STUDY PROTOCOL

A Novel Regimen to Prevent Malaria and STI in Pregnant Women with HIV: The PREMISE Trial

Version 1.1

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I. INTRODUCTION

a) Study Abstract

More than 3 billion people worldwide are at risk of acquiring malaria and HIV-infected pregnant women in Africa are at particular risk. An effective prophylaxis regimen capable of preventing malaria and other common perinatal infections would have great potential to improve adverse birth outcomes. The purpose of this randomized controlled trial is to evaluate a new combination prophylaxis regimen in pregnant women with HIV in Cameroon to determine its efficacy and safety.

b) Primary Hypothesis

A novel regimen of trimethoprim-sulfamethoxazole (TMPS) in combination with azithromycin (AZ) compared to the standard of care (TMPS) will be more effective in preventing infection with *Plasmodium falciparum* (malaria), *Treponema pallidum* (syphilis), *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (GC), and *Streptococcus agalactiae* (GBS) in HIV-infected pregnant women in Cameroon, Central Africa.

c) Protocol Summary

We plan a test-of-concept of our central hypothesis by conducting a randomized, placebo-controlled, double-blinded, Phase II trial with the following 3 aims:

Aim 1: Test the efficacy of a combination malaria prophylaxis regimen (TMPS-AZ) compared to the standard of care regimen (TMPS) in reducing malaria in HIV-infected pregnant women. The goal is to determine whether the addition of azithromycin has an impact on the proportion with submicroscopic parasitemia at delivery.

Approach: Pregnant women with HIV will be randomized to the intervention (TMPS-AZ) or to usual care (TMPS) with monthly follow-up visits to receive medications. Blood collected at delivery will be tested by PCR to assess for infection with *Plasmodium falciparum*.

Aim 2: Measure the reduction in prevalence of curable bacterial STIs and GBS colonization after 35 weeks gestation (or at delivery) in the intervention and usual care groups. The goal is to measure the impact of monthly AZ prophylaxis on the prevalence of pathogens that are associated with adverse birth outcomes (*Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum, Streptococcus agalactiae*).

Approach: Participants will have vaginal and anogenital swabs in late pregnancy or at delivery for GC/CT/GBS nucleic acid amplification testing. Blood will be collected simultaneously for syphilis testing.

Aim 3: Determine the fetal/neonatal safety and adherence/tolerability of TMPS-AZ compared to TMPS. The goal is to collect safety, adherence and tolerability data for this novel regimen used in HIV-infected pregnant women.

Approach: Birth outcomes will be captured by chart review and women will fill out a validated questionnaire to assess medication adherence and tolerance at each visit. The first dose of medication at each visit will be given under directly observed therapy.

II. BACKGROUND

HIV and malaria coinfection in pregnancy is a major public health problem in sub-Saharan Africa.

Up to 40% of the world's population is at risk of malaria, including 25 million pregnant women in sub-Saharan Africa. The parasite *Plasmodium falciparum* transmitted by the anopheline mosquito causes most serious malaria infections with peak mortality rates in pregnant women and children under 5 years. *P falciparum* is the etiology of 96% of malaria infections in Cameroon with a mean entomological inoculation rate of 3.9 infective bites per person each night.(1-3) HIV, malaria and pregnancy are considered the "triple threat" in terms of maternal morbidity and mortality in Africa.(4) Pregnancy is a risk factor for acquiring malaria, particularly among primigravidae because of parity-dependent development of protective immunity to placental antigens.(5-7) (8) Women with HIV have elevated malaria acquisition risk (RR 1.8), irrespective of parity, and lower rates of malaria specific immunity.(9) Women with HIV also have a 70% increased risk of placental infection and more severe clinical disease than HIV-uninfected pregnant women. (10-13) (14) Studies in pregnancy (including those from our collaborators in Cameroon) among *HIV-uninfected* pregnant women have documented peripheral parasitemia in 22-82% of women.(15-19) Placental malaria is associated with a two-fold increased risk of low birthweight but effective prevention improves maternal severe anemia, low birthweight and perinatal mortality by 27-43%.(6, 20, 21) Malaria also leads to a transient elevation in HIV viral load (7 fold for symptomatic disease) and an increased risk of mother to child HIV transmission which is independent of maternal HIV viral load. (RR 7.9, p=0.025). (11, 22-24)

Curable bacterial STIs are common in pregnant women with HIV in Africa and an important cause of maternal and neonatal morbidity.

Accumulating evidence supports infection as a major cause of spontaneous preterm labor, particularly when it occurs before 30 weeks gestation.(25) The underlying pathogenesis is under study, but proinflammatory cytokines IL-6, TNF, IL-1, metalloproteinase-9 and alternations in the maternal microbiome contribute to uterine activation.(26-30) HIV prevalence in pregnancy is elevated in Africa (10% in urban Cameroon) and antenatal screening suggests a high rate of STIs in women with HIV.(31, 32) In one study, 38% of pregnant women with HIV had CT (compared to 7% in HIV-uninfected), 10% had GC (compared to 3%) and 36% had syphilis (compared to 11%). Up to 90% of pregnant women with early syphilis transmit *Treponema pallidum* to the fetus which can lead to stillbirth, neonatal deaths, congenital syphilis and low birth weight. There are an estimated 200,000 adverse pregnancy outcomes attributable to syphilis in sub-Saharan Africa each year and adequate prevention could reduce stillbirths by 80% worldwide.(33, 34) Although GC/CT infections are generally confined to the lower genital tract, GC acquisition in pregnancy has been associated with preterm birth (aOR 2.1, 95% CI 1.02-3.97) and CT infection with low birthweight (aOR 2.07, 95% CI 1.01-4.24).(35, 36)

More effective prevention tools for malaria and sexually transmitted infections are needed for the high-risk population of HIV-infected pregnant women.

Since ART is increasingly available, and HIV-associated mortality rates have fallen, more pregnant women with HIV are in need of malaria prophylaxis.(37) The prevalence of malaria among pregnant women in sub-Saharan Africa ranges from 25-50% despite available prophylaxis.(15-17) The concept of intermittent prophylaxis during pregnancy is to prevent infection and treat asymptomatic infections before negative consequences can occur. Prevention of infection in pregnancy is an attractive concept since antibiotics are only administered during a defined period of exposure and even timely treatment of infection often occurs too late to reverse deleterious inflammatory processes.(38) Although intermittent sulfadoxine-pyrimethamine (SP) is recommended as malaria prophylaxis for many pregnant women, this option is not available for pregnant women with HIV taking TMPS. Co-administration of dual antifolate therapy with TMPS and SP is contraindicated because of side effects including 100-fold higher risk of severe rash. Given this important interaction, in many African countries (including Cameroon), daily TMPS is recommended for malaria prophylaxis in pregnant women with HIV. Available evidence shows that TMPS is as effective as SP (30%-90% efficacy).(39-42) While SP efficacy is jeopardized by emerging resistance, TMPS has good activity against malaria to date.(43, 44)

Azithromycin (AZ) is a useful agent for co-prophylaxis given its broad coverage, favorable pharmacokinetics, track record of safety in pregnancy and association with improved birth outcomes.

AZ has anti-inflammatory and immunomodulatory properties and it has been shown to prevent LPS-associated pregnancy loss in a murine model.(45, 46) It concentrates in tissues and has proven efficacy and safety for malaria prevention when used as part of a combination regimen (recommended by WHO to reduce the risk of parasite resistance).(47) AZ has a prolonged half-life (68 hours) and good oral bioavailability (34-52%). Pharmacokinetic studies have shown that increased AZ dosing in pregnancy is not necessary and the AZ dosing schedule with demonstrated efficacy for malaria prophylaxis is 1 gram daily for 3 days.(47-49) One recent study of *HIV-uninfected* women in Papua New Guinea suggested a reduction in low birthweight (RR 0.74, 95% CI 0.6-0.9) and preterm delivery (RR 0.62, 95% CI 0.4-0.9) with the addition of monthly AZ to SP.(50) SP-AZ also significantly improved low birthweight and infant growth parameters at 12 months in Malawi compared to SP alone.(51, 52) For STI prophylaxis, monthly AZ in Kenyan sex workers lowered the incidence of GC by 64% and CT by 62% compared to placebo.(53)AZ 1gm is CDC recommended therapy for CT (97% efficacy).(54, 55) Combination therapy including AZ 1gm is recommended for GC treatment but a single 2 gram dose of AZ has shown 99.2% efficacy.(56) A recent CDC analysis showed 99.6% GC sensitivity to AZ and response rates averaged 96% worldwide.(57, 58) Given more limited exposure to macrolides, GC response rates to AZ are similar or better in Africa.(59) For syphilis treatment, AZ 1-2gm has similar efficacy as benzathine penicillin in certain populations, but AZ resistance has been documented and penicillin remains the treatment of choice.(60) (54) AZ also has activity against other genital tract pathogens which may contribute to birth outcomes (i.e. *Ureaplasma urealyticum (95%), Mycoplasma genitalium (70%)*) and *Streptococcus agalactiae* (GBS) (70%).(53, 61, 62) Anogenital GBS colonization during pregnancy is a primary preventable cause of neonatal pneumonia, meningitis and sepsis and HIV-exposed infants are at higher risk of invasive disease.(63) GBS colonization rates range from 20-30% worldwide but antenatal screening is not routine in Africa. (64, 65) We

have an active study to document rates of maternal GBS colonization and capture birth outcomes for exposed infants in Cameroon given the paucity of data. (127)

Both TMPS and Azithromycin are effective for malaria prophylaxis with favorable safety profiles individually in pregnancy, but additional data on the combination is needed.
A recent review of malaria prophylaxis regimens in pregnancy discussed the need to capture safety outcomes for new combinations.(66) TMPS is a well-tolerated, inexpensive, widely prescribed, FDA "category C" drug with efficacy against parasitic and bacterial pathogens. It has good pregnancy safety and is part of the WHO-recommended therapy for HIV-infected pregnant women.(67, 68) Azithromycin is a "category B" agent with a favorable safety profile in all trimesters and efficacy against STIs. (48, 69) TMPS/AZ are commonly administered together as prophylaxis in HIV patients and there are no published reports of malaria resistance to TMPS or AZ in Africa.(70)

III. STUDY OBJECTIVES

As resistance spreads, new options are needed to prevent malaria during pregnancy, particularly among women with HIV-infection. The combination of TMPS and Azithromycin has not yet been studied for efficacy in terms of preventing malaria and other STIs that contribute to adverse birth outcomes.

a) Primary Outcomes

Aim 1 Proportion of women with *Plasmodium falciparum* peripheral parasitemia by microscopy or PCR.

Aim 2 Prevalence of a composite STI measure (GC, CT, syphilis infections) will be measured in both groups in late pregnancy (>35 weeks gestation) or at delivery and compared between the two groups.

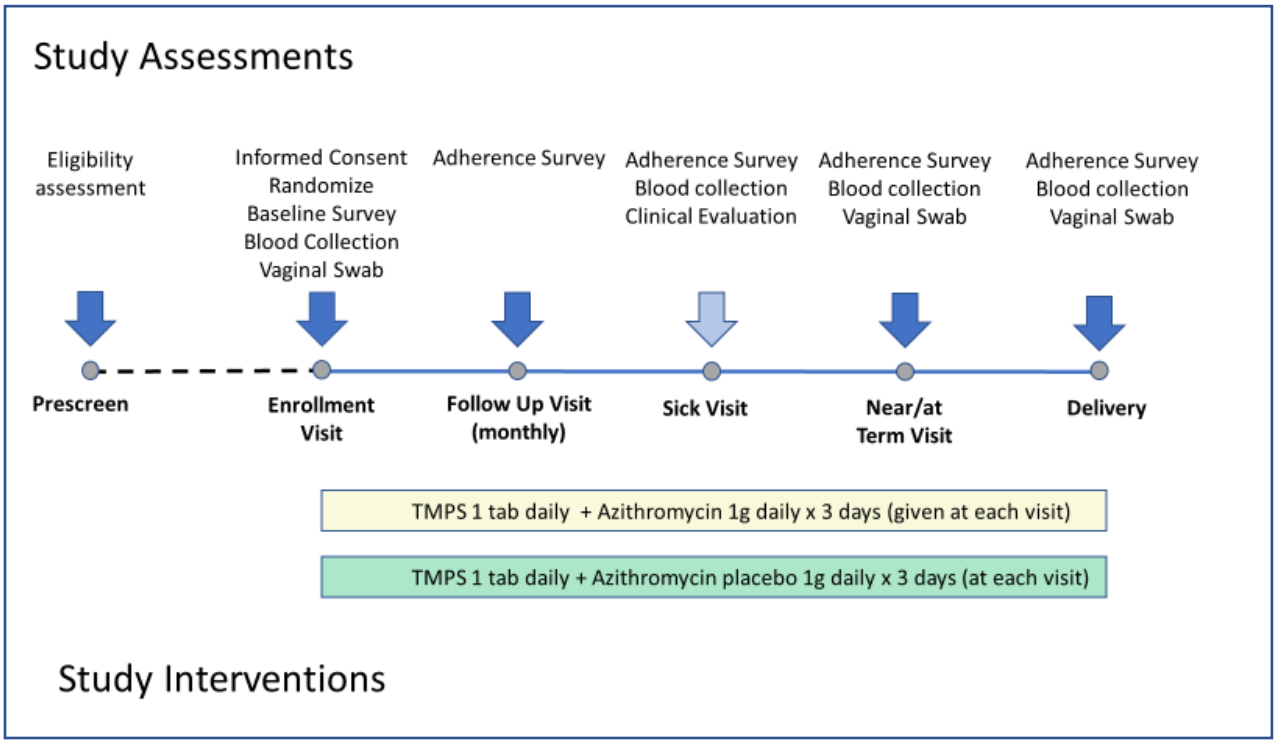
Aim 3 a) Mean infant birthweight; b) Proportion with adverse birth outcomes, including low infant birthweight (<2500 gm), miscarriage (<28 weeks), preterm delivery (<37 weeks), small for gestational age (SGA), stillbirth (>28 weeks), congenital anomaly at birth, early neonatal mortality (within 7 days); and c) maternal adherence to and tolerance of the prophylactic regimen (vomiting, rash/allergic reactions, dizziness, weakness).

b) Secondary Outcomes

Aim 1 a) Episodes of symptomatic malaria during study period; b) geometric mean parasite density at delivery; c) Proportion with placental malaria (impression smear, available on a subset); d) Proportion with anemia at delivery (hgb <11 g/dL); e) Proportion with adverse birth outcomes, including preterm delivery (<37 wks), stillbirth, low birth weight (<2500g) or early neonatal death (<7 days); f) Proportion of infants with poor growth at 6 and 12 months of age.

Aim 2 a) Proportion with anogenital GBS colonization after 35 weeks GA or at delivery; and b) Maternal puerperal and/or neonatal infections prior to hospital discharge c) Proportion with infection with Mycoplasma genitalium (M gen), Trichomonas vaginalis (T vag), and bacterial vaginosis (BV).

IV. STUDY DESIGN



V. STUDY ENROLLMENT

a) Recruitment and Screening for Eligibility

Women will be recruited for the study by study nurses from the waiting room for the antenatal care clinic at one of 2 CBCHS facilities; Mboppi Hospital in Douala and the Baptist Hospital in Mutengene. Study eligibility will be assessed using a standardized form by study nurses with review of the medical record and discussion with the patient in a private room. Subjects will be consented prior to any study procedures.

If the patient appears to meet the criteria for enrollment and expresses interest in the study, she will be told more details about the study and asked to sign the informed consent. The consent form will be available in English and in French. For patients who only understand Pidgin English or are not literate, the study will be explained verbally by the study nurse and the consent will be read aloud. A support person or family member will be allowed to help with the consent process if the patient prefers this option.

b) Participant Inclusion Criteria

- Confirmed HIV-infection (documented in medical record)
- Age ≥16 years
- Confirmed pregnancy, <28 weeks estimated gestational age (by best obstetric estimate which may include ultrasound or fundal height and LMP)
- Live singleton pregnancy

- Receiving prenatal care at Mboppi Hospital or Mutengene Hospital
- Plan to receive follow up prenatal care and deliver at study facility
- Capable of providing written informed consent
- Able and agree to come to facility for febrile episodes or acute illness during pregnancy (with reimbursement of transportation costs).
- Agree to avoid antimalarial medications outside of study protocol.
- Women receiving standard therapy for HIV infection (any antiretroviral regimen) and standard malaria prophylaxis medications (cotrimoxazole) will be eligible to participate.
- Women with HIV-infection who are not taking antiretrovirals (for any reason) are eligible to participate in the trial if all other study criteria are met.
- Participants will be eligible to participate irrespective of prior or active malaria infection detected at the time of study enrollment.

c) Participant Exclusion Criteria

- Severe anemia (last hemoglobin <6)
- History of severe adverse reaction to co-trimoxazole or azithromycin
- Active medical problem requiring inpatient evaluation at the time of screening
- Intention of moving far away from the facility during pregnancy or not likely to return for follow up care or delivery
- Signs or symptoms of early or active labor
- Known congenital anomalies
- History of severe cardiac disease (including congestive heart failure, severe valvular disease or arrhythmias).

d) Randomization Method and Masking

Consenting women will be assigned to one of two prophylaxis groups with a computer generated variable size (2, 4, 6) block randomization sequence prepared in advance by a co-investigator at the University of Alabama at Birmingham. The active and placebo study medication will be indistinguishable in appearance and packaged according to the randomization sequence so that the patient is randomized when she is assigned to the next available individual supply of study medication. The study is double masked; neither the patient nor the clinical staff will be aware of the assigned prophylaxis.

Randomization will be stratified by clinical center to assure balance between the two study groups with respect to anticipated differences among the clinic populations and possible differences in patient management. A unique study ID will be provided to each patient after they are randomized (starting with 5001D for the Douala site, starting at 9001M for the Mutengene site).

The PI and all staff responsible for assessing outcomes (laboratory and clinical) will be blinded to the randomization arm.

VI. STUDY INTERVENTION

a) Study Product Description and Storage

The medications are to be taken orally as pills. They are stable at room temperature in Cameroon. The supply will be maintained by the study nurse on site. The TMPS will be acquired in Cameroon per routine procurement pathways at CBCHS. The CBCHS Pharmacy has internal policies and procedures to verify the quality of the antibiotics administered on site. The azithromycin and matching azithromycin placebo will be created by a US Pharmaceutical Company (Goderich Pharmacy, Houston, TX) and shipped to the Central Pharmacy in Mutengene, Cameroon where the study drugs will be packaged for dissemination.

b) Administration of Study Product

Study nurses will have 30 day supply of medications prepared in advance for each subject according to their study ID. TMPS (1 DS tab 160/800 mg po QD) is routinely offered in clinic and this will be provided for women in both groups. Women will also receive a 1 gram dose (two 500 mg pills) of azithromycin (AZ) or AZ placebo under directly observed therapy and this will be recorded. Subjects will be observed for 5 minutes for adverse events. Women will be sent home with 4 additional azithromycin or placebo pills with written instructions on the bag to take 2 pills on the morning of day #2 and 2 pills on the morning of day #3 after the study visit. The azithromycin has a 2-year shelf life at room temperature.

c) Assessment of Participant Compliance with Study Intervention

Study subjects will be reminded that they will be asked about adherence, tolerance and side effects at the subsequent visit. They will complete a medication adherence questionnaire (MAQ) at subsequent visits.

d) Concomitant Medications/Treatments

Subjects will be encouraged to continue daily antiretroviral therapy throughout pregnancy. They will be advised not to take any outside medications to treat or prevent malaria without discussing it with the study nurse. Antipyretics and any other medications without antimicrobial properties are allowed. All medications taken will be captured at each follow up visit.

VII. STUDY SCHEDULES AND PROCEDURES

	Screen and Enroll	Follow up Visit (1-6)	Sick Visit (1-9)	Term Visit (1)	Delivery Visit (1)	Postpartum (if no Delivery Visit)	Follow Up Call	Infant Follow Up Call or Visit
Timing of Visit/Call	4-28 weeks	Every 4 weeks	As Needed	35-42 weeks	At Delivery	Within 14 days of delivery[1]	Within 6 weeks	3, 6, 9, 12 months
FORMS[2]								
Screening Log (Form 1)	X							
Eligibility (Form 2)	X							
Consent and Randomize (Form 3,4)	X							
Baseline Survey (Form 5)	X							
Follow Up Survey (Form 6)		X		X	X	X		
Med Adherence (Form 7)		X	X	X	X	X		
Sick Call Survey (Form 8)			X					
Outcomes and Labs (Form 9)	X	X	X	X	X	X	X	
Adverse Events (Form 10)		X	X	X	X	X	x	
Postpartum Phone Call (F 11)							X	
Participant Contact Info (Form 12)	X	X	X	X	X	X	X	
Infant Follow Up (Form 13)								X
CLINICAL AND SAMPLING								
Vitals and Exam	X	X	X	X	X	X		
Venipuncture	X		X	X	X	X		
Finger stick	X	X	X	X	X	X		
Vaginal Swab	X			X	X	X		
Placental biopsy					X			
Directly Observed Therapy	X	X	X	X				
LAB TESTING[2]								
CBC and differential	X			X	X	X		
CD4 Count				X				
HIV Viral Load				X				
Thick smear	X			X	X	X		
RDT		X	X	X				
DBS for PCR	X	X	X	X	X	X		
Syphilis (RPR/TPHA)	X[4]			X	X	X		
Xpert GC/CT & GBS NAAT				X	X	X		
SUPPLIES PROVIDED								

Bed Net	X							
Condoms	X	X	X	X				
30 day med supply	X	X	X	X				

[1] Samples collected at postpartum visit only if they were not collected at prior visits
[2] Lab testing to be performed on site. Additional testing at UAB is not part of this table.
[3] In cases of fever or clinical suspicion of malaria.
[4] RPR testing will be performed for women with a positive treponemal test on enrollment if it has not been done.

a) Enrollment Visit

Following the provision of informed consent, study subjects will be randomized to one of two arms. A baseline survey will be administered by study nurses, vital signs will be collected and a brief exam will be performed. The medical chart will be reviewed for additional information. A 30 day supply of medications will be provided by study nurse. Contact information will be collected for the woman and a back-up person (with permission) and women will be given an appointment to return in 30 days. Bed nets, condoms and safe sex counseling will be provided. Partner HIV testing will be recommended, discussed with all women and facilitated, as necessary. Questions will be asked by study staff and entered into a RedCAP database. All forms will be labeled with the unique study ID, visit number and date.

Testing: CBC, thick smear and DBS. RPR confirmatory testing for those with + ANC syphilis screen. Vaginal swab for GC/CT and store. pH. Slides and store.

Treatment: For malaria peripheral parasitemia:
1st trimester – Quinine.
National Guidelines: Three doses of Parenteral Quinine base at 8.3mg/kg x 3 every 8 hours for 24 hours. Each infusion should run for 4 hours. This is relayed by Oral Quinine (tablets) for 3 days if patient can tolerate) and a maximum dose of 1.5 per day of Quinine base. The treatment is for 7 days. If the woman develops contractions on quinine, administer tocolytics.

2nd or 3rd trimester - Artesunate.
Per National Guidelines: Injectable Artesunate IV or IM: 2.4mg/kg at 0, 12, and 24 hours. This is continuous once every 24 hours until the patient can take the oral with ease. This is relayed with Artemether -Lumefantrine for 3 days if she can swallow.

1st dose of study medications will be given under directly observed therapy (DOT).

b) Scheduled Follow Up Visit

Subjects will have vitals and brief exam. If they are noted to be febrile (axillary T>37.5), RDT will be collected. Survey about medication adherence for ART, TMPS, AZ/placebo, pill count, tolerance of prophylaxis and ART, interim treatment, ITN usage. Transportation costs, 30 day medication supply and follow up appointment will be

provided. Contact information will be verified. Questions will be asked by study staff and entered into a RedCAP database.

Testing: DBS for all. RDT if febrile.
Treatment (dosing in section a)):
Malaria with positive RDT: Quinine during the 1st trimester, Artesunate IV during 2nd or 3rd trimester. STI rx from enrollment visit if needed. Syndromic management of STI per routine. DOT ppx meds. Condoms and safe sex counseling will be provided.

c) Unscheduled Sick Call Visit

Per routine 24/7 in maternity unit. Vitals and brief exam. Management will be per routine with RDT for fever. Transportation costs will be covered.
If scheduled appointment had been missed – if possible, administer survey about medication adherence and tolerance and outside medications. Provide medications for 30 days. Questions will be asked by study staff and entered into a RedCAP database.

Testing: RDT for fever per routine, DBS for malaria testing (PCR)
Treatment (dosing in section a)):
Malaria with positive RDT: Quinine during the 1st trimester, Artesunate IV during 2nd or 3rd trimester. STI syndromic management. Other antibiotics per routine if recommended by provider and this will be captured as an outcome. DOT of prophylaxis medications if provided.

d) 35-42 Week Visit

Vitals and brief exam.
Testing: CBC, RDT, DBS and store, vaginal swab for GC/CT and store, anogenital swab for GBS, vaginal pH, slides and store, rapid syphilis test with RPR confirmation. Questions will be asked by study staff and entered into a RedCAP database.

Treatment:
Malaria with positive RDT: Artesunate IV (dosing above). GC/CT/Syphilis (same day if possible). DOT of prophylaxis medications. Condoms and safe sex counseling will be provided.

e) Labor and Delivery Visit

Vitals and brief exam.
Testing (if not performed at 35-42 weeks): CBC, thick smear, DBS and store, vaginal swab for GC/CT and store, anogenital swab for GBS, vaginal pH, slides and store, rapid syphilis test with RPR confirmation. Collect placentas, OK to refrigerate overnight. Biopsy specimen placed in formalin and can be stored on site. Questions will be asked by study staff and entered into a RedCAP database.

Treatment:

Malaria with positive RDT or peripheral parasitemia: Artesunate IV. GC/CT/syphilis if not yet treated from prior visit or newly detected. Ampicillin IV for GBS positive (late pregnancy screen or L+D screen). Treat maternal/neonatal infection per routine.

Survey: FU survey with questions about medication adherence, tolerance, interim medications and source.

Study RN: outcome assessment form including infant weight with electric scale, GA, maternal/neonatal infection, surface examination for major congenital anomalies. Verify contact information – plan to call after 7 days to ask about neonatal mortality. Recommend infant HIV testing.

f) Postpartum visit – 0-14 days with baby

For women who did not deliver at the facility.
Testing: if not done prior (35-42 wk or at delivery) - CBC, thick smear, DBS and store, vaginal swab for GC/CT and store, anogenital swab for GBS, vaginal pH, slides and store, rapid syphilis test with RPR confirmation. No testing if it was done previously. Questions will be asked by study staff and entered onto paper forms for later entry into a RedCAP database.

Treatment: infection detected on current testing or prior testing if not yet treated.

Survey: Follow-up survey about medication adherence, tolerance, interim meds and source.

Study RN: outcome assessment form – review patient medical record (document source of info) and capture birth weight. Ask about maternal/neonatal infections. Perform surface exam for major congenital anomalies. Verify contact information – may need to come back for treatment if testing performed and any new infections noted.

g) Follow Up Phone Call – within 6 weeks

Women will be contacted by telephone to check in to see how mom and baby are doing and to document any new outcomes on the study outcomes form including hospitalizations and deaths.

h) Follow Up Phone Call or Visit for Infant Outcomes – Every 3 months until 1 year

Women will be contacted by phone every three months to ask how the baby is growing. Information from medical visits about the baby's height and weight will be asked as well as any information about infant hospitalizations or sick clinic visits or death. Women will be encouraged to bring the baby to the clinic for a visit at 6 months and 12 months to measure height, weight and head circumference.

Study Forms

Form #	Form Name
0	**Forms List**
1	**Screening Log**
2	**Eligibility Assessment**
3	**Consent**
4	**Randomization Data Form**
5	**Enrollment Visit Baseline Survey**
6	**Follow Up Visit Questionnaire**
7	**Medication Adherence Questionnaire**
8	**Sick Call Visit Questionnaire**
9	**Study Outcomes Including Labs**
10	**Adverse Event Form**
11	**Postpartum Check In Form**
12	**Participant Follow Up and Call Log**
13	**Infant Follow Up Form**

VIII. TRAINING AND QUALITY ASSURANCE

Study staff (RN, data manager, study coordinator) must have the human subject's protection training certificate. New staff members will undergo training on research ethics. Additional training will occur on site prior to study initiation related to study procedures, forms, data entry, sample collection and subject follow up. Specific training will be provided to midwives about how to assess for congenital anomalies at birth.

The participating site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site PI will provide direct access to all trial-related sites, source data/data collection forms, and reports. The site PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

Data QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

IX. MONITORING OF ADVERSE EVENTS

a) Reporting

Adverse Event:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care.

All AEs not meeting the criteria for SAEs should be captured on the appropriate form. Information to be collected includes event description, clinician's assessment of severity, relationship to study product, 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 subject is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product.

Severity of Event: All AEs will be assessed by the clinician using a grading system.

Mild: events require minimal or no treatment; do not interfere with the subject's daily activities.

Moderate: events result in a low level of inconvenience or concern with the therapeutic measures; may cause some interference with functioning.

Severe: events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment; are usually incapacitating.

Relationship to Study Products: The clinician's assessment of an AE's relationship to the study drug is part of the documentation process.

• Related – There is a reasonable possibility that the study drug caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.

• Not Related – There is not a reasonable possibility that administration of the study drug caused the AE.

Serious Adverse Event (SAE):

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes:

- Maternal death
- Neonatal death

- Stillbirth
- Congenital anomalies
- Unanticipated or prolonged maternal hospitalization (longer than expected)
- Prolonged neonatal hospitalization (longer than expected based on gestational age at birth)

All SAEs will be:

• Assessed for severity and relationship to study product and alternate etiology by a study physician.

• Recorded on the appropriate form

• Followed through resolution by a licensed study physician.

• Reviewed and evaluated by the DSMB and the IRB.

b) Data Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial, or other conflict of interest related to the study. The DSMB will consist of three members with appropriate expertise to contribute to the interpretation of the data from this trial: malaria in pregnancy, maternal-fetal medicine and biostatistics.

The DSMB will review and approve the study protocol and safety plan prior to initiation of the trial. It will be convened when 50% of the planned subjects have been enrolled for a review of interim data. The PI will review safety data weekly and report any serious adverse events to the DSMB and IRB and to NIH/NICHD. The DMSB and NIH will receive quarterly adverse event reports and the interim report will include the following information: recruitment, withdrawals, loss to follow up, adverse events, and medication tolerance. The DSMB will also review efficacy and safety data after all subjects have been enrolled in a final closeout meeting, held at the end of the study. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study and to continue, modify, or terminate the study.

X. SPECIMEN COLLECTION AND PROCESSING

All samples will be collected under practices outlined in SOPs and they will be labeled with unique study ID, visit number and date. Malaria testing: Blood will be collected by fingerstick for thick smear microscopy and dried blood spots (DBS) will be collected on filter paper for PCR testing later. Blood will also be collected by venipuncture for CBC, differential and RPR testing, as indicated. RPR will be performed on women with a prior positive treponemal test during antenatal care if not performed previously. Microscopy, CBC, and syphilis testing will be performed at the facility laboratory but same day results cannot be guaranteed. Subjects will be called by telephone with positive results that return after they have left the facility along with

specific follow up instructions. Filter paper with DBS will be stored in the freezer (-20 degrees C) with regular transportation to the University of Buea for long term storage and PCR testing.

Placental biopsies will be collected on as many women as possible at the time of facility delivery. Slides will be created with impression smears and placental blood will be collected on filter paper for PCR testing.

STI testing: Vaginal swabs will be collected at enrollment for storage and at the 35-42 week or delivery or post-delivery visit (whichever comes first) for GC/CT NAAT testing as well as an anogenital swab for GBS NAAT testing per SOPs. pH indicator sticks will be used to collect a sample from the lateral vaginal wall. Slides will be prepared from a vaginal swab at the late pregnancy visit.

Vaginal Swab specimens for Future Testing: Vaginal swabs will be stored in transport media using buffer in a -20 freezer until they can be transported to the UAB STI laboratory for later STI testing. Participants will be asked to sign a consent specifically for their agreement to have these samples stored and shipped to UAB for future analysis. For those who do not consent, the samples will be destroyed at the end of the study. Before specimens leave the clinic, they will be assigned a unique code. Specimens stored for future research will be shipped to the UAB STI Research Laboratory at the University of Alabama at Birmingham (UAB) (Dr. Van Der Pol Lab, Dr. Ken Waites Mycoplasma/Ureaplasma Laboratory) where they will be stored according to GCLP by the Laboratory Managers.

XI. SAMPLE SIZE CONSIDERATIONS

AIM 1: To test the hypothesis that the addition of AZ to standard preventive therapy in pregnant women with HIV will be associated with a lower proportion of women with peripheral parasitemia detected by microscopy or PCR at delivery, we assumed a 30% prevalence of parasitemia in the TMPS arm based on prior studies and 15% prevalence in the TMPS/AZ arm. A sample size of 134 pregnant women per arm has 80% power at a two-sided significance level of 0.05 using a chi-square.

We will plan for 15% loss to follow up (LFU) and will recruit 154 women per arm (308 women total).

AIM 2: Based on the sample size of 308 evaluable participants at the time of delivery and an expected prevalence of 30% for one or more STIs (CT 20%, GC 5%, syphilis 5%) there will be >80% power at a two-sided significance level of 0.05 to detect a 50% lower STI prevalence in the intervention arm.

XII. DATA ANALYSIS AND MANAGEMENT

Data management and analysis will be led by the University of Alabama at Birmingham under the supervision of the study PI (Dr. Dionne-Odom).

The primary analysis will be by intention to treat for women who are randomized and receive at least 1 dose of study medication.

The “per protocol” analysis will be performed on women who came to at least one follow up visit following the enrollment visit, reported excellent (>90%) medication adherence, and had outcomes captured (ie – not lost to follow up).

Statistical Analysis: Descriptive statistics will be used to compare the study participants between each arm and the primary analysis will be intention-to-treat for the primary outcome of proportion of women with parasitemia. The analysis plan for categorical outcomes is chi-square, Fisher’s exact tests as needed for small sample sizes and we plan to use t-test and Wilcoxon Rank-Sum tests for continuous outcomes. Women will be considered lost to follow up if they do not have a study visit after 35 weeks or at delivery for outcome ascertainment.

For the secondary outcomes, the significance of differences in proportion will be explored using the Pearson’s $\chi 2$ test or Fisher’s exact test. Multivariable regression modeling will be used to evaluate baseline factors associated with parasitemia if there is imbalance between the arms despite randomization. Potential covariates include age, parity, educational level, monthly income, marital status, history of negative birth outcomes, CD4 count, ART adherence, bed net usage, malaria treatment received and number of study visits. All analyses will be performed in SAS v 9.3.

Data Management: Data will be collected in clinic on paper forms to be entered into a password-protected, secure, web-based, electronic database (REDCap). Information will be stored locally on the device, then transferred to a server located at the University of Alabama at Birmingham when the internet access is adequate. On site, the paper forms will be kept in a locked cabinet in a room with the study staff and the computer for data entry will be password protected. During the conduct of the study, periodic data checks will occur to systematically evaluate for any missing data or unanticipated problems. The site staff will receive feedback to improve the process as indicated. Adverse events will be reviewed weekly by the PI who will be blinded to study arm randomization. The final data analysis will occur after all participants have been enrolled and procedures completed at both sites.

REDCap (Research Electronic Data Capture) is a secure, Web-based application designed to support data capture for research studies. For multi-center studies, Data Access Groups may be set up to allow users access only to their site’s data. For quality control purposes, REDCap offers real-time range checking during data entry. There are also data visualization tools to assist in data cleaning and evaluation. The Data Export Tool includes methods for data de-identification and exports some or all data to Excel, SAS, SPSS, R, S-Plus, and Stata.

The REDCap database is hosted at the UAB Department of Medicine’s secure data center, which will be used as a central location for data storage, processing, and management. The servers are protected by an aggressive firewall and a log monitoring system. All web communications are protected via SSL encryption. Only IRB approved research team members will have access to the REDCap. Access is granted according to “the principle of least privilege.” Each team member will be granted access to the REDCap data system through a secure login.

The protocol has been registered on clinicaltrials.gov with the study ID number NCT03431168.

XIII. STUDY TIMETABLE

	2017	2018	2019	2020
IRB Approval	X			
Hire Study Staff	X			
Training	X			
Enrollment		X	X	
Subject Follow Up		X	X	
Data Processing		X	X	
Data Analysis				X

a) IRB Approval – see ethical considerations in subsequent section (Section XIV).

b) Study Staff – One study nurse and one data manager will be hired at each facility and the current CHI-UAB Coordinator will assume the duties of study coordination at both sites. The study PI will be onsite several times a year for 1-2 months at a time during the study period. She will also be on site during training, study initiation and enrollment.

c) Training – Before the trial begins, study nurses, coordinators, physician co-investigators and laboratory staff will undergo training on study procedures and data collection, including standardized testing methods for malaria and sexually transmitted infections and how to perform a surface examination for congenital anomalies at birth and collect placental biopsies.

d) Enrollment and Follow Up – In 2014, Mboppi Hospital in Douala had more than 15,000 antenatal care visits and 4000 deliveries. Approximately 400 new pregnant patients are seen each month in clinic and approximately 24 women are HIV-infected (seroprevalence 5.9%). At the Baptist Hospital in Mutengene (BHM), the HIV seroprevalence is 10.2%, and there are 10 new HIV-infected women seen each month in clinic. Approximately 20% of women present for ANC care during their 1st trimester and 75% during the second trimester. Pregnant women routinely have 4 prenatal visits and clinic attendance rates are high with 80% facility delivery rates.

We plan to enroll approximately 18 women each month (12 in Douala, 6 in Mutengene) over an 18 month enrollment period to reach the 308 women needed. This will allow us to have 268 women with evaluable outcomes according to the power calculation stated above (this assumes 15% loss to follow up but we will strive for >95% subject retention).

e) Data Processing and Analysis – After a three-month period for completion for data entry for the trial, the dataset will be locked and available for analysis. Approximately six months will be required to complete the final report and submit it for publication. Group meetings will be held to determine which manuscripts will be written and the appropriate team members for submitted abstracts and publications.

XIV. ETHICAL CONSIDERATIONS

a) The protocol will be reviewed by the Institutional Review Board in Cameroon at CBCHS (Cameroon Baptist Convention Health Services). This is an active and long-standing IRB group that meets regularly and reviews all research protocols for work proposed to

take place at CBCHS facilities. The protocol will also be reviewed by the IRB at the University of Alabama at Birmingham but the primary IRB will be located in Cameroon. Any changes or edits to the protocol will be submitted to both IRB groups and both will be informed of any serious adverse events that occur during the study.

b) Informed Consent Process: Women will be invited to participate and provide informed consent. Anyone 16 years of age or older will be eligible to participate according to Cameroon law which grants "mature minor" status to girls during pregnancy and this allows them to consent without parental involvement.

Malaria detected as part of the study (whether a screening test or a test done in the setting of a fever work up) will be treated with quinine per clinical routine. Positive tests for STIs (GC/CT and syphilis) identified at the end of pregnancy will be treated per CDC recommendations. GBS colonization will be treated with ampicillin IV during labor and delivery for women with facility deliveries. The cost of treatment for infections detected or adverse events as a result of testing or treatment performed for the study will be covered as a part of study expenses but hospitalization and other diagnostic and treatment costs will not be covered.

Women will have the option in the consent of whether or not to submit samples to long term storage and later testing on dried blood spots, vaginal swabs and placental biopsies and infant follow up procedures. No blood or samples will be collected from infants.

c) Participant confidentiality. Given the personal and serious nature of working with a population of pregnant subjects with HIV infection, study related conversations will occur in private although participants will be invited to include a support person in the discussion if they prefer. Subjects will have code numbers and will not be identified by name. The staff at CBCHS is very well versed in caring for women with HIV-infection and they prioritize confidentiality at the highest level in all clinical and research activities and documentation. Subjects will have code numbers and will not be identified by name.
d) Participant Costs. Subjects will be told that they will be provided with study related medications and testing at no cost. They will be treated for infections diagnosed on site and this antibiotic therapy will be provided for free as well.

Compensation. Participants will be reimbursed for transportation (2000 CFA per visit) for routine visits and sick call visits. They will also be provided with a phone card (1000 CFA per visit) at each visit to allow them to call the study nurse if they have questions or illness. Women who deliver at the facility will receive a small token for the baby and there will be follow up phone calls from the study staff to check on how the baby is doing.

Appendix A – DESIGN SUMMARY

The PREMISE Trial: A Randomized Clinical Trial to Prevent Malaria and STI in Pregnant Women with HIV

OBJECTIVE To determine whether or not the addition of Azithromycin (AZ) to standard Cotrimoxazole prophylaxis reduces infection in Cameroon

ORGANIZATION	
Clinical Centers	Mboppi Hospital in Douala, Cameroon Baptist Hospital in Mutengene, Cameroon University of Alabama at Birmingham, US
Principal Investigator	Jodie Dionne-Odom, MD
DESIGN	
Type:	# Phase II, Double masked RCT
Major Eligibility Criteria:	# HIV-infected # Age ≥16 # GA 4-28 weeks # Singleton pregnancy
Groups:	# Experimental: AZ/Cotrimoxazole # Placebo: Cotrimoxazole
Random Allocation:	1:1 allocation
Stratification:	By clinical site
Sample Size:	308 subjects Assumptions: # Outcome event: peripheral parasitemia # Placebo group event rate: 30% # Experimental group event rate: 15% # 15% loss to follow up # Type 1 error 5% (2-sided) # Power 80%
SCHEDULED EVALUATIONS/DATA COLLECTION	
Pre randomization:	# History, GA, HIV status
Post randomization:	# thick smear, DBS and vaginal swab # visits scheduled q 4 weeks to assess medication adherence and tolerance # sick call visits for fever or complications
Near Term or Delivery:	# thick smear, DBS and vaginal swab # placental collection
OUTCOME MEASURES	
Primary:	# proportion with peripheral parasitemia by PCR or microscopy # composite STI score (GC/CT/syphilis) # safety and mean infant birthweight
Secondary:	# episodes of symptomatic malaria # proportion with placental parasitemia # composite adverse birth outcomes # maternal anemia (hgb <11 g/dL) # anogenital GBS colonization # proportion with other STI (Mycoplasma genitalium, Trichomonas vaginalis, BV)
TIMETABLE	
As designed:	# Enrollment: January 2018-July 2019 # Data Collection: January 2018-Dec 2019 # Final Analysis:: June 2020

Registered at Clinical Trials Website (clinicaltrials.gov): NCT03431168

Appendix B (03 April 2018**)**

CONSENT FORM

TITLE OF RESEARCH:	The PREMISE Trial: A Novel Regimen to Prevent Malaria and STI in Pregnant Women with HIV
IRB PROTOCOL NO.:	IRB-300001112
PRINCIPAL INVESTIGATOR:	Jodie Dionne-Odom, MD
SPONSOR:	National Institute of Child Health and Human Development National Institutes of Health, United States of America

Purpose of the Research

This consent form may contain words you do not understand. Please ask the study staff to explain any words or information you do not clearly understand.

We are asking you to take part in a research study because you are pregnant. This research is to look for ways to prevent infections including malaria and certain sexually transmitted infections (STI) in pregnant women who are infected with HIV. Malaria and STIs are common in Cameroon and pregnant women with HIV are at particular risk of becoming infected. You are eligible to participate if you are taking or will take standard medications to prevent malaria during pregnancy.

This is a double blind, randomized placebo controlled trial. A randomized controlled trial is where study participants are put into one of two groups at random (like flipping a coin). People in each group receive different treatments to study if one treatment is better than the other. Double blind means that neither you nor the study staff will know which treatment group you are in and the antibiotic pills will be packaged to look the same.

The medication recommended to prevent malaria in pregnant women with HIV in Cameroon is a pill called co-trimoxazole. This is called the standard of care medication. The PREMISE study will look to see if combination therapy with co-trimoxazole and azithromycin is better at preventing infection in pregnancy compared to co-trimoxazole alone. One group of women will receive cotrimoxazole + azithromycin and the other group will receive cotrimoxazole + placebo (sugar pill.)

This study is funded by the National Institutes of Health in the United States and we plan to enroll approximately 310 pregnant women living with HIV from two Cameroon Baptist Convention Health Services (CBCHS) facilities in Mutengene (105 women) and Douala (205 women), Cameroon.

Explanation of Procedures

If you enter the study, you will have the following research procedures according to the visit schedule that follows.

<u>Enrollment Visit</u>

This visit will take about 3 hours.

- You will have a brief physical exam to look at your skin, listen to your heart and lungs and abdomen and your temperature will be taken.
- You will complete a survey including questions about your background, your medical history, malaria prevention, HIV history, and current medications.
- You will receive the first dose of study medication.

- Your blood will be drawn (fingerstick and 1 teaspoon of blood from your vein) for malaria and STI testing. Testing will be performed in Cameroon.
- A vaginal swab will be collected by the study nurse. This is a swab that is inserted a few inches into your vagina and then removed. This will be tested at UAB.
- You will be given a mosquito bed net if you do not have one and condoms.
- You will be provided with a 30-day supply of medications and a follow up visit for 30 days from the baseline visit.

Follow Up Visit(s) – scheduled for every 30 days after the enrollment visit until delivery.
This visit will take about 30 minutes.

- You will have a brief exam and your temperature will be taken.
- You will be asked about symptoms.
- You be asked to complete a survey about your medications.
- You will receive the next dose of study medication.
- Your blood will be drawn (fingerstick) for malaria testing. Testing will be performed in Cameroon at the end of the study.
- Your blood will be drawn by fingerstick for malaria testing at the CBCHS facility if you have fever.
- You will receive treatment for malaria if the test is positive. If the test returns positive after you have left the clinic, you will be contacted by phone with results.

- You will be offered condoms.
- You will be provided with a 30-day supply of medications and a follow up visit.

Sick Call Visit(s)
This visit will take 30-60 minutes, depending on your symptoms.

- You will have a brief exam and your vital signs will be taken.
- You will be asked about symptoms
- You be asked to complete a survey about your medications.
- Your blood will be drawn (fingerstick) for malaria testing. Testing will be performed in Cameroon at the end of the study.

- Your blood will be drawn by fingerstick for malaria testing at the CBCHS facility if you have fever.

You will receive treatment for malaria if the test is positive. If the test returns positive after you have left the clinic, you will be contacted by phone with results.

- You will be provided with a 30-day supply of medications if you have run out.
- You will receive additional testing and/or treatment if recommended by CBCHS staff depending on your clinical findings.

Near/at Term Visit (35-42 weeks)
This visit will take about 30 minutes.

- You will have a brief exam and your vital signs will be taken.
- You will be asked about symptoms.
- You be asked to complete a survey about your medications.
- Your blood will be drawn by fingerstick for malaria testing at CBCHS if you have fever. Your blood will also be drawn by vein for additional testing in Cameroon
- You will have a vaginal swab collected and an anogenital swab collected for testing at Mboppi Hospital in Douala.

- You will be provided with a 30-day supply of medications and a follow up visit.
- You will receive treatment for malaria if the test is positive. If the test returns positive after you have left the clinic, you will be contacted by phone with results.

Delivery Visit
This visit will take 30 minutes.

- You will have a brief exam and your vital signs will be taken.
- You will be asked about symptoms.
- You will be asked to complete a survey about your medications.
- Your blood will be drawn by fingerstick for malaria testing at CBCHS if you have fever. Your blood will also be drawn by vein for additional testing in Cameroon
- You will have a vaginal swab collected and an anogenital swab for group B streptococcus testing (if not previously provided at 35-42 weeks). This is a swab that is inserted 2 inches into your vagina and then your rectum to look for bacteria. Testing will be performed at Mboppi Hospital in Douala.
- A sample will be taken from the placenta for malaria testing at a later date and will be tested in Cameroon
- You will receive treatment for group B streptococcus colonization if the test returns positive and results are available prior to delivery
- You will receive treatment for malaria if the test is positive. The baby will not be tested.
- You will receive additional treatment if needed for infections detected at the 35-42 week (or other) visit that have not been treated.
- Information will be collected about the baby's weight, age, and appearance, including an examination for any congenital anomalies (birth defects).

Postpartum Visit (within 14 days after childbirth for women who did not deliver at CBCHS facility)
This visit will take about 45 minutes.

- You will have a brief exam and your vital signs will be taken.
- You will be asked about symptoms.
- You will be asked to complete a survey about your medications.
- Your blood will be drawn by vein and fingerstick for malaria testing in Cameroon.
- A vaginal swab and ano-vaginal swab will be collected for testing at Mboppi Hospital in Douala if not collected at the 35-42 week visit.
- You will receive additional treatment if needed for infections detected at the 35-42 week (or other) visit that have not been treated.
- Information will be collected about the baby's weight, age, and appearance.
- You will be contacted by phone if testing returns positive after you have left the clinic.

Follow Up Phone Call (within 6 weeks of delivery)

- You will be asked if you have had any fever or hospitalization since delivery.
- You will be asked about how the baby is doing including any hospitalization or illness.

Follow Up Phone Call or Visit for Infant Outcomes – Every 3 months until 1 year

- You will be contacted by phone every three months to ask how the baby is growing. Information from medical visits about the baby's height and weight will be collected as well as any information about infant hospitalizations or illness.
- You will be encouraged to bring the baby to the clinic for a visit at 6 months and 12 months to measure height, weight and head circumference.

Some of the testing will be performed in Cameroon at CBC with results available to impact your clinical care. Other, later laboratory testing for research purposes will be performed in Cameroon at the University of Buea and/or the University of Alabama at Birmingham in the US. You will not be contacted with these results.

Risks and Discomforts

There is a risk of loss of confidentiality. We will work hard to protect your personal information and only the information that is needed for the study will be collected. You will be assigned a unique study identification number for study paperwork instead of your name.

This study will provide commonly used antibiotics to women with no history of allergy or adverse reaction to co-trimoxazole or azithromycin. All women will receive daily co-trimoxazole as standard of care and some women will receive azithromycin for 3 days monthly. Azithromycin is an antibiotic that although there have been no adequate controlled studies in pregnant women, has been used in pregnant women for many years. The antibiotic, co-trimoxazole has no controlled data in human pregnancy; however, it is part of the World Health Organization (WHO)-recommended therapy for HIV-infected pregnant women in Africa. The study nurse will be asking questions about how you tolerate the medicine and if you have any side effects. There is a risk of randomization since you will be assigned to one of two groups by chance. One group may prove to be less effective or have more side effects than the other group.. You will be asked to return to clinic for illness in between visits and not to take any medications for malaria not prescribed by your provider unless necessary.

The most common side effects of azithromycin are diarrhea, nausea and occasionally pain in the abdomen or vomiting. The common side effects of cotrimoxazole are diarrhea, nausea, vomiting, loss of appetite, skin rash and allergic reaction (itching, rash, difficulty breathing). There are other rare side effects that have occurred. If you feel you are having a side effect from the treatment contact your doctor immediately. There may be some side effects of the combined antibiotics that are not known at this time. We do not expect any harm to the baby as a result of participating in this study and no blood will be drawn from him/her. You may experience some discomfort, bruising or swelling associated with the collection of blood we will draw from you. You may also experience some minimal discomfort with vaginal swab collection.

Benefits

You may or may not benefit from taking part in this study. If an infection is detected as part of the study, you will be offered treatment. This includes treatment for malaria, sexually transmitted infections, and group B streptococcus. This study may help us better understand how to prevent malaria and STIs in pregnant women in the future.

Confidentiality

Information obtained about you for this study will be kept confidential to the extent allowed by law. The findings from the research may be published for scientific purposes; however, your identity will not be given out. All study paperwork will be stored on a password protected computer or in a locked cabinet and your name will not be listed on routine study forms. Information that will not include your name or other personal identifiers will be entered into a computer database that will be transmitted and read at the University of Alabama at Birmingham in the US.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with your provider or with the Cameroon Baptist Convention Health Services Organization (CBCHS).

Cost of Participation

There will be no cost to you for taking part in this study. The costs of your standard medical care will be billed to you in the usual manner.

Payment for Participation in Research

You will receive reimbursement for transportation to attend study visits including sick visits (2000 CFA per visit or $4 USD). You will also be provided with a phone card (1000 CFA or $2 USD) so you can call the study team with questions or problems that may occur between or after study visits. You will receive a small gift at the time of delivery when you deliver at Mboppi or BHM facilities.

Questions

If you have any questions, concerns, or complaints about the research, you may contact Mrs. MBAH Rahel and she will inform Dr. Jodie Dionne-Odom, the Principal Investigator. You may also reach out to a local member of the CBCHS IRB group, Mrs. Grace Ndze.

Rahel Mbah, MPH
CHI UAB Program Coordinator
237 670 671 378

Mrs. Grace Ndze
CBC IRB
237 677 022 470

Jodie Dionne-Odom, MD
Principal Investigator of PREMISE
University of Alabama at Birmingham, USA
237 653 960 213

Seraphine Pekwerake
Research Nurse
Mboppi (MBHD)
237 670 332 709

Legal Rights

You are not waiving any of your legal rights by signing this informed consent document.

Storage of Specimens for Future Use

As part of this study, we would like to store some of the blood, vaginal swabs and placental biopsy collected from you for future research on malaria and sexually transmitted infections in pregnancy that is not planned in the current study. The future research may be conducted by Dr. Jodie Dionne-Odom or by other researchers that obtain approval for their research. The specimens will be labeled with a code that only Dr. Dionne-Odom can link back to your medical information. Results of any future research will not be given to you or your doctor, because that researcher will not have your name or contact information. You do not have to agree to allow your blood or vaginal swabs to be stored to be part of this future research.

You may request at any time that your research samples be removed from storage and not be used for future research. If you decide you want your samples removed, you may contact Mrs. MBAH Rahel at 237 670 671 378. Once the request is received, and if your samples have not already been used for other

research, they will be destroyed. If you do not make such a request, your specimens will be stored until they are no longer scientifically useful.

Initial your choice below:
____I agree to allow these samples to be kept and used for future research on infection in pregnancy.

___ I do not agree to allow my samples to be kept and used for future research on infection in pregnancy. (List here separately which sample types should not be stored_____)

Infant Follow Up (every 3 months)

Initial your choice below:
____I agree to participate in the infant follow up portion of the PREMISE study.

___ I do not agree to participate in the infant follow up portion of the PREMISE study.

Signatures

Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

Signature of Participant _____ Date_____(MM/DD/YY)

Signature of Person Obtaining Consent_____Date_____(MM/DD/YY)

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Protocol Changes

Protocol Version Number	Date	Changes Made Since Prior Version
1.1	20 Aug 2018	Added quarterly infant follow up study procedures. Added dried blood spot collection at every follow up visit. DSMB minutes, quarterly AE and SAE reports sent to NICHD.