SAMPLE CONSENT FORM
FOR WOMEN ON ARV MEDICINES WITHOUT TUBERCULOSIS TREATMENT**

(Note to Sites: For use with Appendix I-A, I-AMR, and II)

IMPAACT P1026s: Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum, Version, 10.0, dated 2 February 2016
(International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network)

INTRODUCTION

You and your baby are being asked to take part in the research study named above because you are infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS, and you are pregnant and are taking one or more of the following HIV medicines during your pregnancy: darunavir/ritonavir twice daily, efavirenz, elvitegravir/cobicistat, darunavir/cobicistat, atazanavir/cobicistat, dolutegravir, tenofovir alafenamide fumarate (TAF)/cobicistat, TAF/ritonavir, TAF alone.

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/allow your baby 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?

The correct amount of HIV medicines needed during pregnancy to treat your HIV infection and to protect your baby from HIV infection while being safe for you and your baby is not known for all HIV medicines. In this study, we will compare levels of HIV medicines in pregnant women to levels in non-pregnant adults on the same medicines. If it is found that the your blood levels of HIV medicines are too low, a new dose may be recommended that is not yet approved by the Food and Drug Administration (FDA). We will also see how well the medicines get into vaginal secretions where they may help to keep the amount of HIV in the vagina at a lower level. The amount of medicine found in blood from your baby's umbilical cord will be compared to the amount of medicine in your blood at the time of delivery. We will also look to see how much of the HIV medicine you took is getting into your baby and how safe these medicines are for you and your baby.

This study will be looking at dosing combinations and dose amounts of certain HIV medicines that are not yet approved by the FDA and are still being studied. For example, the higher doses of darunavir twice daily is not approved by the FDA.

WHAT DO I /DOES MY BABY HAVE TO DO IF I AM IN THIS STUDY?

You will continue to obtain and take your HIV medicines as you would normally. No HIV medicines are supplied by this study. Your doctor may ask your permission to report the medicine you take to a national registry, which collects information anonymously on the use of HIV medicine during pregnancy, and any effects these medicines may have on infants. This information is completely confidential and your name will not be used. You do not have to agree to be in the registry.

Your doctor will review with you any dietary recommendations related to the HIV medicines that you are taking. You will need to be on your HIV medicines for at least 2 weeks before your first study visit.

During Pregnancy

- You will need to come to the clinic to make sure you are eligible for the study before you enroll. This may be done as part of your first study visit when you are 20-26 weeks pregnant or 30-38 weeks pregnant, so a separate visit will not be required. We may test you for HIV to confirm your status. At each visit, a history and physical exam, and routine blood tests will be done. Blood will also be drawn to check how well your body is able to fight infection and to check the amount of HIV in your blood. The total amount of blood for these tests is 13 – 16 mL (2½- to 3 ½ teaspoons). At each visit you will be asked about taking your HIV medicines.
- Checking the Amount of HIV Medicine in Your Blood

Sites outside the U.S. should include: Blood that is drawn during this study will be sent to doctors in laboratories in your country or overseas who have special ways of looking at the amount of HIV medicine in the blood.

If you enter the study when you are 20-26 weeks pregnant, repeat blood samples will be taken to measure the amount of HIV medicine in your blood. These blood samples will be repeated when you are 30-38 weeks pregnant. A small plastic catheter (soft tube) will be placed in a vein in your arm during this visit, so that blood can be drawn multiple times, without having to stick you with a needle several times. The tube will stay in place until all of the blood samples are drawn. Depending on the medicine(s) you are taking and the time you usually take them, 7 blood samples over 12 hours, or 8 blood samples over 24 hours will be taken. The total amount of blood taken for these tests will be between 17-19 mL (about 3½ to 4 teaspoons). You will be asked to provide the times of your previous two doses of medicine and to describe the time and amount of your previous two meals. Before these repeat blood samples are taken, the study staff will review with you any dietary recommendations related to the HIV medicines you are taking. Once your HIV medicine levels have been determined, they will be reported back to you and your doctor as soon as possible. If these levels are low compared to those in non-pregnant adults, you and your doctor will be told. You may decide, in consultation with your doctor, to adjust the dose of the medicine(s). The new dose may be higher than the current FDA approved dose. If you and your doctor choose to increase your dose of medicine, you may choose to have repeat blood sampling and drug measurements taken during the pregnancy and after you deliver to assess the levels of medicine in your blood on the new dose.

- Genetic Testing

Some of your blood collected for other tests will be used for genetic testing. Also, if you agree, between birth and 9 days after birth, your baby will have one drop of blood taken for genetic testing of your baby. This test is to see if there are differences in specific genes that may affect the levels of some medicines. Some people break down medicines differently based on their DNA and this can change the levels of the medicines in their bodies. You may decide that you do not want your or your baby's DNA to be tested either now or at another time, by contacting your care provider during the study. You can still participate in this study even if you make this decision. This test will be done later in the study so you will not receive the results of this test. Please read the following statement carefully and then mark your initials in the appropriate space provided:

I agree to allow my DNA to be tested.

Yes _____ No _____ Initials _____ Date _____

I agree to allow my baby's DNA to be tested.

Yes _____ No _____ Initials _____ Date _____

- Checking the Amount of HIV Medicine in Your Vagina

At some of the same times you have blood drawn to check the levels of HIV medicine in your blood, a small amount of vaginal fluid (about 1/8 of a teaspoon) will be taken before you take your dose of HIV medicine and again one, two, and four hours after your dose to check the amount of medicine in the vagina. The samples can be taken by you or your health care provider. Your provider will talk with you about the different ways vaginal fluid can be collected so that it is as comfortable as possible for you. These drug levels and testing will be done in batches later in the study, so you and your doctor won't get results of these tests. If you have a pregnancy condition such as placenta previa (placenta that is implanted in the lower uterus) or broken water bag that would make it unsafe to collect vaginal specimens, they will not be collected.

- Additional study tests if you are taking darunavir/ritonavir twice daily

If you are taking darunavir/ritonavir twice daily, you will be followed more closely during pregnancy and after delivery because these higher dosing combinations are not yet approved by the FDA. You will have an electrocardiogram (a quick test that looks at how your heart is beating) when you enter the study and again after 30 weeks into your pregnancy. If you have not had a test to check for gestational diabetes done as standard of care by your primary care physician, between 24 weeks gestation and delivery, some blood will be taken after a sweet drink to check the level of glucose (blood sugar) in your blood. If the tests are abnormal, you will be followed by your primary care physician. From the time you enter the study until 30 weeks into your pregnancy, you will have a medical history, physical examination, and routine blood tests done every four weeks. About 6 mL (slightly more than one teaspoon) of blood will be taken for these tests. From 30 weeks until delivery, a medical history and physical examination will be done every two weeks and routine blood tests will be done every 4 weeks. About 6 mL (slightly more than one teaspoon) of blood will be taken for these tests. Two to three weeks after delivery, you will have a medical history, physical examination, and routine blood tests done. About 6 mL (slightly more than one teaspoon) of blood will be taken for these tests.

During Delivery

At the time of delivery, a history and physical exam and routine blood tests will be done. Blood will also be drawn to check how well your body is able to fight infection and to check the amount of HIV in your blood. About 18 mL (about 3½ teaspoons) of blood will be drawn. You will be given the results of these tests. After your baby is born, a small amount of blood will also be drawn from the umbilical cord that is attached to the placenta after the placenta has been separated from the baby. This blood comes from the placenta not your baby.

After Delivery

If you are taking efavirenz, elvitegravir/cobicistat, darunavir/cobicistat, atazanavir/cobicistat, dolutegravir, or tenofovir alafenamide fumarate (TAF)/cobicistat, TAF/ritonavir, TAF alone, you will be seen in the clinic 6-12 weeks after you deliver your baby. At this visit after delivery, you will have a history and physical exam, and routine blood tests. Blood will also be drawn to check how well your body is able to fight infection and to check the amount of HIV in your blood. You will be given the results of these tests. Repeat blood samples will be taken to check the amount of HIV medicine in your blood. The total amount of blood to be drawn at this visit is between 30-32 mL (6 to 6½ teaspoons). A vaginal fluid sample and a

vaginal swab will be taken. The vaginal sample can either be collected by you or your doctor. This testing will be done in batches later in the study, so you and your doctor won't get the results of these tests.

If you are taking darunavir/ritonavir twice daily you will be seen in the clinic at 2-3 weeks after you deliver your baby. At this visit after delivery, you will have a history and physical exam, and routine blood tests. Blood will also be drawn to check how well your body is able to fight infection and to check the amount of HIV in your blood. Repeat blood samples will be taken to check the amount of HIV medicine in your blood like what was done during your pregnancy. The total amount of blood to be drawn at this visit is between 30-32 mL (6 to 6½ teaspoons). At each visit you will be asked about taking your HIV medicines.

Study Visits for Your Baby

After your baby is born, your baby will be examined 3 times during the study: from birth to 3 days after birth, 5-9 days after birth, and again at 4-6 months of age. During these visits, your baby will be weighed and measured and information about your baby's health will be recorded from his/her medical records. Your baby, if able, will have blood samples taken to determine how much of the antiretroviral medication you took during pregnancy got into your baby and how long it takes to go away. Your baby will have blood samples taken at three time points between birth and 3 days after birth and a fourth sample taken between 5 and 9 days after birth. About 1 mL, or less than ¼ teaspoon (*sites-add locally relevant description of blood volume*) of blood will be taken for each sample. The total amount of blood taken for these tests will be around 3 – 4 mL, about 1 teaspoon (*sites-add locally relevant description of blood volume*).

Each of your baby's study visits will last about [*sites add local information about time for study visits*].

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

The study will enroll 25 women per drug/drug combination and their babies.

HOW LONG WILL YOU/YOUR BABY BE IN THIS STUDY?

You and your baby will be in this study until 24 weeks after you deliver your baby.

WHY WOULD THE DOCTOR TAKE ME/MY BABY OFF THIS STUDY EARLY?

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

- The study is cancelled by the IMPAACT network, U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), other local or national regulatory agencies, or the site's Institutional Review Board (IRB) or Ethics Committee (EC). An IRB and EC are committees that watches over the safety and rights of research subjects.
- You are/your baby is not able to attend the study visits as required by the study.
- You need a treatment that you may not take while on study.
- You are not able to take the HIV medicine(s) required by the study.

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

WHAT ARE THE RISKS OF THE STUDY?

The medicines used in this study may have side effects. Your doctor will explain the possible side effects of the medicines you are taking.

Any time a medicine dose is used (both approved and not approved by the FDA), unexpected side effects may occur. If you have any questions concerning the possible side effects of the medicines that you are taking, please ask the medical staff at your site to review them with you.

Risks of Drawing Blood

Blood drawing may cause fainting or lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site. Blood drawing from your baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

Risks of Collecting Vaginal Fluid and Vaginal Swabs

You may feel slight discomfort when collecting vaginal fluid. This should be minimal.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. You may benefit from having the levels of HIV medicine(s) in your blood measured and having your blood checked for safety effects. If these levels are low compared to those in non-pregnant adults, you and your clinician may decide to increase the dose of the medicine(s). Information learned from this study may help others who have HIV.

WHAT ABOUT CONFIDENTIALITY?

For US Sites

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you/your baby, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you/your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the U.S. Food and Drug Administration (FDA).

People who may review your/your baby's records include: the U.S. Food and Drug Administration (FDA), (insert Name of Site) IRB, National Institutes of Health (NIH), the Office for Human Research Protection, study staff, and study monitors. Any publication of this study will not use your/your baby's name or identify you/your baby personally.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you/your baby or your/your baby's participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

For sites outside the U.S

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

Your/your baby's records may be reviewed by the Ministry of Public Health in your country, the FDA, the Office of Human Research Protections (OHRP), the NIH, (*insert name of site*) IRB, Ethics Committee (EC), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study. Any medical costs for your treatment outside this study, including your prescribed medicines for HIV, will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby. You will not receive payment for your participation in this study.

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your/your baby's 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 (NIH). You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH SUBJECT?

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

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

- name of the investigator or other study staff
- telephone number of above

For questions about your/your baby's rights as a research subject, contact:

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

SIGNATURE PAGE

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

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian (print)
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting

Study Staff Signature and Date

Witness' Name (print)

Witness's Signature and Date

APPENDIX VI-B
SAMPLE CONSENT FORM
FOR WOMEN ON ARV MEDICINES WITH TUBERCULOSIS TREATMENT (FIRST LINE
AND SECOND LINE)

(Note to Sites: For use with Appendix I-B, I-AMR, and II)

IMPAACT P1026s: Pharmacokinetic Properties of Antiretroviral and Related Drugs during Pregnancy and Postpartum, Version, 10.0, dated 2 February 2016
(International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network)

INTRODUCTION

You and your baby are being asked to take part in the research study named above because you are infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS and you are pregnant and are taking HIV medicines and tuberculosis medications as described in one of the tables below.

One of the following HIV medications: Efavirenz Lopinavir/ritonavir	At least one of the following additional TB medications: rifampicin ethambutol isoniazid pyrazinamide
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Or

HIV medications: Any	Two of the following TB medications: kanamycin amikacin capreomycin moxifloxacin levofloxacin ofloxacin ethionamide/prothionamide terizidone/cycloserine para-aminosalicylic acid (PAS) isoniazid bedaquiline clofazamine delamanid linezolid pretomanid
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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/allow your baby 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?

The correct amount of tuberculosis medicines needed during pregnancy to treat tuberculosis infection is not known. When tuberculosis medicines are taken together with HIV medicines TB medicines may decrease the amount of the HIV medicines in the blood, so that the correct doses of these HIV medicines to protect your baby from HIV infection while being safe for you and your baby is not known. In this study, we will measure levels of tuberculosis medicines and these HIV medicines in HIV-infected pregnant women. We will compare the levels of tuberculosis medicines to those in HIV-uninfected pregnant women on the same tuberculosis medicines. We will also compare the levels of HIV medicines to those in non-pregnant adults without tuberculosis on the same HIV medicines. If it is found that your blood levels of the HIV medicines are too low, a new dose may be recommended that is not yet approved by the Food and Drug Administration (FDA). The amount of medicine found in blood from your baby's umbilical cord will be compared to the amount of medicine in your blood at the time of delivery. We will also look to see how much of the HIV medicines you took are getting into your baby and how safe these medicines are for you and your baby.

This study will be looking at dosing combinations and dose amounts of certain HIV medicines that are not yet approved by the FDA and are still being studied. For example, the higher doses of lopinavir/ritonavir and efavirenz being studied are not approved by the FDA.

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

You will continue to obtain and take your HIV and tuberculosis medicines as you would normally. No HIV or tuberculosis medicines are supplied by this study. Your doctor may ask your permission to report the medicine you take to a national registry, which collects information anonymously on the use of HIV medicine during pregnancy, and any effects these medicines may have on infants. This information is completely confidential and your name will not be used. You do not have to agree to be in the registry.

Your doctor will review with you any dietary recommendations related to the HIV and tuberculosis medicines that you are taking. You will need to be on your HIV and tuberculosis medicines for at least 2 weeks before your first study visit.

During Pregnancy

- You will need to come to the clinic to make sure you are eligible for the study before you enroll. This may be done as part of your first study visit when you are 20-26 weeks pregnant or 30-38 weeks pregnant, so a separate visit will not be required. We may test you for HIV to confirm your status. At each of these visits you will have a history and physical exam, and routine blood tests. Blood will also be drawn to check how well your body is able to fight infection and to check the amount of HIV in your blood. The total amount of blood for these tests is 13 - 22 mL (slightly more than 4 teaspoons). At each visit you will be asked about taking your HIV medicines.
- Checking the Amount of HIV and Tuberculosis Medicines in Your Blood

If you enter the study when you are 20-26 weeks pregnant, repeat blood samples will be taken to measure the amount of HIV and tuberculosis medicines in your blood. These blood samples will be repeated when you are 30-38 weeks pregnant. A small plastic catheter (soft tube) will be placed in a vein in your arm for an extended period of time, so that blood can be drawn multiple times, without having to stick you with a needle several times. The tube will stay in place until all of the blood samples are drawn. Depending on the medicine(s) you are taking and the time you usually take them, 7 blood samples over 12 hours, or 8 blood samples over 24 hours will be taken. The total amount of blood taken for these tests will be between 31-35 mL (about 7 teaspoons). You will be asked to

provide the times of your previous two doses of medicine and to describe the time and amount of your previous two meals. Before these repeat blood samples are taken, the study staff will review with you any dietary recommendations related to the HIV medicines you are taking. Your HIV medicine level will be reported back to you and your doctor as soon as possible. If the level is low compared to those in non-pregnant adults, you and your doctor will be told. You may decide, in consultation with your doctor, to adjust the dose of the medicine(s). The new dose may be higher than the current FDA approved dose. If you and your doctor choose to increase your dose of medicine, you may choose to have repeat blood sampling and drug measurements taken during the pregnancy and after you deliver to assess the levels of medicine in your blood on the new dose. The tuberculosis drug levels and testing will be done in batches later in the study, so you and your doctor won't get results of these tests.

- Genetic Testing

Some of your blood collected for other tests will be used for genetic testing. Also, if you agree, between birth and 9 days after birth, your baby will have one drop of blood taken for genetic testing of your baby. This test is to see if there are differences in specific genes that may affect the levels of some medicines. Some people break down medicines differently based on their DNA and this can change the levels of the medicines in their bodies. You may decide that you do not want your or your baby's DNA to be tested either now or at another time, by contacting your care provider during the study. You can still participate in this study even if you make this decision. This test will be done later in the study so you will not receive the results of this test. Please read the following statement carefully and then mark your initials in the appropriate space provided:

I agree to allow my DNA to be tested.

Yes _____ No _____ Initials _____ Date _____

I agree to allow my baby's DNA to be tested.

Yes _____ No _____ Initials _____ Date _____

- Additional study tests if you are taking lopinavir/ritonavir

If you are taking an increased dose of lopinavir/ritonavir, you will be followed more closely during pregnancy and after delivery because this higher dosing combination is not yet approved by the FDA. You will have an electrocardiogram (a quick test that looks at how your heart is beating) when you enter the study and again after 30 weeks into your pregnancy. If you have not had a test to check for gestational diabetes done as standard of care by your primary care physician, between 24 weeks gestation and delivery, some blood will be taken after a sweet drink to check the level of glucose (blood sugar) in your blood. If the tests are abnormal, you will be followed by your primary care physician. From the time you enter the study until 30 weeks into your pregnancy, you will have a medical history, physical examination, and routine blood tests done every four weeks. About 6 mL (slightly more than one teaspoon) of blood will be taken for these tests. From 30 weeks until delivery, a medical history and physical examination will be done every two weeks and routine blood tests will be done every 4 weeks. About 6 mL (slightly more than one teaspoon) of blood will be taken for these tests. Two to three weeks after delivery, you will have a medical history, physical examination, and routine blood tests done. About 6 mL (slightly more than one teaspoon) of blood will be taken for these tests.

During Delivery

At the time of delivery, a history and physical exam and routine blood tests will be done. Blood will also be drawn to check how well your body is able to fight infection and to check the amount of HIV in your blood. You will be given the results of these tests. About 18 mL (about 3½ teaspoons) of blood will be drawn. After your baby is born, a small amount of blood will also be drawn from the umbilical cord that is attached to the placenta after the placenta has been separated from the baby. This blood comes from the placenta not your baby.

After Delivery

You will be seen in the clinic 2-8 weeks after you deliver your baby. At this visit after delivery, you will have a history and physical exam, and routine blood tests. Blood will also be drawn to check how well your body is able to fight infection and to check the amount of HIV in your blood. You will be given the results of these tests. If you received injectable TB drugs you will have a hearing test. This hearing test can be scheduled on any day after you deliver. If you are still taking tuberculosis medicines, repeat blood samples will be taken to check the amount of HIV medicine and tuberculosis medicine in your blood. The total amount of blood to be drawn for these tests is between 13-54 mL (about 3 to 11 teaspoons) depending on the tests that will be done. At each visit you will be asked about taking your HIV medicines.

Study Visits for Your Baby:

After your baby is born, your baby will be examined 3 times during the study: from birth to 3 days after birth, 5-9 days after birth, and again at 4-6 months of age. During these visits, your baby will be weighed and measured and information about your baby's health will be recorded from his/her medical records. If you received injectable TB drugs your baby will have a hearing test. This hearing test can be scheduled on any day. Your baby, if able, will have blood samples taken to determine how much of the antiretroviral medication you took during pregnancy got into your baby and how long it takes to go away. Your baby will have blood samples taken at three time points between birth and 3 days after birth and a fourth sample taken between 5 and 9 days after birth. About 1 mL, or less than ¼ teaspoon (*sites-add locally relevant description of blood volume*) of blood will be taken for each sample. The total amount of blood taken for these tests will be around 3 – 4 mL, about 1 teaspoon (*sites-add locally relevant description of blood volume*).

Each of your baby's study visits will last about [*sites add local information about time for study visits*].

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

The study will enroll 25 women per HIV medicine/tuberculosis medicine combination and their babies.

HOW LONG WILL I/MY BABY BE IN THIS STUDY?

You and your baby will be in this study until 24 weeks after you deliver your baby.

WHY WOULD THE DOCTOR TAKE ME/MY BABY OFF THIS STUDY EARLY?

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

- The study is cancelled by the IMPAACT network, U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), other local

or national regulatory agencies, or the site's Institutional Review Board (IRB) or Ethics Committee. An IRB is a committee that watches over the safety and rights of research subjects.

- You are/your baby is not able to attend the study visits as required by the study.
- You need a treatment that you may not take while on study.
- You are not able to take the HIV or TB medicine(s) required by the study.

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

WHAT ARE THE RISKS OF THE STUDY?

The medicines used in this study may have side effects. Your doctor will explain the possible side effects of the medicines you are taking.

Any time a medicine dose is used (both approved and not approved by the FDA), unexpected side effects may occur. If you have any questions concerning the possible side effects of the medicines that you are taking, please ask the medical staff at your site to review them with you.

Risks of Drawing Blood

Blood drawing may cause fainting or lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site. Blood drawing from your baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. You may benefit from having the levels of HIV and TB medicine in your blood measured and having your blood checked for safety effects. If these levels are low compared to those in non-pregnant adults, you and your clinician may decide to increase the dose of the medicine(s). Information learned from this study may help others who have HIV and TB.

WHAT ABOUT CONFIDENTIALITY?

U.S. sites:

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you/your baby, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you/your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the U.S. Food and Drug Administration (FDA).

People who may review your/your baby's records include the U.S. Food and Drug Administration, the site IRB or Ethics Committee, other national regulatory agencies, the National Institutes of Health, the

Office for Human Research Protections, study staff, and study monitors. Any publication of this study will not use your/your baby's name or identify you/your baby personally

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you/your baby or your/your baby's participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

For sites outside the U.S.

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

Your/your baby's records may be reviewed by the Ministry of Public Health in your country, the FDA, the Office of Human Research Protections (OHRP), the NIH, (*insert name of site*) IRB, Ethics Committee (EC), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study. Any medical costs for your/your baby's treatment outside this study, including your prescribed medicines for HIV and tuberculosis will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby. You will not receive payment for your participation in this study.

WHAT HAPPENS IF I AM INJURED?

If you are/your baby is injured as a result of being in this study, you/your baby will be given immediate treatment for your/your baby's 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 (NIH). You will not be giving up any of your/your baby's legal rights by signing this consent form.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH SUBJECT?

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

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

- name of the investigator or other study staff
- telephone number of above

For questions about your/your baby's rights as a research subject, contact:

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

SIGNATURE PAGE

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

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian (print)
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting

Study Staff Signature and Date

Witness' Name (print)

Witness's Signature and Date

APPENDIX VI-C
SAMPLE CONSENT FORM
FOR HIV-UNINFECTED PREGNANT WOMEN ON NO ARV MEDICINES WITH
TUBERCULOSIS TREATMENT

(Note to Sites: For use with Appendix I-C and II)

IMPAACT P1026s: Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum, Version, 10.0, dated 2 February 2016
(International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network)

INTRODUCTION

You and your baby are being asked to take part in the research study named above because you are pregnant and are taking tuberculosis medicines during your pregnancy as described in one of the tables below.

At least one of the following TB medications:
rifampicin
ethambutol
isoniazid
pyrazinamide

or

Two of the following TB medications:

- kanamycin
- amikacin
- capreomycin
- moxifloxacin
- levofloxacin
- ofloxacin
- ethionamide/prothionamide
- terizidone/cycloserine
- para-aminosalicylic acid (PAS)
- isoniazid
- bedaquiline
- clofazamine
- delamanid
- linezolid
- pretomanid

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/allow your baby 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?

The correct amount of tuberculosis medicines needed during pregnancy to treat tuberculosis infection is not known. In this study, we will measure the levels of tuberculosis medicines in the blood of women before and after delivery. We will also look to see how safe these medicines are. .

WHAT DO I/MY BABY HAVE TO DO IF I AM IN THIS STUDY?

You will continue to obtain and take your tuberculosis medicines as you would normally. No tuberculosis medicines are supplied by this study. Your doctor will review with you any dietary recommendations related to the tuberculosis medicines that you are taking. You will need to be on your tuberculosis medicines for at least 2 weeks before your first study visit.

During Pregnancy

You will need to come to the clinic to make sure you are eligible for the study before you enroll. This may be done as part of your first study visit when you are 20-26 weeks pregnant or 30-38 weeks pregnant, so a separate visit will not be required. At each of these visits you will have a history and physical exam, and routine blood tests. You will be given the results of these tests. About 6 - 12 mL (slightly more than 2 teaspoon) of blood will be drawn at each visit depending on what TB drugs you are taking.

- Checking the Amount of Tuberculosis Medicine in Your Blood

At 20-26 weeks and 30-38 weeks of your pregnancy, blood samples will be taken to measure the amount of tuberculosis medicine in your blood. A small plastic catheter (soft tube) will be placed in a vein in your arm and will stay there for about a half a day, so that blood can be drawn about 7 times, without having to stick you with a needle more than about once. . The tube will stay in place until all of the blood samples are drawn. Seven (7) blood samples will be taken over 12 hours. The total amount of blood taken for these tests will be about 17 mL (about 3 ½ teaspoons) depending on the number of tuberculosis medicines you are taking. You will be asked for the times and amounts of your previous two doses of medicine and last two meals. The study staff will review with you the best diet for the tuberculosis medicines you are taking. The tuberculosis drug levels will be done in batches later in the study, so you and your doctor won't get results of these tests until about the end of the study.

During Delivery

At the time of your delivery, a history and physical exam and routine blood tests will be done. About 6 mL (slightly more than one teaspoon) of blood will be taken. You will be given the results of these tests.

After Delivery

You will be seen in the clinic 2-8 weeks after you deliver your baby. At this visit you will have a history and physical exam, and routine blood tests. If you received injectable TB drugs you will have a hearing test. This hearing test can be scheduled for any time after you deliver. If you are still taking tuberculosis medicines, repeat blood samples will be taken to determine the amount of TB medicine in your blood. The total amount of blood to be drawn for these tests is between 6 and 29 mL (about 1 to 6 teaspoons) depending on the tests to be done.

Study Visits for Your Baby

After your baby is born, your baby, will be examined 2 times during the study: from birth to 3 days after birth and again at 4 – 6 months of age. During these visits, your baby will be weighed and measured and

information about your baby's health will be recorded from his/her medical records. If you received injectable TB drugs your baby will have a hearing test. This hearing test can be scheduled on any day.

Each of your baby's study visits will last about [sites add local information about time for study visits].

Genetic Testing

Some of your blood collected for other tests will be used for genetic testing to help understand how your body handles your medications based on your genes and DNA. Also, if you agree, between birth and 3 days of age, your baby will have one drop of blood taken for genetic testing of your baby. You may decide that you do not want your or your baby's genes to be tested. Tell your health care provider if you decide this. You can still participate in this study even if you make this decision. This test will be done later in the study so you will not receive the results of this test. Please read the following statement carefully and then mark your initials in the appropriate space provided:

I agree to allow my DNA to be tested.

Yes _____ No _____ Initials _____ Date _____

I agree to allow my baby's DNA to be tested.

Yes _____ No _____ Initials _____ Date _____

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

The study will enroll 25 women for each tuberculosis treatment and their babies.

HOW LONG WILL I/MY BABY BE IN THIS STUDY?

You and your baby will be in this study until 24 weeks after you deliver your baby.

WHY WOULD THE DOCTOR TAKE ME/MY BABY OFF THIS STUDY EARLY?

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

- The study is cancelled by the IMPAACT network, U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), other local or national regulatory agencies, or the site's Institutional Review Board (IRB) or Ethics Committee. An IRB is a committee that watches over the safety and rights of research subjects.
- You are/your baby is not able to attend the study visits as required by the study.
- You need a treatment that you may not take while on study.
- You are not able to take the tuberculosis medicine(s) required by the study.

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

WHAT ARE THE RISKS OF THE STUDY?

The medicines used in this study may have side effects. Your doctor will explain the possible side effects of the medicines you are taking. If you have any questions concerning the possible side effects of the medicines that you are taking, please ask the medical staff at your site to review them with you.

Risks of Drawing Blood

Blood drawing may cause fainting or lightheadedness or some discomfort. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of an infection at the blood draw site. Blood drawing from your baby can also be done by heel stick. Heel stick may cause some discomfort, bleeding or bruising at the site of the heel stick. There is a small risk of infection at the site of the heel stick.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be no direct benefit to you but you will have more doctor visits where you can be checked that your medicines are safe. Information learned from this study may help others who are pregnant and have tuberculosis.

WHAT ABOUT CONFIDENTIALITY?

For US Sites:

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you or your baby, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the U.S. Food and Drug Administration (FDA).

People who may review your/your baby's records include: the U.S. Food and Drug Administration (FDA), (insert Name of Site) IRB, National Institutes of Health (NIH), the Office for Human Research Protection, study staff, and study monitors. Any publication of this study will not use your/your baby's name or identify you/your baby personally.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you/your baby or your/your baby's participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

(For sites outside the U.S.)

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

Your/your baby's records may be reviewed by the Ministry of Public Health in your country, the FDA, the Office of Human Research Protections (OHRP), the NIH, (*insert name of site*) IRB, Ethics Committee (EC), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study. Any medical costs for your/your baby's treatment outside this study, including your prescribed medicines for tuberculosis, will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby. You will not receive payment for your participation in this study.

WHAT HAPPENS IF I AM/MY BABY IS INJURED?

If you are/your baby is injured as a result of being in this study, you/your baby 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 (NIH). You will not be giving up any of your/your baby's legal rights by signing this consent form.

WHAT ARE MY/MY BABY'S RIGHTS AS A RESEARCH SUBJECT?

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

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

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

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

- name of the investigator or other study staff
- telephone number of above

For questions about your/your baby's rights as a research subject, contact:

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

SIGNATURE PAGE

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

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian (print)
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting

Study Staff Signature and Date

Witness' Name (print)

Witness's Signature and Date

APPENDIX VI-D
SAMPLE CONSENT FORM
FOR POSTPARTUM WOMEN ON ANTIRETROVIRAL MEDICINES AND HORMONAL
CONTRACEPTIVES

(Note to Sites: For use with Appendix I-D)

IMPAACT P1026s: Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum, Version, 10.0, dated 2 February 2016
(International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network)

INTRODUCTION

You are being asked to take part in the research study named above because you are infected with the Human Immunodeficiency Virus (HIV), the virus that causes AIDS and are taking the HIV medicines, efavirenz or atazanavir/ritonavir/tenofovir or darunavir/cobicistat or atazanavir/cobicistat, and plan to start using an oral contraceptive pill containing ethinyl estradiol, or an etonogestrel implant after you deliver your baby.

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?

Some HIV medicines interact with hormonal birth control, potentially changing the levels of the birth control (increasing the chance of side effects or of pregnancy) or of the HIV drug (increasing side effects or decreasing HIV activity). We want to study whether oral contraceptive pills containing the estrogen agent ethinyl estradiol or the contraceptive etonogestrel implant have significant interactions with darunavir/cobicistat, atazanavir/cobicistat, efavirenz or atazanavir/ritonavir/tenofovir. We want to look at the levels of these medicines in your blood before you start one of the two types of hormonal birth control. Then we will measure the levels of these medicines again after you have been on birth control for several weeks and see if the levels have changed. We will also measure the levels of the hormones in your blood from the birth control and compare those levels to results from women using the same birth control but not taking antiretroviral medicines. We can see if the hormones and antiretroviral (ARV) medicines interact or not and see if hormonal birth control should work as well in women on certain ARV drugs. We will also look to see how safe these medicines are for you.

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

You will continue to obtain and take your HIV medicines as you would normally. No HIV medicines or hormonal contraceptives are supplied by this study. Your doctor will review with you any dietary recommendations related to the HIV medicines that you are taking. You will need to be on the same dose of your HIV medicines for at least 2 weeks before your first study visit.

2-12 weeks after you deliver your baby

You will need to come to the clinic to make sure you are eligible for the study before you enroll. This may be done as part of your first study visit, so a separate visit will not be required. We may test you for HIV to confirm your status. You will have a history and physical exam, and routine blood tests to see if it is safe for you to be in the study. You will be asked about taking your HIV medicines. Blood will be

drawn to check how well your body is able to fight infection and to check the amount of HIV in your blood. The total amount of blood taken from these tests will be 13 – 16 mL (about 2½ to 3 ½ teaspoons). You will be given the results of these tests. You will be asked to sign this consent form.

If you are able to be in this study, blood tests will be done to measure the amount of HIV medicine in your blood. A small plastic catheter (soft tube) will be placed in a vein in your arm and stay there for about a half a day so that blood can be drawn about 7 -8 times, without having to stick you more than about once. Depending on the medicine(s) you are taking, 7 blood samples over 12 hours, or 8 blood samples over 24 hours will be taken. The total amount of blood taken for these tests will be 17-19 mL (about 4 teaspoons). You will be asked to provide the times and amounts of your last two doses of medicine and last two meals. Before these blood samples are taken, the study staff will review with you any food recommendations related to the HIV medicines you are taking. After these blood tests are taken, you will start the oral contraceptive pills as prescribed by your regular doctor or have the etonogestrel implant inserted by your doctor.

6 to 7 weeks after you have started hormonal contraceptives

You will come to the clinic 6-7 weeks after you have started hormonal contraceptives and the same tests that were done 2-12 weeks after you delivered your baby will be repeated. We will ask you questions about how you are taking your medicines. A pregnancy test will also be done. You will take your HIV medicine at the same time of day you take your hormonal contraceptives three days before you have repeat blood samples drawn and on the day you have repeat blood samples drawn to check the levels of hormone and HIV medicine in your blood. If you are using the etonogestrel implant 4mL (about one teaspoon) of blood will be taken from you. If you are using oral contraceptives eight (8) blood samples (about 3 teaspoons) will be taken over 24 hours. The total amount of blood taken for all these tests will be between 35-49 mL (about 7 to 10 teaspoons) depending on which contraceptive method you are using. This testing will be done in batches later in the study, so you and your doctor won't get the results of these tests until the end of the study. You will be asked about taking your HIV medicines.

Genetic Testing

Some of your blood collected for other tests will be used for genetic testing to help understand how your body handles your medications based on your genes and DNA. You may decide that you do not want your genes to be tested. Tell your health care provider if you decide this. You can still participate in this study even if you make this decision. This test will be done later in the study so you will not receive the results of this test. Please read the following statement carefully and then mark your initials in the appropriate space provided:

I agree to allow my DNA to be tested.

Yes _____ No _____ Initials _____ Date _____

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

The study will enroll 100 women; 25 women per HIV medicine/hormonal contraceptive combination.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study until 6-7 weeks after you start taking hormonal contraceptives.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

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

- The study is cancelled by the IMPAACT network, U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), the Office for Human Research Protections (OHRP), other local or national regulatory agencies, or the site's Institutional Review Board (IRB) or Ethics Committee. An IRB is a committee that watches over the safety and rights of research subjects.
- You are not able to attend the study visits as required by the study.
- You need a treatment that you may not take while on study.
- You are not able to take the HIV medicines or hormonal contraceptives required by the study.

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

WHAT ARE THE RISKS OF THE STUDY?

The medicines used in this study may have side effects. Your doctor will explain the possible side effects of the medicines you are taking. If you have any questions concerning the possible side effects of the medicines that you are taking, please ask the medical staff at your site to review them with you.

Risks of Drawing Blood

You may feel faint or lightheaded or feel some discomfort when blood is drawn for this study. Other risks include bleeding or bruising where the needle enters the body. A small blood clot may form where the needle enters the body or swelling of the surrounding skin may occur. There is also a small risk of a minor infection at the blood draw site.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be no direct benefit to you but you will have more doctor visits where you can be checked for safety on your medications. Information learned from this study may help others who are taking HIV medicines and want to use hormonal contraceptives.

WHAT ABOUT CONFIDENTIALITY?

For US Sites

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the U.S. Food and Drug Administration (FDA).

People who may review your records include: the U.S. Food and Drug Administration (FDA), (insert Name of Site) IRB, National Institutes of Health (NIH), the Office for Human Research Protection, study staff, and study monitors. Any publication of this study will not use your name or identify you personally.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about you or your participation in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate of Confidentiality to withhold that information.

(For sites outside the U.S.)

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 of identify you personally.

Your records may be reviewed by the Ministry of Public Health in your country, the FDA, the Office of Human Research Protections (OHRP), the NIH, *(insert name of site)* IRB, Ethics Committee (EC), study staff, and study monitors.

WHAT ARE THE COSTS TO ME?

There is no cost for the study-related clinic visits, examinations, and laboratory tests in this study. Any medical costs for your treatment outside this study, including your prescribed HIV medicines or hormonal contraceptives will be charged to you or your health insurance company. This study will not cover any cost related to your pregnancy and delivery or care of your baby. You will not receive payment for your participation in this study.

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 (NIH). 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 staffs 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 Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

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

Participant's Name (print)

Participant's Signature and Date

Participant's Legal Guardian (print)
(As appropriate)

Legal Guardian's Signature and Date

Study Staff Conducting

Study Staff Signature and Date

Witness' Name (print)

Witness's Signature and Date

APPENDIX VII HISTORY OF VERSION 1.0 TO VERSION 9.0

Versions 1.0 and 6.0 of P1026s never opened to enrollment.

Version 2.0 opened on March 17, 2003 and included 5 study arms:

- nevirapine 200 mg twice a day
- amprenavir 1200 mg twice a day
- abacavir 300 mg twice a day
- lopinavir/ritonavir (Kaletra) 400/100 mg twice a day
- indinavir/ritonavir 800/100 mg twice a day

Version 3.0 opened on May 19, 2004 and included 8 study arms:

- The nevirapine arm was discontinued as there are sufficient pharmacokinetic data between P1026s and P1022.
- The indinavir/ritonavir arm was discontinued due to lack of enrollment.
- The amprenavir arm was replaced with fosamprenavir/ritonavir 700/100 mg twice a day.
- abacavir 300 mg twice a day
- increased dose of Kaletra 400/100 mg twice a day until 30 weeks gestation, then 533/133 mg twice a day until results of postpartum PK evaluation were available
- atazanavir/ritonavir 300/100 mg once a day
- didanosine delayed release (Videx® EC) 400 mg once a day if weight > 60 kg; 250 mg once a day if weight < 60 kg
- emtricitabine 200 mg once a day
- tenofovir (300 mg once a day
- tenofovir/atazanavir/ritonavir 300/300/100 mg once a day

Version 4.0 opened on May 17, 2005 and included 10 study arms:

- lopinavir/ritonavir (Kaletra®) 400/100 mg twice a day until 30 weeks gestation, then 533/133 mg twice a day until results of postpartum PK evaluation were available
- fosamprenavir/ritonavir 700/100 mg twice a day
- atazanavir/ritonavir 300/100 mg once a day
- didanosine delayed release (Videx® EC) 400 mg once a day if weight > 60 kg; 250 mg once a day if weight < 60 kg
- emtricitabine 200 mg once a day
- tenofovir 300 mg once a day
- tenofovir/atazanavir/ritonavir 300/300/100 mg once a day
- nelfinavir [625 mg tablets] 1250 mg twice a day
- efavirenz 600 mg once a day
- tipranavir/ritonavir 500/200 mg twice a day

Version 5.0 opened on February 6, 2006 and included 10 study arms:

- lopinavir/ritonavir (Kaletra®) tablets 400/100 mg [2 tablets] twice a day until 30 weeks gestation, then 600/150 mg [3 tablets] twice a day until postpartum hospital discharge; and 400/100 mg [2 tablets] twice a day after postpartum hospital discharge, until 2 week postpartum PK sample is drawn
- fosamprenavir/ritonavir 700/100 mg twice a day
- atazanavir/ritonavir 300/100 mg once a day

- didanosine delayed release (Videx® EC) 400 mg once a day if weight > 60 kg; 250 mg once a day if weight < 60 kg
- emtricitabine 200 mg once a day
- tenofovir (300 mg once a day)
- tenofovir/atazanavir/ritonavir 300/300/100 mg once a day
- nelfinavir (625 mg tablets) 1250 mg twice a day
- efavirenz 600 mg once a day
- tipranavir/ritonavir 500/200 mg twice a day

Version 7.0 opened on May 12, 2009 and included 14 study arms

- The lopinavir/ritonavir, standard dose atazanavir/ritonavir, emtricitabine, tenofovir, standard dose tenofovir/atazanavir/ritonavir, and standard dose nelfinavir arms were closed.
- fosamprenavir/ritonavir 700/100 mg twice a day
- didanosine delayed release (Videx® EC) 400 mg once a day if weight > 60 kg; 250 mg once a day if weight < 60 kg
- efavirenz 600 mg once a day
- tipranavir/ritonavir 500/200 mg twice a day
- raltegravir 400 mg twice a day
- etravirine 200 mg twice a day
- maraviroc 150 mg or 300 mg twice a day
- darunavir/ritonavir 800/100 mg once a day
- darunavir/ritonavir 600/100 mg twice a day
- atazanavir/ritonavir 300/100 mg once a day until 30 weeks gestation then 400/100 mg once a day until postpartum hospital discharge; then 300/100 mg once a day after postpartum hospital discharge until 2 week postpartum PK samples drawn
- tenofovir/atazanavir/ritonavir 300/300/100 mg once a day until 30 weeks gestation; then 300/400/100 mg once a day until postpartum hospital discharge; then 300/300/100 mg once a day after postpartum hospital discharge until 2 week postpartum PK samples drawn
- nelfinavir [625 mg tablets] 1250 mg twice a day until 30 weeks gestation; then 1875 mg twice a day until postpartum hospital discharge; then 1250 mg twice a day after postpartum hospital discharge until 2 week postpartum PK samples drawn
- indinavir/ritonavir 400/100 mg twice a day only to participants enrolling in Thailand
- lopinavir/ritonavir (Alluvia tablets) 400/100 mg [2 tablets] twice a day until 30 weeks gestation; then 600/150 mg [3 tablets] twice a day until postpartum hospital discharge; then 400/100 mg [2 tablets] twice a day after postpartum hospital discharge until 2 week postpartum PK sample drawn only to participants enrolling in Uganda

Version 8.0 opened on April 18, 2013 and included 18 study arms:

➤ Antiretrovirals without TB treatment (10 arms):

- darunavir/ritonavir twice daily (600/100 mg b.i.d. or 800/100 mg b.i.d. until 30 weeks gestation; then 800/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn)
- darunavir/ritonavir twice daily (600/100 mg b.i.d. or 900/100 mg b.i.d. until 30 weeks gestation; then 900/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn)
- didanosine delayed release (Videx® EC) (400 mg q.d. if weight ≥ 60 kg; 250 mg q.d. if weight < 60 kg)
- etravirine (200 mg b.i.d.)

- maraviroc (150 mg b.i.d. or 300 mg b.i.d.)
 - nelfinavir 625 mg tablets (1250 mg b.i.d. until 30 weeks gestation; then 1875 mg b.i.d. until postpartum hospital discharge; then 1250 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn)
 - rilpivirine (25 mg q.d.)
 - tipranavir/ritonavir (500/200mg b.i.d.)
 - efavirenz (600 mg q.d.) (sites outside of Thailand)
 - lopinavir/ritonavir (Alluvia[®]) tablets (400/100 mg [2 tablets] b.i.d. until 30 weeks gestation, then 600/150 mg [3 tablets] b.i.d. until postpartum hospital discharge; and 400/100 mg [2 tablets] b.i.d. after postpartum hospital discharge, until 2 week postpartum PK samples are drawn) (African sites only)
- Antiretrovirals with Tuberculosis Treatment (3 study arms) (Receiving one of the following ARV drug drugs/drug combinations and rifampicin containing TB treatment with at least one of the following TB drugs.):
- efavirenz 600 mg q.d.
 - lopinavir/ritonavir 800/200 mg b.i.d.
 - nevirapine 200 mg b.i.d
- TB drugs:
- rifampicin 8-12 mg/kg (max 600 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w. and at least one of the following drugs:
 - ethambutol 15-20 mg/kg q.d., 25-35 mg/kg t.i.w.
 - isoniazid 4-6 mg/kg (max 300 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
 - pyrazinamide 20-30mg/kg q.d.; 30-40mg/kg t.i.w.
- HIV-uninfected women - No Antiretrovirals with Tuberculosis Treatment (1 study arm)
- Antiretrovirals with Postpartum Contraceptives (4 study arms):
- lopinavir/ritonavir 400/100 b.i.d. postpartum and starting combined oral contraceptives formulated with 30-35 µg ethinyl estradiol
 - atazanavir/ritonavir/tenofovir 300/100/300 mg q.d. postpartum and starting combined oral contraceptives formulated with 30-35 µg ethinyl estradiol
 - lopinavir/ritonavir 400/100 b.i.d. postpartum and starting etonogestrel implant.
 - atazanavir/ritonavir/tenofovir 300/100/300 mg q.d. postpartum and starting etonogestrel implant.

Version 9.0 opened on September 30, 2014 and included 16 study arms:

- Antiretrovirals without TB treatment (8 arms):
- darunavir/ritonavir twice daily (600/100 mg b.i.d. or 800/100 mg b.i.d. until 30 weeks gestation; then 800/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn)
 - darunavir/ritonavir twice daily (600/100 mg b.i.d. or 900/100 mg b.i.d. until 30 weeks gestation; then 900/100 mg b.i.d. until postpartum hospital discharge; then 600/100 mg b.i.d. after postpartum hospital discharge until 2 week postpartum PK samples are drawn)
 - etravirine 200 mg b.i.d.
 - elvitegravir/cobicistat 150/150 mg q.d.
 - dolutegravir 50 mg q.d.
 - tenofovir alafenamide fumarate (TAF) 10 mg q.d.

- efavirenz 600 mg q.d. (Sites outside of Thailand only)
 - lopinavir/ritonavir (Alluvia®) tablets (400/100 mg [2 tablets] b.i.d. until 30 weeks gestation, then 600/150 mg [3 tablets] b.i.d. until postpartum hospital discharge; and 400/100 mg [2 tablets] b.i.d. after postpartum hospital discharge, until 2 week postpartum PK samples are drawn) (African Sites Only)
- Antiretrovirals with Tuberculosis Treatment (3 study arms) (Receiving one of the following ARV drug drugs/drug combinations and rifampicin containing TB treatment with at least one of the following TB drugs.):
- efavirenz 600 mg q.d.
 - lopinavir/ritonavir 800/200 mg b.i.d.
 - nevirapine 200 mg b.i.d
- TB drugs:
- rifampicin 8-12 mg/kg (max 600 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w. and at least one of the following drugs:
 - ethambutol 15-20 mg/kg q.d., 25-35 mg/kg t.i.w.
 - isoniazid 4-6 mg/kg (max 300 mg) q.d.; 8-12 mg/kg (max 900 mg) t.i.w.
 - pyrazinamide 20-30mg/kg q.d.; 30-40mg/kg t.i.w.
- HIV-uninfected women - No Antiretrovirals with Tuberculosis Treatment (1 study arm)
- Antiretrovirals with Postpartum Contraceptives (4 study arms):
- atazanavir/ritonavir/tenofovir 300/100/300 mg q.d. postpartum and starting combined oral contraceptives formulated with 30-35 µg ethinyl estradiol
 - efavirenz 600mg q.d. postpartum and starting combined oral contraceptives formulated with 30-35 µg ethinyl estradiol
 - atazanavir/ritonavir/tenofovir 300/100/300 mg q.d. postpartum and starting etonogestrel implant.
 - efavirenz 600mg q.d. postpartum and starting etonogestrel implant