

Single Dose Pharmacokinetics of Doravirine in HIV-infected Pregnant Women

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5 A.1	Sexually transmitted infection testing removed.	This testing will be done as part of routine obstetrical care.
1, 5.A.1, 7, 8	Breastmilk sampling added.	Breastmilk samples will be obtained from participants at the postpartum visit when applicable.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812) National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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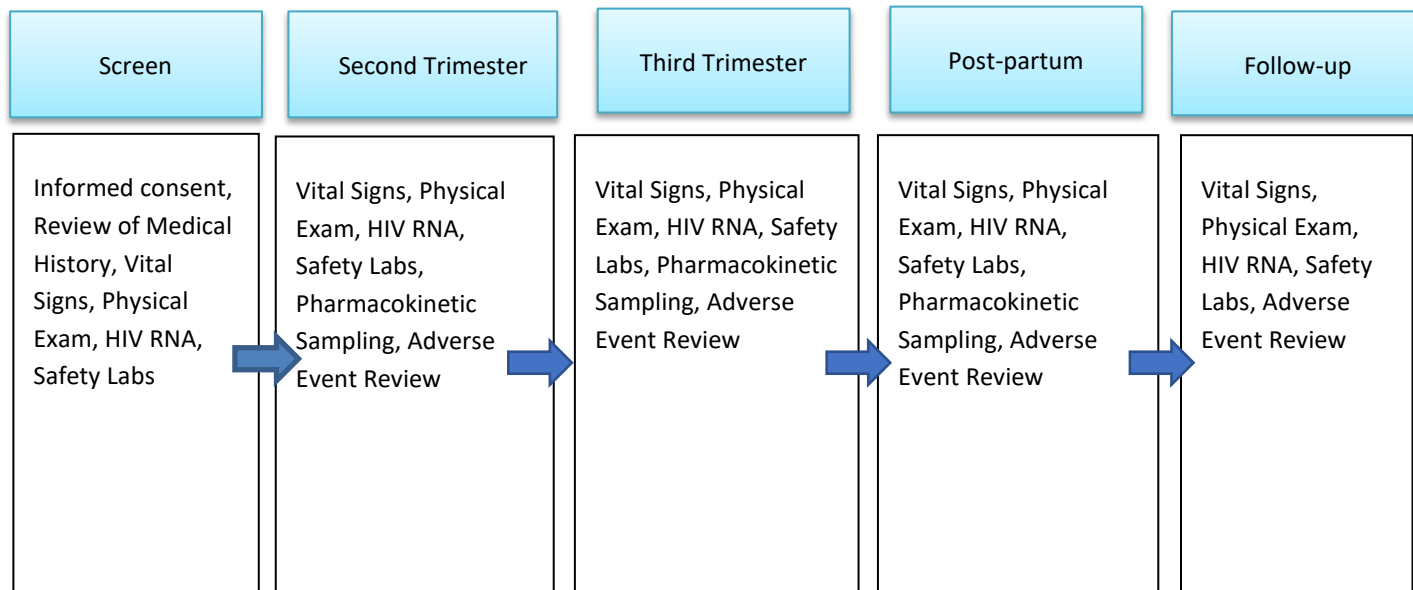
1 PROTOCOL SUMMARY**SYNOPSIS**

Title:	Single Dose Pharmacokinetics of Doravirine in HIV-infected Pregnant Women
Study Description:	The proposed study is a single-site Phase 1 evaluation of doravirine across the gestational period. This project proposes to give single doses of doravirine (DOR) to gravid females living with Human Immunodeficiency Virus (HIV) currently on antiretroviral therapy with undetectable plasma HIV RNA. Single doses will be given in the second and third trimester, and post-partum. Pharmacokinetic sampling will occur over a 72-hour dosing interval, and total and protein-unbound drug concentrations will be assessed across the three dosing phases.
Objectives:	Primary Objective: To describe single-dose pharmacokinetics of Doravirine in the blood plasma of women living with HIV during three phases of pregnancy.
Study Population:	The study participants will be cisgender pregnant females over the age of 18, who are currently living with HIV. Participants will have been on a stable antiretroviral regimen for at least 30 days prior to enrollment and have an undetectable plasma HIV RNA.
Phase:	1
Description of Sites/Facilities Enrolling Participants:	The study will include only one site, UNC Medical Center, a large academic hospital-based primary and tertiary care center in Chapel Hill, North Carolina. The study procedures will be conducted in the hospital's Clinical & Translational Research Center (CTRC) and the UNC Infectious Diseases (ID) Clinic, which serves approximately 1900 HIV-positive patients living with HIV from a wide catchment area.
Description of Study Intervention:	Participants will receive single doses of Doravirine at three visits over the second and third trimesters and postpartum. Pharmacokinetic sampling will occur over at least a 24-hour post-dose period (and up to 72h if available), and include blood plasma assessments at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours around each observed dose. A breastmilk sample will be obtained through hand expression or using an electronic breast pump at the 4, 8, and 24-hour post-dose time points at the postpartum sampling visit from participants who are able to provide the sample.

Study Duration: The estimated duration of patient recruitment is 18 months.

Participant Duration: Participants will be on study for up to 34 weeks, depending on the individual scheduling of their visits within the allotted windows.

SCHEMA



SCHEDULE OF EVENTS (SOE)

Time Period →	Screen	2nd Trimester	3 rd Trimester	Post-partum	Follow-up
Activity ↓	(-28 to 0 Days)	(20-26 weeks)	(30-34 weeks)	(4-8 weeks after delivery)	(within 14 days after last sample)

Informed Consent	X				
Review of Medical History	X				
Vital Signs ^a	X	X	X	X	X
Physical Examination	X	X	X	X	X
HIV RNA	X	X	X	X	X
Infant HIV DNA ^d				X	
Safety Labs ^b	X	X	X	X	X
Pharmacokinetic Sampling ^c		X	X	X	
Adverse Event Review		X	X	X	X

- a. Vital signs include: blood pressure, pulse, respiratory rate, temperature, and weight. Height should be documented at the screening visit.
- b. Safety labs include: CBC with differential, and the following serum chemistries: Na, K, Cl, CO₂, BUN, Creatinine, glucose, Ca, Alb, total protein, AST, ALT, Alkaline phosphatase, total Bilirubin, total Cholesterol, Triglycerides, HDL, LDL, and lipase. Urinalysis will be completed if it has not been done as part of obstetrical care in the previous month.
- c. As outlined in Study Design section, pharmacokinetic samples for total blood plasma concentrations will be obtained at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours around an observed dose of doravirine during all PK visits. Samples will be collected at 48 and 72-hours after the observed dose on participants that are able to return to the clinic. Breastmilk samples will be collected at the 4, 8, and 24-hour time points at the postpartum sampling visit when applicable.
- d. Infant HIV DNA data will be obtained from electronic medical records.

2 INTRODUCTION

STUDY RATIONALE

Pregnant and postpartum women are usually excluded from clinical drug trials, including pregnant women who are living with HIV. This leaves providers without adequate dosing information of many commonly used medications. It can take seven or more years before dosing information for pregnancy is included in product labelling. The 21st Century Cures Act established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). In September 2018, this committee presented their report to the Secretary of Health and Human Services and Congress. This report outlines strategies for identifying and addressing knowledge and research gaps regarding drug use during pregnancy and for improving the development of safe and effective therapies for pregnant and lactating women. Recently, a New England Journal of Medicine (NEJM) Perspective discussed several approaches to obtaining efficacy, safety, and pharmacokinetic information in pregnancy [3]. We believe an additional and important approach can be taken to obtain early pharmacokinetic information in this population.

In this clinical study, we propose to give single doses of doravirine to women living with HIV with undetectable plasma HIV RNA on antiretroviral therapy. Single doses will be given in the second and third trimester, and postpartum. Pharmacokinetic sampling will occur up to 72h post-dose, and total and protein-unbound drug concentrations will be compared across these three dosing phases. The first trimester is the period of organogenesis, which is the most critical period of fetal growth and development. We have designed the study to avoid the first trimester, as well as only administering single doses at three independent time points, to obtain the necessary pharmacokinetic and safety information in the lowest risk scenario.

Doravirine is an FDA-approved non-nucleoside reverse transcriptase inhibitor (NNRTI) used to treat HIV infection. In animal reproduction studies, no adverse developmental effects were observed when doravirine was administered at exposures ≥ 8 times the exposure in humans at the recommended human dose (Doravirine package insert 10/2019). Doravirine can be transferred to the fetus through the placenta in animal embryo-fetal studies, with fetal plasma concentrations of up to 40% (rabbits) and 52% (rats) that of maternal concentrations observed on gestation day 20. However, no information is currently available in the most recent pregnancy registry interim report regarding pregnancy outcomes in women taking doravirine (Jan 1989 – Jan 2020). Using single doses of doravirine in the second and third trimester of pregnant women significantly minimizes any risk to the fetus.

Doravirine is predominantly metabolized by CYP3A. While co-administration of doravirine with drugs that induce or inhibit CYP3A may alter its plasma concentrations, doravirine is unlikely to have a clinically relevant effect on the concentrations of other drugs and is not expected to alter the exposures of the study participants' other medications. However, pregnancy itself can significantly increase the clearance of CYP3A substrates, as well as alter protein-unbound concentrations. Since there is significant potential for pregnancy to alter the pharmacokinetics of doravirine, this study will address

how to appropriately dose doravirine in pregnant women. These data are critical as HIV continues to be a chronic illness and more HIV-infected women, both treatment-experienced and naive, are becoming pregnant.

A. BACKGROUND

Women are largely under-represented in clinical trials of antiretrovirals (ART) and constitute only approximately 20% of participants. Trials often exclude women of childbearing potential from participation to minimize fetal risk should the woman become pregnant while on study. Women that are included in clinical trials, are often discontinued from the study drug or the study entirely if they have a positive pregnancy test [6]. These exclusions limit the amount of data regarding pharmacokinetics and drug dosing of many ARVs during pregnancy. Extensive physiologic changes occur during pregnancy which can alter absorption, distribution, metabolism and elimination of drugs [6]. As pregnancy progresses, physiologic changes continue to occur and often do not return to baseline until 2-12 weeks postpartum [2]. Understanding how the physiologic changes during pregnancy affect the PK of a drug is vital to ensuring women are receiving appropriate dosing. This is particularly important in HIV-infection to avoid the development of HIV drug resistance with underdosing. However, excluding pregnant women from pre-NDA clinical trials leads to gaps in data, which leads to substantial delays (eg years) before medications become available to pregnant women

Doravirine (DOR) (tradename PIFELTRO™) and DOR/3TC/TDF (tradename DELSTRIGO™) were approved in the US, EU, Canada, and Australia in 2018 for the treatment of HIV-1 infection in adult patients. DOR is a highly potent NNRTI exhibiting a unique resistance profile compared with the most widely used NNRTI, efavirenz, when tested against a broad array of clinically relevant NNRTI resistant viruses (>90 mutant viruses) in antiviral assays. The antiviral activity of DOR versus WT virus ($EC_{50}=12$ nM) is more potent than many effective agents currently licensed for the treatment of HIV-1 infection, such as efavirenz (EC_{50} of 30 nM). Preclinical data, including in vitro inhibition assays and safety assessment, and clinical assessment suggest that DOR has the potential to fulfill a significant and growing medical need by providing a next generation NNRTI.

Phase 1 and Phase 2 clinical studies have already been conducted to elucidate safety and efficacy data of DOR in nonpregnant women of childbearing potential as well as in pregnant animal models. The results of the human studies showed that there were no effects on cardiovascular, neurological, and respiratory function. In pregnant animal models, there were no developmental or fertility effects from DOR on the rat and rabbit models. Based on these findings, DOR might have the ability to be given to pregnant women; however, extrapolation of PK data from nonpregnant adults fails to consider the physiologic changes that occur during pregnancy [8].

Generally, there are two approaches to ascertaining PK data in pregnancy: “opportunistic studies” in women who become pregnant while taking ARVs, and studies that are specifically designed to evaluate PK in pregnancy [6]. In “opportunistic studies,” PK and safety evaluations are conducted at several time points during pregnancy or postpartum in women that are receiving ARVs post licensing as part of a clinical trial or as part of their routine care. Data from these studies are often not available until many years after a drug is approved by the FDA. In contrast, conducting small controlled PK/safety studies in pregnant women yields more timely data which could expedite the use of newer drugs during pregnancy

[6]. Since the preclinical reproductive toxicity data for DOR showed minimal risk to maternal and fetal health, DOR appears to be a good candidate for a small controlled PK/safety trial in pregnant women.

To minimize risk to the fetus in our research study, pregnant women will not be dosed with DOR until the second trimester. This study will take plasma samples in the second and third trimester, as well as postpartum, to see how the physiology of pregnancy alters drug concentrations. After a single oral dose of DOR, peak plasma concentrations occur at approximately 2 hours post dose. Given that DOR has a $t_{1/2}$ of approximately 15 hours, taking serial plasma samples over a 24-hour period will adequately describe the PK profile as it reaches peak concentration and as the drug is metabolized and eliminated from the body. To ensure minimal maternal and fetal health risks, this study will only be giving women a single dose of DOR at each sampling visit. Safety labs and adverse event monitoring will be conducted throughout the woman's time on study.

RISK/BENEFIT ASSESSMENT

2.A.1 KNOWN POTENTIAL RISKS

Blood Draw Risks

Participants may experience possible discomfort from the insertion of the catheter in their vein to obtain the blood specimens. Other risks may include pain, bleeding, bruising, and swelling as well as a small risk of infection at the site where the catheter was inserted. There is also a risk of lightheadedness, fainting, and blood clots.

Confidentiality Risks

Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions. Although the study site makes every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result (i.e., because participants could become known as HIV-infected). For example, participants could be treated unfairly or discriminated against or could encounter lack of acceptance by their families and/or communities. Several systems are in place to maintain participant confidentiality. All hard copies of study records, including all documents with personally identifiable information, will be kept in a locked drawer in a locked office to which only the study investigators will have access. Samples, study data, and study report forms will not contain patient names; rather they will be labeled with a unique study identification (ID) number with a combination of letters and numbers. The file that links participant identification numbers to their names and other identifiable information will be password-protected and kept by one study investigator on a secure internal computer network, separate from the study data. All electronic data for this study will be stored on a dedicated University server which contains extensive protections and securities. The server is housed and administered at the server farm at the Manning data center located at 211 Manning Drive Chapel Hill, NC 27599-3420. Though every effort will be made to keep research records private, there

may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required; UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. Additionally, all patient recruitment and screening phone calls will be conducted in a private room with the door closed to prevent inadvertent disclosure of participant information. All recruitment emails will use a standard IRB-approved script including only general information that the patient may be eligible for a research study at the UNC Medical Center and requesting that they contact the study staff by phone, if interested, to learn more.

Safety in Pregnancy

The safety of DOR during pregnancy has not been fully determined. No effects on early embryonic development were observed in a female rat fertility study, where higher doses up to 450mg/kg/day were evaluated. There were no embryonic-fetal developmental toxicities observed in rats or rabbits up to the highest doses tested (up to 8.5-fold above the DOR human exposure). No toxic or developmental, growth, behavior, reproductive performance, and fertility of rats were seen following DOR dosing from gestation day 6 to lactation day 20.

Placental and lactational transfer of drug has been demonstrated in studies of both rats and rabbits. Many antiretroviral drugs can be excreted into breast milk. However, we do not know the effect of antiretroviral drugs on breast-feeding babies. Therefore, it is recommended that women on ART do not breastfeed their babies.

Risks from doravirine

DOR has been evaluated in a comprehensive nonclinical safety assessment program that included pharmacokinetic studies, in vitro and in vivo genetic toxicity assays, and repeat-dose oral toxicity studies in mice up to 3 months duration, in rats up to 6 months duration and in dogs up to 9 months duration. Developmental and reproductive toxicology studies conducted with DOR included a male and female rat fertility study, placental and/or lactation transfer assessments and embryo-fetal developmental toxicity studies in rats and rabbits, a prenatal and postnatal toxicity study in rats, and juvenile toxicity studies in rats. In addition, a 6-month oral carcinogenicity study in rasH2 transgenic mice, a 2-year carcinogenicity study in rats, and a rat phototoxicity study have been conducted.

DOR had no effects on cardiovascular, neurological, and respiratory function in well characterized safety pharmacology models. DOR was neither mutagenic or genotoxic. In repeat-dose toxicity studies in mice, rat and dogs, there were no adverse antemortem or postmortem findings when DOR was evaluated either up to the maximum feasible oral dose, at a dose of 1000 mg/kg/day and/or up to a plateau in systemic exposure. The DOR systemic AUC_{0-24hr} exposures achieved in animals were at least 5-fold above clinical AUC_{0-24hr} exposures associated with the 100-mg DOR QD dose. DOR was negative for carcinogenic potential in rodent carcinogenicity studies. There was no phototoxicity observed in pigmented rats exposed to DOR. There were no developmental or reproductive DOR effects in rats or rabbits (on male and female fertility in rats, on embryo-fetal development in rats or rabbits, on prenatal and postnatal development in rats, or on juvenile rat development). Placental and/or lactational transfer of DOR was demonstrated in rats and rabbits.

A comprehensive clinical pharmacology program characterized the initial safety and tolerability, as well as the PK, pharmacodynamics, and potential drug interactions of DOR. Thirty-six Phase 1 clinical trials were conducted to assess safety, tolerability, PK, and PD of DOR. In these trials, 678 participants received at least 1 dose of DOR administered as a single dose (up to 1200 mg) or as multiple doses (up to 750 mg QD for 10 days). The trials included two rising single- and rising multiple- dose trials, a monotherapy PD and PK trial in treatment-naïve HIV-1 infected male subjects, a single-dose thorough QT/QTc trial (conducted with a supratherapeutic dose [1200 mg] of DOR, which achieved exposures 3.1-fold and C_{max} 4.1-fold those associated with the clinical dose at steady state), and a definitive food-effect trial. Key intrinsic factors of renal and hepatic impairment, and age and gender were evaluated in dedicated clinical pharmacology trials. Of the 36 Phase 1 trials, 16 were conducted to evaluate DOR as a perpetrator and/or victim of DDIs.

In a study comparing single dose doravirine in patients with severe renal impairment with a healthy control arm, only three subjects (19%) reported post-dose adverse events [1]. Of the three events reported, only nausea was considered drug related. All AEs were considered transient and resolved by the end of the study. There were no clinically meaningful changes in clinical laboratory values, vital signs, or electrocardiograms (ECGs) [1].

The majority (77%) of adverse reactions associated with multiple dosing of doravirine occurred at severity Grade 1 (mild). The most common side effects of doravirine (incidence greater than or equal to 5%, all grades) include:

- nausea
- dizziness
- headache
- tiredness
- diarrhea
- stomach (abdominal) pain
- abnormal dreams

In addition, there may be uncommon or previously unknown risks that might occur. Participants will be frequently surveyed for any adverse events.

2.A.2 KNOWN POTENTIAL BENEFITS

Participants may not receive a direct benefit from being in this study other than additional screening, as this research is designed to generate information to benefit others in the future.

2.A.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The proposed research presents minimal risks to the participants and has the potential to benefit future patients by giving information on dosing antiretrovirals in pregnancy. Investigators will also be able to assess safety and feasibility of study design for obtaining pharmacokinetic information across the gestational period with single dose assessment of future antiretrovirals. This provides a lower-risk avenue to explore drug safety and dosing information in pregnancy.

3 OBJECTIVES AND OUTCOMEOUTCOMES

OVERALL DESIGN

This is a Phase I, open label, single sequence study to characterize the pharmacokinetics of oral doravirine, single 100mg doses, in the blood plasma of pregnant women living with HIV. This novel single-dose approach will allow pharmacokinetic evaluation of doravirine in pregnant women without extensive or prolonged exposure to the fetus. This study will be conducted at a single site in the U.S; at the University of North Carolina at Chapel Hill. The second trimester PK evaluation will occur between weeks 20-26 gestation. The 3rd trimester PK evaluation will occur at 30-34 weeks gestation. Post-partum PK evaluation will occur 4-8 weeks after delivery. Within 14 days after the last PK visit, patients will have a follow-up safety visit. Participant recruitment will continue until a complete pharmacokinetic dataset has been collected for ten study participants.

The following clinical hypotheses will be investigated in this study:

1. Doravirine total plasma concentrations will decrease in the 3rd trimester as compared to the 2nd trimester, while protein-unbound concentrations will remain unchanged.
2. Doravirine total plasma concentrations will return to standard (nonpregnant) exposures by 4-8 weeks post-partum.

Objectives

Primary Objective:

To describe single-dose total and protein-unbound pharmacokinetics of doravirine in the blood plasma of women living with HIV during the 2nd trimester, 3rd trimester, and post-partum

Secondary Objective:

To evaluate the safety and tolerability of single doses of doravirine in pregnant participants living with HIV

Summary of Major Outcomes

3.A.1.1 PRIMARY OUTCOME:

- Concentrations and pharmacokinetic descriptors of total and protein unbound doravirine in blood plasma during the 2nd trimester, 3rd trimester, and post-partum

3.A.1.2 SECONDARY OUTCOME:

- Adverse experiences associated with single dose doravirine in the gestational and post-partum period

SCIENTIFIC RATIONALE FOR STUDY DESIGN

In order to minimize risk to patient and fetus, the single dose strategy while on an FDA-approved optimized antiretroviral background regimen provides the greatest opportunity to obtain the needed information. Scientific evaluation will provide information on safety, drug concentrations, and the potential need for dose adjustments across the gestational period.

JUSTIFICATION FOR DOSE

Doravirine is available in 100mg oral tablet and is also co-formulated with other antiretrovirals. Providing a single observed dose with subsequent pharmacokinetic assessment across 3 phases of pregnancy provides the lowest risk avenue to obtain this information for female patients living with HIV who need antiretrovirals during the gestational period.

END OF STUDY DEFINITION

A participant is considered to have completed the study if she has completed the three sampling visits while providing the minimum number of samples. Ideally, all participants who receive study drug will complete the safety follow-up visit.

4 STUDY POPULATION

INCLUSION CRITERIA

Inclusion Criteria

- Pregnant women living with HIV ≥18 years of age
- Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.
- Evidence of a personally signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the trial.
- On stable cART for at least 30 days prior to enrollment
- Plasma HIV RNA < 50 copies/mL within 90 days prior to enrollment
- Ability and willingness of participant to not change their cART regimen to avoid any confounding of PK parameters.
 - Note: Women who change cART regimens will be replaced.
- Aspartate aminotransferase and alanine aminotransferase < 3xULN
- Hemoglobin lower than DAIDs Grade 2 (9.0 g/dL)

EXCLUSION CRITERIA**Exclusion Criteria**

- Women with multiple gestation, active opportunistic infections, present obstetrical complications that would deem them unsuitable for study participation, or evidence of fetal anomalies in present pregnancy will be excluded.
- Women with severe renal impairment, end stage renal disease, undergoing dialysis, or severe hepatic impairment (Child-Pugh C)
- Women with a significant illness/condition at the time of enrollment that, in the judgment of the investigator, would interfere with, or serve as a contraindication to, protocol adherence or assessment of safety.
- Women with pregnancies that have become complicated are excluded for safety reasons.
- Active hepatitis C infection as defined by anti-hepatitis C virus serology (as determined by multi-antigen EIA) and detectable HCV RNA.
- Clinically significant labs greater than Grade 2 on the NIH Division of AIDs Table for Grading the Severity of Adult and Pediatric Adverse events
- Receiving CYP3A inducers including carbamazepine, phenobarbital, phenytoin, enzalutamide, rifampin, rifapentine, mitotane, or St. John's wort or other drugs, including antiretrovirals, that influence drug concentration or alter pharmacokinetic profiles (atazanavir, maraviroc, darunavir, norvir, efavirenz, tipranavir)
- Receiving moderate to strong CYP3A inhibitors including clarithromycin, boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir, posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, grapefruit juice, idelasib, nefazodone, and nelfinavir.

LIFESTYLE CONSIDERATIONS

<Not Applicable>

SCREEN FAILURES

Screen failures are defined as participants who complete the screening visit and are found to not currently be eligible for any reason. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants and to respond to queries from regulatory authorities. Minimal information includes demographic characteristics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Rescreening: Participants may be rescreened at any point during open recruitment if their eligibility requirements align with the protocol. Rescreened participants should be assigned the same participant number they were assigned for the initial screening (if they were assigned one).

STRATEGIES FOR RECRUITMENT AND RETENTION**Recruitment and retention strategies for patient participants:**

We plan to enroll 10 participants who are patients at a single U.S. site, the UNC ID Clinic, a hospital-based outpatient clinic in Chapel Hill, North Carolina. Data collection will occur in the UNC ID Clinic, the Clinical & Translational Research Center (CTRC), and possibly other areas of the UNC-Chapel Hill campus such as the UNC Obstetrical clinics.

Of all the people living with HIV who attend the UNC ID Clinic, 95% have consented to having their patient information available in a secure clinic database where it can be viewed to identify potential eligibility for open research studies and to being notified of studies for which they are potentially eligible (as per IRB form 99-MED-408). The ID Clinic has a full-time research screener to assess patient eligibility for open research projects. We will use the IRB-approved screening and recruitment process that has been used in the ID Clinic for over ten years, whereby the clinic screener pre-screens patients in the clinic database and alerts research staff to potentially eligible patients. Specific recruitment methods used (phone, email, in person) for any individual patient participant will depend upon the methods for which that patient has previously provided permission (on IRB form 99-MED-408).

We will use the following recruitment strategies and steps:

- Posting IRB-approved culturally appropriate flyers in designated areas of the clinics for the duration of study enrollment with information about the name and overarching purpose of the study.
- Contacting prospective, pre-screened patients, who have given permission to be contacted by phone, using an IRB-approved script to notify them about the study and verify their eligibility using a brief standardized IRB-approved script/screening form. Phone calls will be conducted in a private room to prevent inadvertent disclosure of participant information.
- Contacting potentially eligible patients, who have given permission to be contacted by secure email, using an IRB-approved template to notify them about the study, provide them with a contact phone number, and ask them, if interested, to contact the study staff by phone to undergo a brief IRB-approved initial screening process. Emails will be sent from an encrypted email server. Follow-up screening phone calls will be conducted in a private room to prevent inadvertent disclosure of participant information.
- For patients who cannot be contacted by phone and/or email after multiple (a maximum of three) attempts, research staff will approach them in the clinic waiting room (if the patient has given permission to do so) on the day of their visit to notify them that they may be eligible for a study. Those who are interested will be asked to move to a private room in the UNC ID Clinic or research clinic to undergo further screening and, if eligible and interested, informed consent. The private room will have a closed door to prevent inadvertent disclosure of subject information.

- If one or more of the basic inclusion criteria are not met, the individual will be informed that they are not eligible.

Research staff will obtain informed consent from each potential participant before starting any study procedures according to the standards set forth in the ICH Good Clinical Practice guidelines and per unit SOPs.

The UNC ID Clinic saw 1900 patients living with HIV in 2018 (approximately 150 patient visits/month). Based on the number of patients seen in the ID Clinic, the high percentage of participants prescribed eligible ARV medications for this study, the ID Clinic's commitment to public health research, and past experience with recruitment, we do not expect difficulty enrolling an adequate number of patient participants. Out of 547 active female clients living with HIV in UNC Adult domain, there were nineteen pregnant at some point in the last year who received some level of care in our clinic.

5 STUDY INTERVENTION

STUDY INTERVENTION(S) ADMINISTRATION

5.A.1 STUDY INTERVENTION DESCRIPTION

All research visits will be conducted in our Clinical and Translational Research Center at the University of North Carolina at Chapel Hill.

Eligible participants will be referred to study staff. They will be pre-screened for eligibility using a standardized IRB-approved pre-screening questionnaire either in person or over the phone.

Participants who are deemed potentially eligible via the pre-screen, will be scheduled for a screening visit in our research clinic. This will be scheduled in the 28 days prior to the anticipated 2nd trimester enrollment.

Upon arrival to the screening visit, all participants will review the HIPAA and Informed Consent forms with a study team member. Standard operating procedures will be followed for the consent process. If a participant provides consent, the screening visit will commence. The study team will obtain and record the participants medical, medication, and obstetrical histories. A physical examination will be performed, and vital signs will be assessed. The study team will review documentation of the obstetrical ultrasound performed as part of standardized obstetrical care in order to document a healthy single intrauterine gestation.

Safety labs will be obtained to assess major organ function as noted in the Schedule of Events. Documentation of an undetectable HIV RNA will be obtained for the prior 90 days.

For participants who pass initial screening, subsequent study visits will be scheduled. The 2nd trimester visit will be scheduled within a window of 20-26 weeks gestation.

Upon admission, initial vital signs will be obtained to verify participant safety. Then, blood for safety laboratory tests will be obtained to evaluate the hematologic, metabolic, and endocrine systems as noted in the SOE. If the participant is deemed still eligible, they will be administered a single dose of

doravirine as witnessed by study staff. Blood plasma sampling will occur at the following time points at and after the observed dose: 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours. Total blood volume for the study samples will be 30mL (2 tablespoons). Review of an adverse events questionnaire will be completed preceding discharge. Obstetrical standard of care evaluations will be completed with the participants' regular care providers.

Participants will be scheduled for another visit in the 3rd trimester between 30-34 weeks gestation where upon arrival current eligibility will be assessed. Safety vitals and labs will be obtained as noted for the previous visit. PK samples will be obtained at the same time points. Review of an adverse events questionnaire will be completed preceding discharge.

Participants will be scheduled for another visit in the postpartum period between 4-8 weeks where upon arrival current eligibility will be assessed. Safety vitals and labs will be obtained as noted for the previous visit. PK samples will be obtained at the same time points. A 5mL (1 teaspoon) breastmilk sample will be obtained through hand expression or using an electronic breast pump at the 4, 8, and 24-hour time points from participants who are able to provide the sample. Review of an adverse events questionnaire will be completed preceding discharge.

Within the 14 business days following completion of sampling, all participants will return to clinic for a final safety assessment. Vital signs and physical exam will be conducted. Documentation of maternal outcomes will be completed, as well as those for the neonate (including HIV DNA, infant outcomes at delivery, APGARs and similar assessments).

Any adverse events will be assessed. Participants are off study when study activities are completed and when all adverse events are followed to completion or resolution.

Additional study visits and evaluations will be scheduled as indicated based on any clinical outcomes over the course of the study.

5.A.2 DOSING AND ADMINISTRATION

Merck & Co. will provide 100mg tabs of doravirine for conduct of the study. Study product will be directly shipped to the UNC Investigational Drug Pharmacy (IDS), so that drug accountability can be maintained.

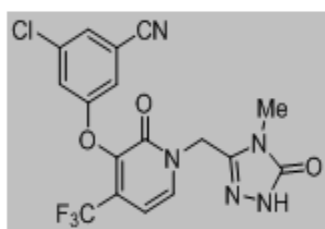
All eligible participants will have prescriptions for study product sent to IDS. Medication will be transported from IDS to the clinic by study staff. All doses will be observed by study and/or research clinic staff and documented.

All participants will receive three single doses of doravirine: one in the 2nd trimester visit, one in the 3rd trimester visit, and one post-partum.

All participants will maintain their routine antiretroviral regimen, which will continue to be supplied by their regular mechanism. This study will not provide regular antiretroviral coverage, nor will it change a regular antiretroviral regimen outside of the single doses under investigation.

PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY**5.A.3 ACQUISITION AND ACCOUNTABILITY**

The study product will be supplied by Merck & Co. and dispensed by the UNC Investigational Drug Services (IDS). UNC IDS will maintain shipment receipt logs, as well as dispensing and temperature logs.

5.A.4 FORMULATION, APPEARANCE, PACKAGING, AND LABELING**STRUCTURE****MK-1439 (Doravirine, DOR):**

DOR is a film-coated tablet containing 100 mg doravirine for oral administration. It is white, oval-shaped and film-coated, and is debossed with the corporate logo and 700 on one side and plain on the other side.

Each tablet includes the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate (HPMCAS), lactose monohydrate, magnesium stearate, microcrystalline cellulose and carnauba wax. The tablets are film coated with a coating material containing the following inactive ingredients: hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

5.A.5 PRODUCT STORAGE AND STABILITY

Doravirine tablets are stored at room temperature between 68°F to 77°F (20°C to 25°C), excursions permitted to 15°C to 30°C (59°F to 86°F). IDS will maintain temperature logs for drug storage.

MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

There will be no randomization on this study, as all enrolled participants will receive the same study product. No participants or study team members will be blinded to the study product.

STUDY INTERVENTION COMPLIANCE

This study will be conducted in full compliance with the protocol and all study procedures will be tracked for compliance. All protocol amendments must be submitted to and approved by the relevant IRB prior to implementing the amendment.

CONCOMITANT THERAPY

CYP3A inducers can have a clinically meaningful reduction on the PK of DOR; special instructions are needed for the coadministration of moderate and strong CYP3A inducers. Concomitant use of strong and moderate CYP3A inducers is likely to reduce DOR plasma concentrations leading to decreased efficacy. Therefore, the use of CYP3A inducers, such as the anti-mycobacterials rifampin and rifapentine, the anticonvulsants carbamazepine, oxcarbazepine, phenytoin, and phenobarbital, and the herbal supplement St John's wort (*Hypericum perforatum*) are contraindicated with DOR. CYP3A inhibitors have been shown to increase plasma concentrations of DOR when administered together. Therefore, women using moderate to strong CYP3A inhibitors will be excluded from this trial.

Participants will be excluded if they regularly take any of the following:

CYP3A Inducers	CYP3A Inhibitors
<ul style="list-style-type: none"> • oxcarbazepine • carbamazepine • phenobarbital • phenytoin • enzalutamide • St. John's wort • rifampin • rifapentine • mitotane • atazanavir • maraviroc • darunavir • ritonavir • efavirenz • tipranavir • etravirine • nevirapine 	<ul style="list-style-type: none"> • clarithromycin • boceprevir • cobicistat • danoprevir and ritonavir • elvitegravir and ritonavir • indinavir and ritonavir • itraconazole • ketoconazole • lopinavir and ritonavir • paritaprevir and ritonavir • posaconazole • ritonavir • saquinavir and ritonavir • telaprevir • tipranavir and ritonavir • grapefruit juice • idelasib • nefazodone • nelfinavir

5.A.6 RESCUE MEDICINE

Not Applicable.

**6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/
WITHDRAWAL****DISCONTINUATION OF STUDY INTERVENTION**

If one participant experiences a Serious Adverse Event (SAE) deemed related to the study, enrollment will be held while the protocol undergoes review. SAEs will be reported to the IRB, the FDA and Merck and the protocol team will collaborate with Merck and the FDA to determine how to proceed.

PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Enrolled participants are free to withdraw from participation in the study at any time and for any reason upon request. If they received study product, they will still complete the follow-up safety visit. Reasons for participant discontinuation/withdrawal from the study will be documented in the study database.

LOST TO FOLLOW-UP

All participants who do not complete all three pharmacokinetic visits will be replaced. The 48 and 72-hour blood draws for each sampling visit are optional for participants at the designated time points. A participant who completes all study samples but is lost to follow-up before the final safety visit will still be considered evaluable. Efforts to minimize loss to follow-up will include the following: maintain close communication with participants in between the study visits to maintain contact, and verify participant is complying with routine obstetrical standard of care evaluations.

7 STUDY ASSESSMENTS AND PROCEDURES***Screen***

The following study procedures will be completed with all women during the screening visit:

- Informed Consent
- Review of Medical History
- Obstetrical History
- Vital Signs: Height, blood pressure, pulse, respiratory rate, temperature, and weight

- Full Physical Examination
- Documentation of a healthy gestation by prior ultrasound
- Safety Laboratory Tests: CBC with differential, urinalysis, and the following serum chemistries: Na, K, Cl, CO₂, BUN, Creatinine, glucose, Ca, Alb, total protein, AST, ALT, Alkaline phosphatase, total bilirubin, total cholesterol, triglycerides, LDL, HDL, and lipase. Labs obtained within the 30 days prior to screening as part of routine obstetrical care can be used.
- Documentation of HIV RNA <50 copies/mL within the previous 90 days.

Once all screening safety labs have been resulted, the participant will be notified if she is eligible. If she meets entry criteria, her sampling visits will be scheduled.

Second Trimester PK Visit

For all enrolled participants, the second trimester study visit will be scheduled between weeks 20-26 gestation. The following study procedures will be completed with all participants during this visit:

- Vital Signs: blood pressure, pulse, respiratory rate, temperature, and weight
- Full Physical Examination, including Fetal Heart Tones
- A peripheral intravenous (IV) catheter will be inserted and the following safety laboratory tests will be sent with high priority to Mclendon labs: CBC with differential, urinalysis, and the following serum chemistries: Na, K, Cl, CO₂, BUN, Creatinine, glucose, Ca, Alb, total protein, AST, ALT, Alkaline phosphatase, total bilirubin, total cholesterol, triglycerides, LDL, HDL, and lipase. An HIV RNA viral load will also be obtained and sent to the lab for routine processing.

If vital signs, physical assessment and safety labs reveal the participant is still eligible, the study product will be administered, and dosing will be witnessed. 6mL (one teaspoon) blood plasma will be obtained at the following time points: 0, 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose. Participants will return the following morning to have a blood sample drawn via phlebotomy at the 24-hour time point post-dose.

Adverse events will be assessed using a standardized IRB-approved form, and the participant will be discharged if indicated.

Participants who are able to return the following mornings will have blood samples collected via phlebotomy at the 48 and 72-hour post-dose time points.

Third Trimester PK Visit:

All participants will complete a 3rd trimester visit between 30-34 weeks gestation. The following study procedures will be completed with all participants during this visit:

- Vital Signs: blood pressure, pulse, respiratory rate, temperature, and weight
- Full Physical Examination, including Fetal Heart Tones
- A peripheral IV catheter will be inserted and the following safety laboratory tests sent with high priority to Mclendon labs: CBC with differential, urinalysis, and the following serum chemistries:

Na, K, Cl, CO₂, BUN, Creatinine, glucose, Ca, Alb, total protein, AST, ALT, Alkaline phosphatase, total bilirubin, total cholesterol, triglycerides, LDL, HDL, and lipase. An HIV RNA viral load will also be obtained and sent to the lab for routine processing.

If vital signs, physical assessment and safety labs reveal the participant is still eligible, the study product will be administered, and dosing will be witnessed. 6mL (one teaspoon) Blood Plasma will be obtained at the following post-dose time points: 0, 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose. Participants will return the following morning to have a blood sample drawn via phlebotomy at the 24-hour time point post-dose.

Adverse events will be assessed using a standardized IRB-approved form, and the participant will be discharged if indicated.

Participants who are able to return the following mornings will have blood samples collected via phlebotomy at the 48 and 72-hour post-dose time points.

Post-Partum Visit:

The following procedures will be completed with all study participants during the post-partum visit which will occur 4-8 weeks after delivery:

- Documentation of maternal outcomes or pregnancy complications including but not limited to diabetes, hypertensive diseases of pregnancy, premature labor
- Vital Signs: blood pressure, pulse, respiratory rate, temperature, and weight
- Full Physical Examination
- A peripheral IV catheter will be inserted and the following safety laboratory tests sent with high priority to Mclendon labs: CBC with differential, urinalysis, and the following serum chemistries: Na, K, Cl, CO₂, BUN, Creatinine, glucose, Ca, Alb, total protein, AST, ALT, Alkaline phosphatase, total bilirubin, total cholesterol, triglycerides, LDL, HDL, and lipase. An HIV RNA viral load will also be obtained and sent to the lab for processing.

If vital signs, physical assessment and safety labs reveal the participant is still eligible, the study product will be administered, and dosing will be witnessed. 6mL (one teaspoon) Blood Plasma will be obtained at the following time points: 0, 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose. Participants will return the following morning to have a blood sample drawn via phlebotomy at the 24-hour time point post-dose. A 5mL breastmilk sample will be obtained through hand expression or using an electronic breast pump at the 4, 8, and 24-hour time points from participants who are able to provide the sample.

Adverse events will be assessed using a standardized IRB-approved form, and the participant will be discharged if indicated.

Participants who are able to return the following mornings will have blood samples collected via phlebotomy at the 48 and 72-hour post-dose time points.

The following infant outcomes will be documented: delivery information, gestational age at delivery, Apgar scores, height, weight, head circumference, HIV DNA at 0-2 days of life.

- Per standard procedures, all outcomes will be reported by UNC staff to the Antiretroviral Pregnancy Registry.

Follow-up Visit:

The following procedures will be completed with all study participants during the follow-up visit, which will be scheduled within the 14 business days following the last study samples:

- Vital Signs: blood pressure, pulse, respiratory rate, temperature, and weight
- Full Physical Examination
- Review of Adverse Events
- Safety Laboratory Tests: CBC with differential, urinalysis, and the following serum chemistries: Na, K, Cl, CO₂, BUN, Creatinine, glucose, Ca, Alb, total protein, AST, ALT, Alkaline phosphatase, total bilirubin, total cholesterol, triglycerides, LDL, HDL, and lipase
- HIV RNA

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS**7.A.1 DEFINITION OF ADVERSE EVENTS (AE)**

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).] As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. Study participants will be instructed to contact the study site staff to report any AEs they may experience at any time during the study period.

In the case of a life-threatening event, they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based, and to request that the clinician be contacted upon their arrival. Sites will obtain written permission from the participant to obtain and use records from non-study medical providers to complete any missing data element on a CRF related to an adverse event. All participants reporting an untoward medical occurrence will be followed clinically, until the occurrence resolves (returns to baseline) or stabilizes.

The site clinicians will determine AE resolution or stabilization in their best clinical judgment but may seek PSRT medical consultation regarding follow-up or additional evaluations of an AE. Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Study staff also will record all AEs on study logs.

7.A.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

No ARVs, outside of the study product, or HIV-related conditions will be considered for expedited reported as protocol-related adverse events.

Study staff will report all AEs that meet serious adverse event (SAE) reporting requirements according to the DAIDS-defined "standard" reporting requirements. Information on all AEs will be included in reports to any applicable government and regulatory authorities. Study staff will report information on all AEs and SAEs to the IRB and the sponsor in accordance with all applicable regulations and requirements.

7.A.3 CLASSIFICATION OF AN ADVERSE EVENT

7.1.3.1 SEVERITY OF EVENT

All AEs will be categorized with regard to severity, by the study clinician, using the following guidelines to describe severity.

- **Grade 1 Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Grade 2 Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3 Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. [Of note, the term "severe" does not necessarily equate to "serious".]
- **Grade 4 Life-threatening** – A life-threatening event is one where the patient is in immediate danger of death unless intervention is done. It does not mean that the patient may die at some time in the future from the event or may have died if the event had been more serious or specific.

7.1.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) will have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment.

The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect. Determination of relationship to study intervention will be based on what is known about the natural history of the underlying disease, a subject(s) concurrent illness(es), concomitant therapy, study-related procedures, accidents, temporality and other external factors.

Instead of SAE reporting category, the SUSAR (Suspected, Unexpected Serious Adverse Events) reporting category will be utilized.

The terms used to assess the relationship of an event to the study intervention are:

Related—There is a reasonable possibility that the AE may be related to the study intervention

Not Related—There is not a reasonable possibility that the AE is related to the study intervention

We will document the outcome of the AE, categorizing the outcome as unknown, ongoing, death, resolved, or resolved with sequelae.

7.1.3.3 EXPECTEDNESS

Expected adverse reactions are AEs that are known to occur for the study intervention being studied and should be collected in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. With only 3 single doses separated in time, there is a low rate of expected adverse events related to the study product. The study physician will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.A.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The research team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days after the last day of study participation. At each study contact occurring after consent, the researchers will inquire about the occurrence of **unsolicited** AE/SAEs since the last visit using a standardized questionnaire. Events will be followed for outcome information until resolution or stabilization.

7.1.5 ADVERSE EVENT REPORTING

Information regarding all AEs regardless of seriousness or severity will be recorded in the participant's source files. Grade 1 clinical symptoms (non-laboratory, e.g., headache, nausea) that lead to a temporary or permanent hold of study intervention, and all Grade 2 and higher AEs, will be collected on standard case report forms (CRFs) for entry into the study database and future reporting to appropriate agencies at stated intervals consistent with all local policies.

7.1.6 SERIOUS ADVERSE EVENT REPORTING

Study staff will report all AEs that meet serious adverse event (SAE) reporting requirements according to the DAIDS-defined "standard" reporting requirements. Information on all AEs will be included in reports to any applicable government and regulatory authorities. Study staff will report information on all AEs and SAEs to the IRB, FDA, and the sponsor in accordance with all applicable regulations and requirements.

Expedited Adverse Event Reporting

No background ARVs or HIV-related conditions will be reported as expedited reporting as protocol-related adverse events.

7.1.7 REPORTING EVENTS TO PARTICIPANTS

Any new safety information learned during the course of study conduct that might affect participant willingness to participate will be shared.

7.1.8 EVENTS OF SPECIAL INTEREST

Not applicable.

7.1.9 REPORTING OF PREGNANCY

Not Applicable.

UNANTICIPATED PROBLEMS

7.1.10 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.11 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Protocol Safety Review Team (PSRT), which includes the study PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the PSRT and study sponsor in accordance with the DAIDS-defined “standard” reporting requirements, which is as soon as possible, but in no event later than within 7 days of the investigator becoming aware of the event.

- Any other UP will be reported to the IRB and to the PSRT/study sponsor in accordance with the DAIDS-defined “standard” reporting requirements, which is as soon as possible, but in no event later than within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) in accordance with the DAIDS-defined “standard” reporting requirements, which is within 7 days of the IRB’s receipt of the report of the problem from the investigator.

7.1.12 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Any new safety information or problems that occur during the conduct of the study that might affect a participant’s willingness to participate will be shared.

8 STATISTICAL CONSIDERATIONS

STATISTICAL OUTCOMES AND MEASURES

Statistical Analysis:

The study investigators will perform summary statistics on the data and provide interpretation of the results. The safety and pharmacokinetics from subjects who do not complete the study will not be evaluated.

Variables/Time Points of Interest

Primary variables of interest will be subject demographics and blood plasma drug concentrations. Pharmacokinetic sampling in blood plasma will be completed on study visits during the second and third trimesters, as well as the post-partum phase at the following time points: $t = 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48$ and 72 hours post-dose. Breastmilk sampling will occur at the 4, 8, and 24-hour time points at the postpartum visit when applicable. Data obtained through pharmacokinetic sampling will permit computation of the pharmacokinetic parameters of doravirine in the blood plasma and breastmilk of pregnant HIV-positive females.

Statistical Methods

Concentration-time profiles of total and protein-unbound doravirine in blood plasma will be analyzed using noncompartmental methods (Phoenix WinNonlin Software) to generate an AUC during the second and third trimesters, as well as the post-partum state. Descriptive summary statistics for exposure (C_{max} , T_{max} , C_{12h} , C_{24h} , AUC) and elimination (CL/F , $t_{1/2}$) will also be computed. Graphical representation of data will be made using SigmaPlot.

SAMPLE SIZE DETERMINATION

The proposed sample size was pragmatically chosen to generate preliminary pharmacokinetic data adequate for understanding blood plasma pharmacokinetics of doravirine in pregnant women living with HIV. After successfully completing screening evaluations, ten healthy adult pregnant women living with HIV will be enrolled. If necessary, additional participants will be enrolled to replace any dropouts or regimen changes to ensure a total of ten evaluable participants. Although the resulting pharmacokinetic estimates will not be as precise as those obtained with a larger sample size, the comprehensive evaluation of drug concentration should provide reasonable estimates of central tendency to inform future clinical studies. Our experience with previous pregnancy pharmacokinetic investigations suggest that this number will provide us with reasonable estimates of drug exposure.

POPULATIONS FOR ANALYSES

All enrolled participants will be in the same cohort. They will be pregnant females currently living with HIV a stable antiretroviral regimen resulting in an undetectable HIV RNA viral load.

STATISTICAL ANALYSES

8.1.1 GENERAL APPROACH

8.1.2 ANALYSIS OF THE PRIMARY OUTCOMES

Primary Outcome:

1. Concentrations and pharmacokinetic descriptors of total and protein-unbound doravirine in blood plasma over the 24-hour post-dose interim in ng/mL in the 2nd trimester, 3rd trimester, and post-partum (and over the 72h time period, if applicable):

Secondary Outcome:

1. Adverse experiences, including safety lab studies (hematologic, renal, and hepatic function) from enrollment through the end of study.

8.1.3 SAFETY ANALYSES

Refer to Section 7.

Social Harms Reporting

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result.

For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. Social harms that are judged by the Investigator of Record to be serious or unexpected will be reported to the responsible site IRB at least annually, or according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. While maintaining participant confidentiality, study sites may engage their CABs in exploring the social context surrounding instances of social harm.

8.1.4 BASELINE DESCRIPTIVE STATISTICS

We will conduct descriptive statistics to characterize the demographics and baseline data of participants.

8.1.5 PLANNED INTERIM ANALYSES

There are no interim analyses planned on this protocol.

8.1.6 SUB-GROUP ANALYSES

There are no sub-group analyses on this protocol.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

The investigators will obtain informed consent from each patient before starting any study procedures according to the standards set forth in the ICH Good Clinical Practice guidelines and per unit SOPs. The process will include reviewing consent forms with potential patients in a confidential setting and explaining all risks and benefits associated with participation of the study. This involves reading over the IRB-approved consent form with the patient in a private space, soliciting questions from the patient, allowing the patient ample time alone to review the form, soliciting questions again, and then offering the patient the opportunity to sign the consent form. To ensure understanding, study staff will ask questions of the patients regarding study procedures. The consent forms will use language that is sufficiently simple for lay persons to comprehend. Patients will not be coerced into participating. Children under the age of 18 years, decisionally impaired adults and non-English speakers will not be enrolled in this study. Each patient will be provided with a photocopy of all documents that they sign. The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of importance to this study:

- The unknown safety and unproven efficacy of the study interventions
- The importance of patients in both study groups to the success of the study

- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

The informed consent process will include an assessment, through a series of questions, of each potential patient's understanding prior to enrollment and sequential assignment of concepts identified by the protocol team as essential to the informed consent decision. Patients who are not able to demonstrate adequate understanding of key concepts after exhaustive educational efforts will not be enrolled in the study.

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

One IRB-approved informed consent document will be reviewed with all patients on study. All patients will also review and sign a HIPAA form approved by the IRB. All documents will clearly state that this is research, and that participation is completely voluntary.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Our informed consent process begins with the initial participant contact and continues until study completion.

Most of our initial patient contact will be through phone contact, during which an IRB-approved phone screening questionnaire will be administered. If the patient agrees and passes the screening, they will provide basic demographic data needed to schedule their appointment in the clinical research management system (CRMS) and this is done under an IRB-approved limited HIPAA waiver. Full HIPAA and informed consent occur during the first patient visit.

The study team will keep the original consent, and a copy will be given to the participant and into their electronic medical record.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

The study may be discontinued at any time by the sponsor, site investigators, site IRBs, or other government or regulatory authorities. For any study that is prematurely terminated or temporarily suspended, the PI will promptly inform study patients, the IRB, and the sponsor providing the reason(s) for the termination or temporary hold.

When a study is prematurely terminated, refer to Section 6, **Study Intervention Discontinuation and Participant Discontinuation/Withdrawal**, for handling of enrolled study participants.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients or to provider participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary outcome has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

9.1.3 CONFIDENTIALITY AND PRIVACY

Confidentiality will be maintained by storing all specimens for current and future use with a unique identifying number, which will be linked to the subject's name, social security number, address, telephone number, and hospital medical record (MR) number. The principal investigators and study staff will be the only people with access to the identifying information. Any information provided to other people working on this study will be given with the study ID number, not other identifying information. The records will be secured in a locked file cabinet in a locked room in a badge access only office suite of the principal investigator.

All electronic data for this study will be stored on a dedicated University server which contains extensive protections and securities.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data, will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

9.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed. Any blood sample specimens will be stored in the secure lab of the Principal Investigator at the address noted previously in this protocol. No data will be transmitted outside of study staff. All samples will be destroyed in accordance with Environmental Health and Safety policies and local SOPs one year after the results have been published. No samples will be stored long term.

9.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

<i>Principal Investigator</i>	<i>Medical Officer</i>	<i>Co-Investigator</i>
<i>Angela Kashuba, BScPhm, PharmD, DABCP, FCP, Professor</i>	<i>Cynthia Gay, MPH, MD, Associate Professor</i>	<i>Lisa Rahangdale, MD, MPH</i>
<i>Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy</i>	<i>Division of Infectious Diseases, Department of Medicine UNC School of Medicine</i>	<i>Division of Obstetrics and Gynecology</i>
<i>Address: CB# 7569, 3318 Kerr Hall, 310 Pharmacy Lane Chapel Hill NC, 27599-7569, USA</i>	<i>Address: 130 Mason Farm Rd. (Bioinformatics), CB# 7030 Chapel Hill, NC 27599-7030, USA</i>	<i>1001 Bondurant Hall CB 9500 Chapel Hill, NC 27599-7215</i>
<i>Phone Number: 919-966-9998</i>	<i>Phone Number: 919-843-2726</i>	<i>Phone Number: 919-962-8331</i>
<i>Email: akashuba@unc.edu</i>	<i>Email: cynthia_gay@med.unc.edu</i>	<i>Email: lisa_rahangdale@med.unc.edu</i>

9.1.6 SAFETY OVERSIGHT

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are the first layer of this tiered system and are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the Protocol Safety Review Team (PSRT) if unexpected concerns arise. The PSRT will consist of the following study site investigators: Angela Kashuba, PharmD (Principal Investigator), Lisa Rahangdale, MD (Co-Investigator), Cindy Gay, MD (Medical Officer), and Amanda Poliseno (Project Manager).

9.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s):

- Onsite monitoring will occur at regular intervals. Comprehensive source monitoring will occur. Database monitoring will be targeted at 10% of data entry.
- Monitoring follow up clarifications will be completed within 14 business days as noted in our local SOPs.

9.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control and Quality Assurance

The study site will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites available at:

(<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/QMPPolicy.pdf>).

9.1.9 DATA HANDLING AND RECORD KEEPING

Research Records are stored in a locked cabinet in a locked room, in an office suite of the investigator under badge access. Only study team members have access to this space. Research records will be stored, or in the possession of study team members at all times.

A study database will be generated to create an electronic version of source documentation. This will be in an industry accepted program, such as RedCap.

9.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The study site will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials

(<http://www3.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/PDF/Source DocPolicy.pdf>).

The investigator will maintain, and store securely, complete, accurate and current study records throughout the study. The investigator will retain all study records for at least three years following the completion of the study, unless directed otherwise by the National Institutes of Health (NIH). Study records must be maintained on site for the entire period of study implementation.

9.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

9.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 14 working days of identification of the protocol deviation, or within 14 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported annually to our local IRB and NIH. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](#) upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 1 year after the completion of the primary outcome by contacting the lead contacts notated through ClinicalTrials.gov.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these

data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.]

9.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. This is required by our local research offices at the onset of IRB submission and no less than annually. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 ADDITIONAL CONSIDERATIONS

N/A

9.3 ABBREVIATIONS

ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTG	AIDS Clinical Trials Group
AE	Adverse Events
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
cART	Combination Antiretroviral Therapy
CD4	Cluster of Differentiation 4
COC	Certificate of Confidentiality
CO	Cardiac Output
CONSORT	Consolidated Standards of Reporting Trials
CPAC	Clinical Pharmacology and Analytical Chemistry
CQMP	Clinical Quality Management Plan
CRF	Case Report Form
CTRC	Clinical and Translational Research Center
DOR	Doravirine
EAE	Expedited Adverse Event
EDTA	Ethylene diamine tetraacetic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	Glomerular Filtration Rate
GWAS	Genome-wide Association Studies
HIV	Human Immunodeficiency Virus
HPMCAS	Hypromellose Acetate Succinate
ICH	International Conference on Harmonization
MO	Medical Officer
MTCT	Mother to Child Transmission
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor

NRTI	Nucleos(t)ide Reverse Transcriptase Inhibitor
NVP	Nevirapine
PD	Protocol Deviation
PI	Principal Investigator
PK	Pharmacokinetics
PSRT	Protocol Safety Review Team
QD	Every Day
RBC	Red Blood Cell
SAE	Serious Adverse Event
SOE	Schedule of Events
SOP	Standard Operating Procedure
TDF	Tenofovir Disoproxil Fumarate
UNC	University of North Carolina
US	United States
WT	Wild Type
3TC	Lamivudine

9.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2.0	16Dec2021	Sexually transmitted infection testing removed	This testing will be obtained during routine obstetrical care.
3.0	06Oct2022	Breastmilk sampling added.	Breastmilk samples will be obtained from eligible participants for exploratory analysis.

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