**Pharmacokinetic Statistical Analysis Plan**

Version # 1.0

# IMPAACT P1026S

Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum

ClinicalTrials.gov Identifier: NCT00042289

**July 27, 2021**

**This is IMPAACT P1026s Pharmacokinetic SAP Version 1.0 with names of authors, names of publication writing team members, and analysis timeline redacted.**

**Table of Contents**

## 1. Introduction

This Pharmacokinetic Statistical Analysis Plan (PK SAP) describes the non-compartmental pharmacokinetic (PK) analyses to be performed by the IMPAACT P1026S protocol pharmacologist(s) on the completed study dataset and included in the study manuscript(s).

Note: From the beginning of the study in 2003, pharmacologists followed the analysis plan in the Clinical Pharmacology Plan section of the protocol, and this separate PK SAP is created for submission to ClinicalTrials.gov.

## 2. PK-Related Study Background

P1026s 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.

## 3. Pharmacokinetic Population

For analysis purposes, **evaluable** participants for PK are defined as having adequate pharmacokinetic evaluations to determine the PK exposure parameter. For calculation of descriptive statistics for a PK parameter at a specific time point for women or infants, a participant's data will be deemed **unevaluable** if they do not include adequate pharmacokinetic evaluations to determine the PK parameter of interest.

## 4. Pharmacokinetic Study Objectives

PK-related objectives for IMPAACT P1026S are as follows:

**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.*

* Note: These 5 secondary objectives were intended to be exploratory, and will be considered as "Other study objectives". Therefore, this SAP will not include the outcome measures/analysis contents related to these objectives.

**KEY PK OUTCOME MEASURES**

PK Outcome Measures for ARVs, first-line TB drugs, second-line TB drugs, ethinyl estradiol and progestins:

Primary:

- AUC, and number of participants who achieved AUC above target (if a target was identified).
- Cmax, Ctrough after an observed dose

Secondary:

-

- Infant washout sampling: t ½, drug concentrations

- Genital secretions: ARV concentrations in vaginal secretions and plasma

PK Outcome Measures for etonogestrel:

Primary:

- Concentration in plasma

## 5. Pharmacokinetic Analyses

For all components, observed concentrations of each drug will be provided in listings. Any deviations from the planned PK analyses listed below that may be needed based on the emerging data will be described in the analysis report for individual study arms. PK parameter comparisons/statistical tests will be performed by protocol statisticians.

### 5.1. Below the Level of Quantitation

Concentration values that are below the level of quantification (BQL) will be set to zero for real-time therapeutic drug monitoring reports for calculation of AUC, and will be set to ½ the lower limit of quantitation (LLOQ) for end-of-arm summary calculations, unless otherwise noted in the manuscript for that study arm. If an entire concentration-time profile is BQL, the profile will be reported separately and excluded from the summary PK analysis. Any embedded BQL value (BQL value occurring between two quantifiable concentrations) in a profile will be set to missing for the purposes of PK analysis.

The ratio of cord blood concentration to maternal concentration at delivery will be calculated when both maternal plasma at delivery and cord blood are quantifiable, unless otherwise noted in the manuscript for that study arm.

### 5.2. Non-Compartmental Analysis

The PK sampling schedules are outlined in the IMPAACT P1026S protocol version 10.0 (Appendix III). For drugs with 12-hour sampling, time points are Pre-dose, and at 1, 2, 4, 6, 8 and 12 hours post-dose. For drugs with 24-hour sampling, time points are Pre-dose, and at 1, 2, 4, 6, 8, 12, and 24 hours post-dose.

Standard non-compartmental methods for PK parameter derivation will be performed using Phoenix 64 (Certara USA, Inc). Where possible, the following PK parameters will be determined from plasma concentrations following intensive PK sampling after oral dosing:

**PK Parameters from Non-Compartmental Analysis**

| PARAMETER | DEFINITION |
|---|---|
| **$C_{MAX}$** | Observed maximum plasma concentration |
| **$T_{MAX}$** | Time of maximum plasma concentration |
| **$C_{MIN}$** | Observed minimum plasma concentration |
| **$T_{MIN}$** | Time of minimum plasma concentration |
| **CL/F** | Apparent oral clearance |
| **$C_0$** | Observed pre-dose concentration |
| **$C_{LAST}$** | Observed trough concentration at the end of the dose interval |
| **AUC** | Area under the concentration-time curve over the dose interval |

| | |
|---|---|
| $T_{1/2}$ | Half-life derived from the terminal slope of the plasma concentration versus time curve |

Additional PK parameters may be determined where appropriate. Concentrations for PK analyses will be used as supplied by the analytical laboratory.

#### 5.2.1. AUC Values

AUC is calculated by the trapezoidal rule using actual sampling times.

#### 5.2.2. AUC Calculation for Profiles with Unexpected Concentrations

When C0 is BQL, $AUC_{0\text{-inf}}$ will be used, calculated as $AUC_{0\text{-last}} + C_{last}/ke$, where $AUC_{0\text{-last}}$ is the AUC to the last measurable concentration and ke is the elimination rate constant.

## 6. Population (POP) Pharmacokinetic Analysis

POP PK analyses may be performed using the IMPAACT P1026S PK data alone or in combination with existing adult PK data using appropriate methodology. Any POP PK analysis undertaken to inform different dosing regimen scenarios or to assist the study team with assessment of safety or dosing will be considered outside of the scope of this protocol and will be reported separately.

## 7. Summary Statistics

Individual concentrations and pharmacokinetic parameters will be summarized using descriptive statistics where data allow. These may include the number of observations available, geometric mean, geometric coefficient of variation (CV), geometric 95% confidence intervals, arithmetic mean, standard deviation (SD), CV, median, $5^{th}$ percentile, $95^{th}$ percentile, interquartile range, minimum, and maximum.

## 8. Presentation of Data

Concentration time profiles will be presented graphically. For summary statistic plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.