Prenatal Treatment to Prevent Mother to Child Transmission of Hepatitis B Virus in the DRC: The Arresting Vertical Transmission of Hepatitis B (AVERT-HBV) Study

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PROTOCOL TITLE: Prenatal Treatment to Prevent Mother to Child Transmission of Hepatitis B Virus in the DRC: The Arresting Vertical Transmission of Hepatitis B (AVERT-HBV) Study

Short Title: AVERT-HBV

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I confirm that I have read this protocol and understand it.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
DBS	Dried blood spot
DRC	Democratic Republic of the Congo
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B viral load
MCH	Maternal and child health
MTCT	Mother-to-child transmission
PMTCT	Prevention of mother-to-child transmission
VT	Vertical transmission

PROTOCOL SYNOPSIS

Study Title	Prenatal Treatment to Prevent Mother to Child Transmission of Hepatitis B Virus in the DRC: The Arresting Vertical Transmission of Hepatitis B (AVERT-HBV) Study
Funder	Gillings Innovation Labs
Clinical Phase	N/A
Study Rationale	Hepatitis B virus (HBV) is a leading cause of chronic liver disease globally, with devastating complications such as cirrhosis, hepatocellular carcinoma and death. Vertical transmission (VT) of HBV is a worldwide public health concern because infected children are at high risk of developing chronic liver disease. It is a particular problem in the Democratic Republic of the Congo (DRC); our preliminary data suggest that approximately 3% of children have HBV infection due to VT. However, VT is preventable. Pregnant women with risk factors can be identified and treatments given which can virtually eliminate transmission. Unfortunately, despite the high burden of HBV, neither HBV testing of pregnant women nor interventions to prevent HBV VT are routinely performed in the DRC and elsewhere in sub-Saharan Africa. Our pilot feasibility study will address this healthcare gap by identifying women with HBV early in their pregnancies and intervening to prevent VT by (1) treating mothers with high-risk HBV (defined as HBeAg positivity and/or HBV viremia $>10^6$) with tenofovir +/- lamivudine and (2) providing HBV vaccine to HBV-exposed infants within 24 hours of birth. Our pilot study will piggyback onto an existing study that is evaluating the DRC's HIV Prevention of Maternal-to-Child Transmission Option B+ (PMTCT+) strategy. Combining programs to prevent VT of HBV and HIV enables using the same personnel and infrastructure to implement both interventions. Furthermore, tenofovir and lamivudine, used to treat HBV infections, are already used in the DRC to treat HIV. We hypothesize that utilizing the existing PMTCT+ infrastructure in the DRC will provide a cost-effective platform to prevent HBV VT. If effective, this model of treatment will inform future public health efforts and wider policy recommendations that can be applied in the DRC and throughout the Sub-Saharan African region to reduce the burden of HBV.

Study Objective(s)	**Specific Aim 1: Conduct a pilot feasibility study of two-step HBV prenatal screening for HBV infection among pregnant women in the DRC.** We will screen 4,000 pregnant women with HBV rapid diagnostic testing (HBV surface antigen [HBsAg]) and will identify a subset of women with high-risk disease by evaluating viral loads and HBV e antigen (HBeAg) performed on both venous blood and dried blood spots. The major outcome of this aim will be the feasibility of this testing strategy: acceptability to patients and staff, collection of samples, and time from sample collection to results. Other outcomes will include the test characteristics of these studies (sensitivity, specificity, positive predictive value and negative predictive value to assess agreement between dried blood spot (DBS) and gold standard venous blood sampling) and the cost of adding them to the existing PMTCT program. **Specific Aim 2: Conduct a pilot feasibility study of an intervention program to prevent HBV VT.** We anticipate screening 4,000 pregnant women for HBV, of whom we expect that 2.5% (100) will have positive HBV testing. Of these 100, we expect 30-50% (30-50 women) to have high-risk disease (defined as positive HBeAg and/or HBV viremia $>10^6$) and to therefore require prophylactic antiviral therapy with tenofovir +/- lamivudine. A small subset of women who are HIV-positive (an estimated 3-5 women) will receive tenofovir and lamivudine as part of their HIV treatment, and so will not receive it as part of this study. All HBV-exposed infants will receive HBV vaccine within 24 hours of delivery. If successful, this model could be easily exported to other countries in sub-Saharan Africa. The major outcomes of this aim are (1) adherence to treatment; (2) acceptability of antiviral therapy; (3) maternal HBV viral load at delivery and 24 weeks post-partum and (4) infant HBsAg at 24 weeks post-partum; and (5) additional cost to the existing PMTCT program.
Test Article(s) *(If Applicable)*	Tenofovir +/- lamivudine Monovalent HBV vaccine
Study Design	This pilot feasibility study will involve identification of a cohort of HBV-infected pregnant women and their infants, who will receive proven interventions to prevent vertical transmission of HBV in a resource-poor setting. Of 4,000 women screened for HBV with HBsAg, we expect 100 (2.5%) to have positive testing. The HBsAg-positive participants will undergo further testing with HBV viral load and HBeAg to identify those at high risk of transmission (positive HBeAg and/or HBV viremia $>10^6$). We expect 30-50 women to be categorized as high-risk. Women with high-risk HBV

	will be treated with prophylactic tenofovir +/- lamivudine starting at 28-32 weeks' gestation and continuing through 12 weeks' postpartum. A small subset of these women (3-5) will be co-infected with HIV, and so will already be receiving tenofovir and lamivudine as part of their HIV therapy. HIV-negative women with low-risk HBV will not receive antiviral therapy, but will undergo the similar testing procedures as those with high-risk HBV. All HBV-exposed infants will receive a monovalent HBV vaccine dose within 24 hours of life and their HBV status will be assessed at 24 weeks.
Subject Population **key criteria for Inclusion and Exclusion:**	Inclusion criteria: • Pregnant women receiving care at Binza and Kingasani maternity centers who present prior to 24 weeks gestation • Infants born to HBV-positive women will be included in the study Exclusion criteria: • The study will not enroll participants who are severely sick and who require prolonged hospitalization. • Any women who do not intend to stay in Kinshasa for prenatal care through delivery
Number Of Subjects	**4,100 (4,000 pregnant women screened in order to enroll 100 HBsAg+ women and 100 HBV-exposed infants)**
Study Duration	**Participation of mothers will last for up to 12 months and that of infants will last 6 months.** **The entire study is expected to last for 2 years.**
Study Phases **Screening** **Study Treatment** **Follow-Up**	**(1) <u>Screening</u>: Consent and screening for HBV (HBsAg).Determination of HBV risk status among HBsAg-positive women.** **(2) <u>Intervention</u>: Antiviral prophylaxis for HIV-negative pregnant women with high-risk HBV. Vaccination of HBV-exposed infants.** **(3) <u>Follow-up</u>: Repeat laboratory testing of mothers at delivery, and at 10 and 24 weeks' postpartum. Exit interview for mothers at 6 months postpartum. Laboratory testing of infants at 6 months of life.**
Efficacy Evaluations	**Feasibility of the study, as determined by responses to questionnaires by study participants and research personnel. Additional costs to HIV PMTCT program. Loss-to-follow-up of study participants. Rate of MTCT of HBV. Comparison of HBV test characteristics for DBS versus venous blood sampling.**

Safety Evaluations	**Adverse effects of tenofovir, lamivudine and/or monovalent HBV vaccine**
Statistical And Analytic Plan	**For specific aim 1, we will determine the feasibility of the testing strategy by measuring the following: acceptability to patients and staff, ease of sample collection and transport, and time from sample collection to results. Secondary measures will be the agreement of test characteristics (sensitivity, specificity, positive predictive value and negative predictive value of (1) HBeAg and (2) HBV viral loads) between DBS and gold standard venous blood sampling. If agreement is demonstrated, DBS testing is a more cost-effective manner for such testing in low-resource areas. We will also determine the additional costs of HBV screening to the PMTCT+ program. For specific aim 2, we will measure how many and when women and their infants are lost to the treatment cascade; the percentage of women with highly active HBV who receive antiviral treatment and who achieve reduction or suppression of HBV viremia, the development of ALT elevation during or after treatment, and resolution of e antigen positivity; loss-to-follow-up (LTFU, percentage of women who are initiated on antiviral treatment but are not able to complete the recommended course) and adherence to tenofovir +/- lamivudine and vaccination; and the rate of mother-to-child transmission (MTCT) of HBV, defined as the proportion of infants born to HBV-positive mothers who test positive for HBV.**
DATA AND SAFETY MONITORING PLAN	**PI, co-investigators and research coordinators in Kinshasa will be responsible for data quality management and ongoing assessment of safety. Data will be gathered in the form of paper charts and questionnaires. Study site supervisors will check paper forms for completeness and consistency, and will enter the completed forms into the electronic database (Access or EpiData). The research team at UNC will upload data on a biweekly basis to conduct quality assurance.** **Safety monitoring will occur on an ongoing basis by the Kinshasa-based study team, and any concerns will be reported to the study physician. Monitoring by the PI and co-investigators will occur on a monthly basis. While the likelihood of terminating the study early due to safety concerns is minimal, study personnel will consider this if there is a high frequency of safety concerns related to antiviral therapy.**

1 BACKGROUND AND RATIONALE

HBV is a major cause of chronic liver disease, liver cancer, and death worldwide. **Despite the presence of effective vaccines and antivirals, there are still more than 300,000 deaths each year from HBV-related cirrhosis and an equal number of deaths due to HBV-induced liver cancer**.[1] The burden of HBV is highest in Southeast Asia as well as the sub-Saharan region of Africa in countries like the DRC.

HBV is highly transmissible and is commonly spread from mother to infant by vertical transmission (VT). Since there is a 90% chance that chronic infection will develop in vertically infected children, interventions that prevent HBV VT offer tremendous public health value by reducing overall infections and minimizing the pool of individuals that could spread HBV to others later in life.[2,3] Through existing collaborations with the DRC Ministry of Health (MOH) and Abbott Laboratories and a new collaboration with Ohio State University, we will conduct the Arresting Vertical Transmission of HBV (AVERT-HBV) study.

At the request of the DRC Ministry of Health, we recently established a collaboration with Abbott Laboratories to estimate the prevalence of viral hepatitis in the DRC. We are testing dried blood spots collected from subjects enrolled in the 2013-2014 DRC Demographic and Health Survey (DHS), a national population-based survey conducted by MEASURE-DHS (ICF International, Rockville, MD). Our preliminary data indicated that 3.3% of children ≤5 years of age in the DRC are HBV DNA positive, most likely as a result of VT.

When a pregnant woman has HBV infection, the risk of VT can be reduced by 90% when vaccine coupled with HBV Immune Globulin (HBIG) are administered to the infant at birth.[2,3] HBIG is not a part of standard World Health Organization (WHO) guidelines due to its limited availability and is not currently accessible in the DRC, but HBV vaccine and HBV antiviral supply lines are well-established.[4] While the HBV vaccine is part of the DRC's Expanded Program on Immunization (over 70% of DRC infants completed a 3-dose HBV vaccination series country-wide),[5] **it is not administered until the child is 6 weeks old, outside of the 24-hour window recommended for the prevention of VT.** The present study seeks to leverage existing infrastructure to address HBV VT in the DRC with available tools. **It is clear that a new approach to infant HBV vaccination is needed in order to reduce the very high ongoing and future burden of HBV in the DRC**.

Even with HBV vaccination, infants born to high-risk women, with high-level HBV DNA viremia (>10^6 IU/mL) and/or HBeAg positivity, remain at high risk for breakthrough transmission.[6-8] The standard of care in the US and other parts of the world is to initiate antiviral therapy with tenofovir and/or lamivudine among high-risk mothers during pregnancy. This reduces HBV viral loads by >3-4 logs and subsequently minimizes the risk of HBV VT.[9] This screening and intervention works and has been codified into U.S. guidelines for care,[4,11] **but it has not been implemented in the DRC, where the burden is high.**

In this project, we propose to capitalize on existing infrastructure in the DRC to screen for HBV early in gestation and initiate treatment. This intervention has the potential to reduce breakthrough cases of HBV VT by 60-90%,[9,12] which would lead to health benefits of reduced cirrhosis and liver cancer that would last years into the future.

1.1 Introduction

Study enrollment will take place in two antenatal clinics located in Kinshasa Province that have ongoing PMTCT programs for prevention of VT of HIV. Our collaborator, Dr. Yotebieng (who received his PhD at UNC) has an ongoing study of the PMTCT program at both centers (NIH R01HD087993). Approximately 500 pregnant women

in his study underwent HBsAg testing, and 5% were HBV-positive. We will screen 2,000 pregnant women for HBV, and expect 100 women to have positive HBV testing.

1.2 Name and Description of Investigational Product or Intervention

Pregnant women with high-risk HBV infection will receive antivirals as prophylactic therapy starting at 28-32 weeks' gestation and continuing through 12 weeks' postpartum. Both tenofovir and lamivudine are key components of highly-active antiretroviral therapy (HAART) for HIV. Therefore, the mothers who are HIV-HBV co-infected will receive it as part of their HAART therapy and will not require additional treatment for HBV. Mothers with high-risk infection who are HBV mono-infected, however, will require tenofovir +/- lamivudine initiation as part of our study intervention to prevent VT of HBV.

Infants in the DRC normally receive a pentavalent vaccine including HBV at 6 weeks of life. For HBV-exposed infants in our study, we will provide a birth dose of monovalent HBV vaccine in addition to the regularly scheduled HBV doses (at 6, 10 and 14 weeks).

1.3 Non-Clinical and Clinical Study Findings

The determination of the prevalence of HBV infection among pregnant women in Kinshasa Province, DRC will contribute to knowledge about the burden of disease and need for interventions. The combination of antiviral therapy administered to pregnant women at high risk for VT of HBV and vaccination of their infants within 24 hours of life has the potential to substantially reduce the burden of chronic HBV infection in high-burden countries like the DRC. While most countries in sub-Saharan Africa already have the PMTCT infrastructure in place for the delivery of these interventions, the implementation of these interventions has yet to be integrated into routine care settings. Pending success of our model of care, we anticipate that this framework will inform the development of guidelines on how to integrate these interventions into the public health system throughout sub-Saharan Africa.

Potential benefits of this study are the interruption of MTCT of HBV. Risks are associated with blood sample collection, vaccination and tenofovir treatment. The study will require blood collection from infants via heel prick, which is painful but less so than a venous blood collection. Vaccination will cause minimal discomfort to infants. There is a possibility for an adverse reaction to the HBV vaccine, in which case study personnel will clearly document the reaction and the infant will be closely monitored. Infants delivered at the maternity health centers are not sent home with their mothers until day 2 or 3 of life, so there will be adequate time to observe the infants after vaccination. Previous studies have demonstrated minimal risk to fetuses exposed to tenofovir (TDF) and lamivudine, with rates of birth defects similar among treatment and control groups.[9,10] While TDF and 3TC therapy has not been associated with harm to the fetus, the main concern among mothers is the development of immune-active hepatitis in the post-partum period after discontinuation of tenofovir. In the study by Pan et al, statistically significant elevations in alanine aminotransferase (ALT) levels were seen after discontinuation of TDF in the treatment arm compared with the control arm. Our study will routinely monitor mothers in the post-partum period after discontinuation of antivirals for elevations in liver enzymes, and will refer mothers with active hepatitis to our study gastroenterologist. The benefit of treatment – prevention of VT of HBV – far outweighs the potential risk to mothers of the development of immune-active hepatitis after treatment. Based on previous studies cited above, there is minimal risk to the fetus involved in maternal treatment with tenofovir +/- lamivudine.

1.4 Relevant Literature and Data

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2 STUDY OBJECTIVE

This pilot feasibility study of HBV-infected pregnant women in the DRC will allow for early identification and treatment of HBV-positive pregnant women and their newborns in order to reduce maternal-to-child transmission of HBV.

2.1 Specific Aim 1

Conduct a pilot feasibility study of two-step HBV prenatal screening for HBV infection among pregnant women in the DRC. We will screen 4,000 pregnant women with HBV rapid diagnostic testing (HBV surface antigen [HBsAg]) and will confirm the results with viral loads and HBV e antigen (HBeAg) testing performed on both venous blood and dried blood spots. We expect 100 women (2.5%) to have positive HBsAg testing, and 30-50 to have high-risk disease (defined as positive HBeAg and/or HBV viremia $>10^6$). The major outcome of this aim will be the feasibility of this testing strategy: acceptability to patients and staff, collection of samples, and time from sample collection to results. Other outcomes will include an analysis of agreement between test characteristics (sensitivity, specificity, PPV and NPV) for HBeAg and HBV DNA testing of DBS samples compared to the gold standard of venous blood sampling, and the cost of adding them to the existing PMTCT program.

2.2 Specific Aim 2

Conduct a pilot feasibility study of an intervention program to prevent HBV VT. We anticipate screening 4,000 pregnant women for HBV infection, of whom we expect that 2.5% (100) will have positive HBV testing. HIV-negative women identified as having high-risk disease (defined as HBeAg positivity and/or HBV viremia $>10^6$) will be given prophylactic tenofovir +/- lamivudine starting at 28-32 weeks' gestation and continuing through 12 weeks' postpartum. A subset of these women (an estimated 3-5 women) who are HIV-positive will already be receiving tenofovir and lamivudine as part of their HIV therapy. HIV-negative women with low-risk HBV will undergo routine HBV testing but will not receive antiviral therapy. All infants born to HBV-positive women will be enrolled in the study and will receive HBV vaccine within 24 hours of life. If successful, this model could be easily exported to other countries in sub-Saharan Africa. The major outcomes of this aim are (1) adherence to treatment; (2) acceptability of treatment by pregnant women; (3) maternal HBV viral load at delivery and 24 weeks post-partum and (4) infant HBsAg at 24 weeks post-partum; and (5) additional cost to the existing PMTCT program.

3 INVESTIGATIONAL PLAN (brief overview)

3.1 Study Design

Type of design: pilot feasibility study

This is a cohort study of pregnant women and their infants who will receive a package of proven interventions to prevent vertical transmission of HBV in a resource-limited setting. It is not a clinical trial. The purpose of the study is to prove the feasibility of testing and treatment for HBV among pregnant women in the DRC using the HIV PMTCT framework.

After the study is described to participants and verbal consent is obtained, pregnant women will be screened for HBV with HBsAg testing. Formal written consent will be obtained for those with positive HBsAg testing. We anticipate screening 4,000 pregnant women, of whom we expect 100 (2.5%) to have positive HBV testing. Screening may end prematurely if 100 HBV-positive women are identified prior to reaching the anticipated number of 4,000. Based on rates of HBV positivity of 5% in the ongoing HIV PMTCT+ study, we anticipate being able to enroll 100 HBV-positive women. **However, if 2,000 women are screened and the number of HBV-positive participants falls below 100, the study will continue to screen additional participants until 100 HBV-positive women are identified. Because of an actual HBsAg prevalence of 2.8%, we are increasing the number of anticipated participants for screening to 4,000 in order to reach a goal of 100 HBsAg+ enrollees.**

The HBV-positive mothers will be sub-divided into those with high-risk HBV (defined as HBeAg positivity and/or HBV viremia $>10^6$) versus low-risk HBV. HBV mono-infected women with low-risk disease will undergo additional laboratory testing as outlined in study procedures, but will not be treated with antivirals during pregnancy. HBV mono-infected women with high-risk disease will receive tenofovir +/- lamivudine as prophylactic therapy starting at 28-32 weeks' gestation and continuing through 12 weeks' postpartum. The small subset of HIV-HBV co-infected mothers will already be receiving tenofovir and lamivudine as part of their HIV therapy. Mothers will be followed at enrollment, 2-4 weeks after enrollment, at routine antenatal visits, at delivery, and at 10 and 24 weeks postpartum.

Appendix B outlines the study design, from initial screening through final study visit.

All infants born to HBV-infected mothers will be given a birth dose of monovalent HBV vaccine within 24 hours of life. Infants will be enrolled at birth and followed at 10 weeks and 24 weeks.

3.2 Study Duration, Enrollment and Number of Subjects

The entire study is expected to last 3.5 years (1 year of enrollment, 1.5 years of follow-up, and 1 year for data analysis).

Enrollment of individual mothers will be a maximum of 12 months (as early as 12 weeks' gestation through 24 weeks postpartum). Infants will be enrolled for a total of 6 months.

We expect to enroll a total of 4,100 subjects, including 4,000 pregnant women for screening in order to enroll 100 HBsAg+ pregnant women and 100 HBV-exposed infants.

3.3 Study Population

The study will not enroll participants who are severely sick and who require prolonged hospitalization.

Pregnant women who establish care prior to 24 weeks' gestation at Binza and Kingasani maternity centers will be eligible for enrollment. They must enroll prior to 24 weeks in order to have time to classify their disease status as high-risk and start antiviral prophylaxis between 28 and 32 weeks of gestation. Eligible women should intend to deliver their infants and follow up for post-partum visits only at Binza and Kingasani.

Regarding infant enrollment criteria, all infants born to HBV-infected mothers will be eligible for the study. All should undergo HBV testing at birth and at 6 months of life. All HBV-exposed infants will receive the birth dose of HBV vaccine, regardless of birth weight (https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm224503.pdf, Section 5.3).

4 STUDY PROCEDURES (what will be done) – Refer to Appendix B for an outline of these procedures.

4.1 Screening/Baseline Visit procedures

Visit 1: Enrollment and baseline data collection

1. **HBsAg screening**: All pregnant women presenting to the two selected MCH clinics for their first ANC visit will be eligible for enrollment in the study. Once verbal consent is obtained, the women will be screened for HBV with point-of-care HBsAg testing. Those who test positive for HBsAg will provide written consent to participate in the study. The counseling and testing will be integrated into the existing counseling and testing for HIV during the first ANC visit, and will be carried out by clinic nurses in charge of PMTCT. Women with new HBV diagnoses will have individual counseling regarding the study and to answer any questions they have prior to going through the consent process.
2. **Consent:** Verbal consent will be obtained from all women by trained nursing personnel prior to testing for HBsAg. Women who test positive for HBsAg will then be consented using written consent forms. The eligibility screening document in Appendix D will be used to determine if an HBV-positive woman is eligible for interventions. If she is not eligible, the reason will be noted in Appendix C. If the woman is eligible, the consent form will be read to her to make sure she is willing to voluntarily participate in the study. If she refuses to consent to the study, the reasons for her refusal will be noted in Appendix C. If she would like to discuss the study with family

members prior to consenting, another meeting will be arranged. If she consents to participate, enrollment will proceed.

3. **Enrollment interview**: Study personnel will ensure that there is sufficient space to guarantee confidentiality during the interview. They will then administer the questionnaire (Appendix J) and note responses. At the end of the interview, study personnel will verify that all questions have been completed, that the woman understands the process of the study and that she knows the date of her next visit.
4. **Maternal testing:** A venous blood sample will be collected from the mother to test for the following: HBV viral load, HBeAg, platelets, BUN/Cr, ALT and AST. HIV status will also be determined. At the same time, a DBS sample will be obtained from the mother to test for HBV viral load and HBeAg.

4.2 Intervention/Treatment procedures (by visits)

Visit 2: 2-4 weeks post-enrollment

1. **Results of laboratory testing**: Study personnel will share the results of the HBV viral load and/or HBeAg testing with the participant. Baseline laboratory results (platelets, BUN/Cr, ALT, AST) will be reviewed by the study physician and any abnormalities will be communicated with the participant.
2. **Discussion of antiviral treatment initiation**: HIV-negative mothers with positive HBeAg and/or high HBV viral load ($>10^6$) should be started on tenofovir +/- lamivudine between 28 and 32 weeks of gestation. Women with significant baseline lab abnormalities (either GFR <50 and/or other significant abnormalities as determined by the study physician) will be excluded from receiving antiviral therapy.

Visits 3 and 4: Subsequent pre-delivery visits

There are no particular procedures at these visits. Study personnel will ensure, however, that any HIV-negative women who require antiviral treatment are started on therapy at the appropriate time (between 28 and 32 weeks gestation). The Medication Documentation Form (Appendix G) will be used to monitor adherence using pill count during the monthly refill visit. Also, if any women have baseline laboratory abnormalities and require additional testing, they may undergo additional testing at these visits under the guidance of the study physician.

Visit 5: Delivery/Birth

1. **Maternal testing:** A venous blood sample will be collected from the mother to send for HBV viral load, BUN/Cr, ALT and AST. A DBS sample will be collected at the same time for HBV viral load testing.
2. **Infant testing**: Research personnel will collect a blood sample (via heel stick) from the infant for HBsAg testing.
3. **Infant vaccination:** The infant should receive the first dose of HBV vaccine *within 24 hours of life*. The date and time of administration of the vaccine will be documented in the Vaccine Log (Appendix H).

4.3 Follow- up procedures (by visits)

Visit 6: 10 weeks post-partum

1. **Maternal testing:** A venous blood sample will be obtained from mothers who are receiving antiviral therapy for ALT and AST testing.
2. **Preparation for treatment cessation:** 12 weeks marks the end of antiviral treatment for the woman. If her ALT is greater than 2x the upper limit of normal at the 10-week visit, she will require a referral to Dr. Mbendi, the gastroenterologist at KSPH.

Visit 7: 6 months post-partum

1. **Maternal testing:** A venous blood and DBS sample will be collected from the mother for HBV viral load, AST and ALT testing. If the ALT level is greater than 2x the upper limit of normal, she should be referred to Dr. Mbendi.
2. **Infant testing:** Serum and DBS samples will be collected from the infant for HBsAg and HBsAb testing.
3. **Exit Interview**: The exit interview (Appendix K) will be administered to all HBV-positive mothers.

4.4 **Unscheduled visits:** All pregnant women will be seen at scheduled antenatal visits, and will be able to present for care as needed at other points in the antenatal period. Women will be encouraged to seek care if they experience any side effects from the medication. No additional interventions will be planned at these unscheduled visits.

4.5 **Concomitant Medication documentation:** Appendix I is the medication documentation form that will be filled out at each follow-up visit while the mother is taking tenofovir +/- lamivudine.

4.6 **Subject Completion/ Withdrawal procedures:** The exit survey will be administered to all HBV-positive mothers upon completion of the study (at 24 weeks postpartum). Women may be withdrawn from the study if they wish to withdraw from the study, if they experience a loss of their pregnancy or fetal demise, or if they fail to comply with study procedures. The reason for withdrawal will be clearly documented (Appendix F).

4.7 **Screen failure procedures**: Women who screen negative for HBV initially will not be enrolled in the intervention cohort.

5 STUDY EVALUATIONS AND MEASUREMENTS (how measurements will be made)

5.1 Feasibility Evaluation

For specific aim 1, we will determine the feasibility of the testing strategy by measuring acceptability to patients and staff, and ease of sample collection and transport. Feasibility will be measured qualitatively, as an aggregate of questionnaire responses from study participants and research staff. The final questionnaire is still in progress, but a draft of the questionnaire can be found in the appendix of the protocol document. Additionally, an implementation science component of this study will be added in the near future, to include focus groups comprised of research staff. The goal of this implementation science part of the study will be to determine factors that allow for feasibility and to extend the study to include areas outside of Kinshasa Province for future, larger studies.

We will also measure time from sample collection to return of results to mothers and additional cost of HBV testing to the PMTCT+ program.

For specific aim 2, we will determine the feasibility of the interventions by evaluating patient and staff survey responses. We will also measure how many and when women and their infants are lost to the treatment cascade.

5.2 Laboratory Evaluation

Secondary measures of specific aim 1 will include agreement between test characteristics (sensitivity, specificity, positive predictive value, negative predictive value) of HBeAg and HBV viral loads in DBS and venous blood samples.

For specific aim 2, we will measure the following: percentage of women with highly active HBV who achieve reduction or suppression of HBV viremia, development of ALT elevation during or after antiviral treatment, resolution of e antigen positivity, and rate of MTCT of HBV (measured as the proportion of infants born to HBV-positive mothers who test positive for HBV).

5.3 Safety Evaluations

At each follow-up visits, research staff will complete the medication documentation form, which will include information on pill counts as well as any reported side effects. The study physician will review these forms if side effects are reported. If a woman experiences severe side effects or severe intolerability, the medication will be discontinued. Infants will be monitored for at least 24 hours after receipt of the monovalent HBV vaccine, and any adverse reactions will be recorded.

Safety monitoring will occur on an ongoing basis by the Kinshasa-based research team, by reporting adverse side effects and other concerns to the study physician. The UNC-based research team will evaluate these concerns on a monthly basis. While the likelihood of terminating the study early due to safety concerns is minimal, study personnel will consider this if there is a high frequency of safety concerns related to antiviral therapy and/or monovalent HBV vaccine. See Appendix B (Part 2) for an algorithm concerning monitoring of women on antiviral therapy.

6 STATISTICAL CONSIDERATION

6.1 Outcomes

For specific aim 1, the feasibility of the testing strategy will be determined by responses to questionnaires for both study participants and staff. Dr. Rohit Ramaswamy will help to determine cutoff values for feasibility upon creation of final versions of the questionnaires. Additionally, agreement of test characteristics (sensitivity, specificity, positive predictive value and negative predictive value) between DBS and venous blood testing of HBeAg and HBV DNA will be assessed. The purpose of this analysis is to determine whether DBS is a reliable measure for HBeAg and HBV viral load testing. If this is true, it could be a more cost-effective manner of screening women for high-risk disease in low-resource settings. We will also determine the additional costs of HBV screening to the PMTCT+ program. HBeAg positivity will be defined as a titer of ≥1.000 according to the Architect system.[19] Subjects with HBV DNA values above 2,000 IU/mL (the assay's limit of detection) will be considered HBV-positive and those >200,000 IU/mL will be considered high-risk HBV.

For specific aim 2, we will measure how many and when women and their infants are lost to the treatment cascade; the percentage of women with highly active HBV who receive antiviral treatment and who achieve reduction or suppression of HBV viremia, the development of ALT elevation during or after treatment, and resolution of e antigen positivity; loss-to-follow-up (LTFU, percentage of women who are initiated on antiviral treatment but are not able to complete the recommended course) and adherence to antivirals and vaccination; and the rate of mother-to-child transmission (MTCT) of HBV, defined as the proportion of infants born to HBV-positive mothers who test positive for HBV.

Of note, no hypothesis testing will be performed for this study. Rates of MTCT of HBV in this study will be compared to historical controls.

6.2 Statistical Methods

Specific Aim 1. Frequencies of responses on surveys will be calculated and aggregate responses will be reported. We will determine agreement of test characteristics (sensitivity, specificity, negative predictive value and positive predictive value) of HBeAg and viral load using DBS compared to the gold standard of venous blood testing using Bland-Altman plots.

Specific Aim 2. Percentages of women with highly active HBV will be compared with historical results obtained from the literature. Rates of infant HBV vaccination will be calculated. HBV MTCT will be determined by assessing infant HBsAg status at 6 months of age (the standard post-natal follow-up visit). These outcomes will be analyzed by proportional odds regression modeling. We will assess the percentage of women who initiate treatment during pregnancy who achieve suppression of HBV DNA (defined as HBV viral load <200,000 IU/mL). We will also assess the rate of development of immune-active hepatitis during or after the treatment period. LTFU and adherence rates will be compared between HIV-positive and HIV-negative groups, and time to drop out will be considered in our analysis. Cost analysis of interventions, including vaccination, antiviral treatment and healthcare provider time, will be performed. KAB survey results will be compiled and analyzed to determine the acceptability of this model of care.

All population parameters will be accompanied by corresponding confidence intervals (CIs). Sensitivity analyses will also be performed to evaluate the study's main results and to explore the influence of extreme or questionable data values. Statistical computations will be performed by Kristin Sullivan (PhD candidate in the department of epidemiology). Dr. Jonathan Parr will review all calculations. We expect very little missing data (i.e. Landis et al. Epid Infection, 2009). We will limit our final analyses to subjects with complete exposure and outcome data, with a table comparing demographics to assess for bias.

6.3 Sample Size and Power

An estimated 5-9% of inhabitants of sub-Saharan Africa are infected with HBV.[13-16] Based on these data and the preliminary rates of HBV positivity among pregnant women in the HIV PMTCT+ study and children in the DHS, we expected that of 2,000 women screened, about 5% (100 women) will have positive testing for HBsAg. However, in actuality, with a HBsAg prevalence of 2.8%, we will now screen 4,000 women in order to enroll 100 HBsAg+ women. We will perform reflex HBeAg and HBV DNA testing in these patients who screen positive for HBsAg. Based on rates of HBeAg positivity reported in the literature,[17,18] we expect that approximately 30-50% (30-50) of these women will be classified as high-risk and will be treated accordingly.

The sample size of 100 HBV-positive women has been chosen *a priori* due to limited funding for this pilot feasibility study. We expect to collect data in this study in order to apply for additional funding to conduct a

much larger study that will examine the influence of these testing and intervention strategies on the reduction of MTCT of HBV.

6.4 Interim Analysis: We do not expect to have to terminate the study early. However, we will be monitoring all women on tenofovir treatment for possible side effects and will perform appropriate quality control.

7 STUDY INTERVENTION (drug, device or other intervention details)

7.1 Tenofovir therapy: Tenofovir disoproxil fumarate will be obtained from Gilead, or combination lamivudine/tenofovir disoproxil fumarate will be obtained from PNLS. Per the package inserts (found at https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021356s042,022577s002lbl.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022141s000lbl.pdf), tenofovir and combination lamivudine/tenofovir can be stored at room temperature. It will be packaged and labeled by pharmacy personnel at the designated maternity centers. Dosing of the antivirals will be 1 pill (300mg of each component or 300mg of TDF alone) once daily. We will monitor treatment compliance by use of a pill count when mothers present for monthly refills of the medication (to be documented in Appendix I). Treatment will be planned for ~6 months (starting at 28-32 weeks' gestation and continuing through 24 weeks postpartum). Any returned drug will be destroyed according to existing policies within the maternity centers. The medication is not to be administered to anyone except for the designated pregnant female participants.

7.2 Monovalent HBV vaccine: Monovalent HBV vaccine (Euvax-B) will be obtained in the DRC. The vaccine will be stored refrigerated (between 2 and 8 degrees Celcius), according to FDA regulations. The dose will be 0.5mL for all HBV-exposed infants. The infant must receive the vaccine within 24 hours; date and time of administration will be recorded in Appendix J. Vials and needles will be disposed of in sharps containers after administration of the dose.

8 SAFETY MANAGEMENT

The research team will monitor data for any safety concerns through routine quality assurance procedures that are already in place for the HIV PMTCT study. Mothers will be asked about any side effects while on tenofovir therapy at each monthly refill visit. As reported in the package insert**s** for tenofovir disoproxil fumarate **and lamivudine + tenofovir disoproxil fumarate**, the most common side effect **of TDF alone is** nausea (infrequent, 9%, mild severity), **while common adverse reactions for the combination therapy include headache, pain, diarrhea and rash (>10%, mild severity)**. Severe reactions, including severe exacerbation of hepatitis, renal impairment, lactic acidosis, **pancreatitis** and bone effects, are rare. Women may develop immune-active hepatitis (ALT>2x the upper limit of normal) upon discontinuation of the medication. Per the study protocol, we will monitor pregnant women with ALT and creatinine at delivery, followed by ALT at 10 and 24 weeks postpartum. The medication will be discontinued if any severe reactions are noted by clinical or study personnel. Any safety concerns surrounding antiviral treatment of pregnant women or vaccination of infants will be noted by the study nurses and reported to the appropriate study personnel (study physician and study coordinator) as soon as possible. These events will be reviewed by the rest of the research team. Safety monitoring will occur on an ongoing basis by the Kinshasa-based research team, by reporting any adverse events or other concerns to the study physician. The UNC-based research team will review these adverse events on a monthly basis. While the likelihood of terminating the study early due to safety concerns

is minimal, study personnel will consider this if there is a high frequency of safety concerns related to antiviral therapy.

There is a possibility for an adverse reaction to the HBV vaccine, in which case study personnel will clearly document the reaction and the infant will be closely monitored. Infants delivered at the maternity health centers are not sent home with their mothers until day 2 or 3 of life, so there will be adequate time to observe the infants after vaccination.

There are no known harms of tenofovir or lamivudine treatment of pregnant women on the developing fetus. There is no contraindication to breastfeeding while on tenofovir +/- lamivudine therapy.

9 DATA COLLECTION AND MANAGMENT

Our study team will make every effort to maintain confidentiality of the data. This will occur mainly by the use of a unique maternity code for participants, rather than PHI. This code will be used on documents (including questionnaires) and to label patient specimens.

Data will be collected by research personnel in the form of paper questionnaires and forms, and then will be entered into the electronic system. Each week, all completed data collection forms will be returned to the central office in Kinshasa, where the study site supervisors (Noro Lantoniaina, Bienvenu Kawende and Fathy Malongo) will check the forms for completeness and consistency. Incomplete forms will be returned to the interviewer for correction. Completed forms will be entered into the electronic database (Access or EpiData) and uploaded on the server through a secured FTP channel. The research team at UNC will upload data on a biweekly basis to run frequency distributions in order to identify unreasonable values, which will be returned to the research team in Kinshasa for correction.

The paper documents that contain PHI will be stored in locked containers with the key stored separately. The electronic databases that contain PHI will be password-protected and only accessible to appropriate study personnel. Data that is shared with the rest of the research team will be done so in a de-identified manner when possible, using only maternity codes as identifiers. Data that is shared electronically will be done so only through secure, encrypted pathways. Public presentations and publications will not include any identifying information.

10 RECRUITMENT STRATEGY

We will select study participants from the population of pregnant women presenting for care at two antenatal clinics in Kinshasa Province, DRC. Women who consent to participating in the study will be screened for HBV with HBsAg testing. Those who are negative will not be enrolled into the intervention cohort in the study. Women with positive testing will be enrolled, further blood specimens will be obtained, and the rest of the procedures of the study will be explained in depth to them at that time.

Binza and Kingasani maternity centers combined see over 1,000 deliveries a month. With an estimated HBV prevalence of 5% among pregnant women (from the ongoing R01 study of PMTCT of HIV), we could theoretically screen 4,000 women and enroll all 100 HBV mono-infected pregnant women within the first

several months of the study. We have already screened 1,884 women in a 2-2.5 month period. Since our recruitment will occur over a one-year period, we should have no trouble recruiting these women.

We hope to enroll a total of 100 infants, to whom we will administer the monovalent HBV vaccine at birth.

We will maintain confidentiality of the individual study participants by interviewing them in a private room or area of the maternity center, away from other mothers or family members. Once the initial enrollment is complete, subjects will subsequently be identified using a maternity code. The same maternity code will be used for their infants. The linkage code that contains PHI will be stored in a locked cabinet, with access limited to research personnel.

11 CONSENT PROCESS

Research personnel in Kinshasa will obtain consent from study participants in their native language (French or Lingala). These personnel will be separate from those providing clinical care. We will train research personnel to emphasize in the consent process that participation in the study is completely voluntary and will not affect their prenatal care. The consent process will occur in a private area of the maternity center, separate from other patients and family members. Mothers could choose to delay enrollment to a subsequent prenatal visit, as long as they present for the first antenatal visit early enough in gestation (prior to 24 weeks) for this to be a feasible option.

As part of the initial consent process, mothers will be consented provide permission to enroll their infants upon birth. Some mothers may be younger than 18, however they will be considered emancipated minors given their pregnant status, and will be able to sign the consent forms themselves as long as they are over the age of 15 years.

12 PLANS FOR PUBLICATION

Upon completion of this study, we plan to present our findings at an international conference such as the Conference on Retroviruses and Opportunistic Infections (CROI). We will then publish findings in a journal such as Clinical Infectious Diseases.

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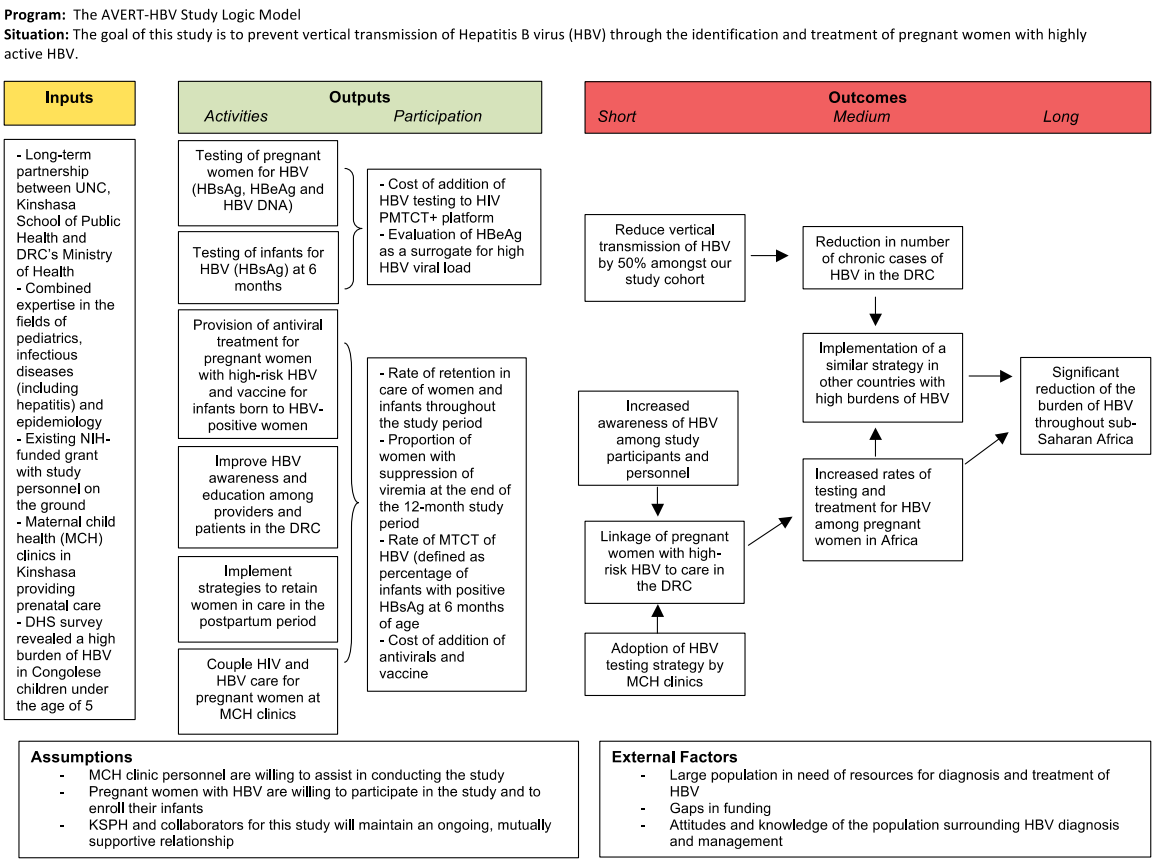
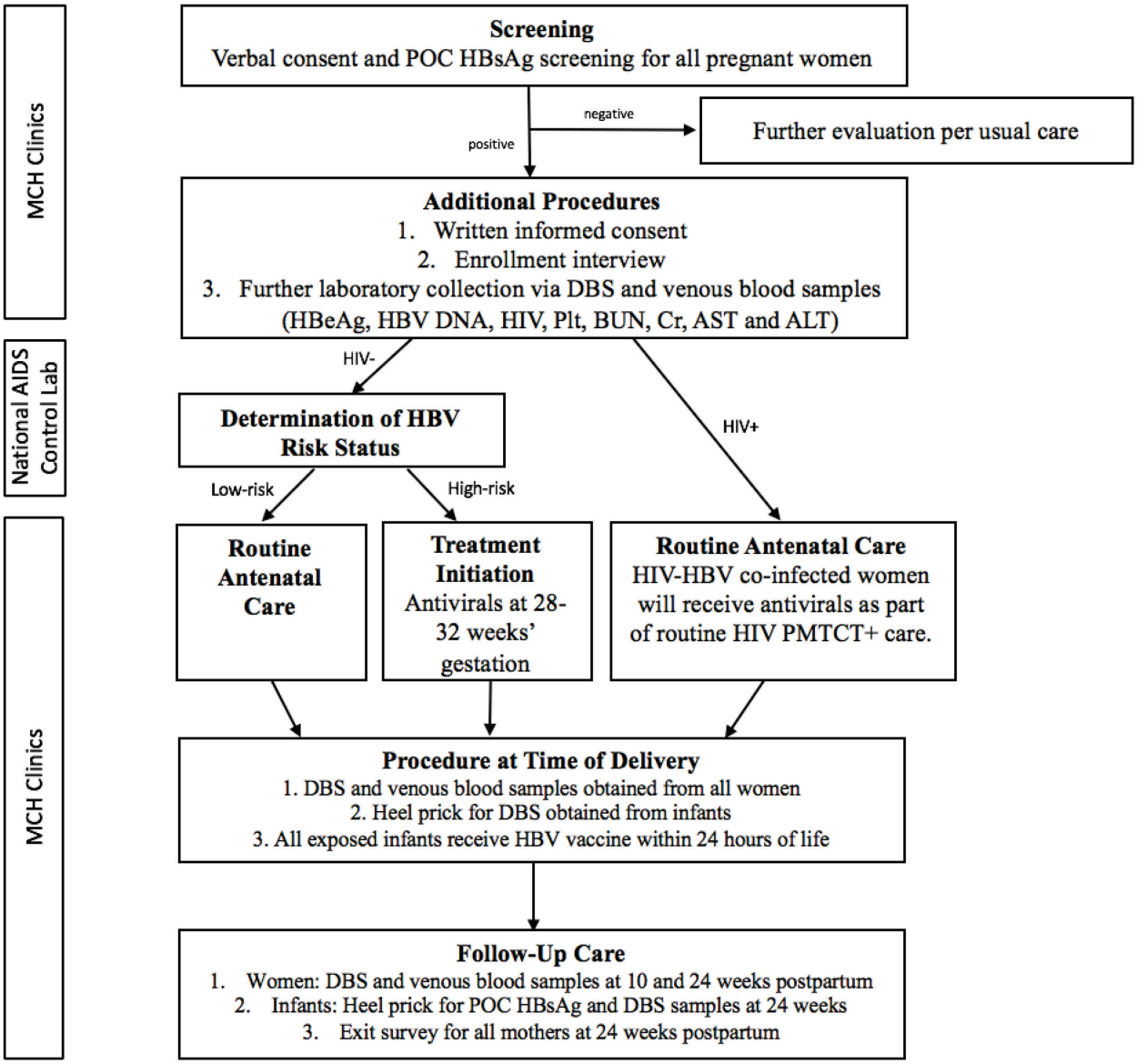
15 APPENDICES

Appendix A: Logic Model

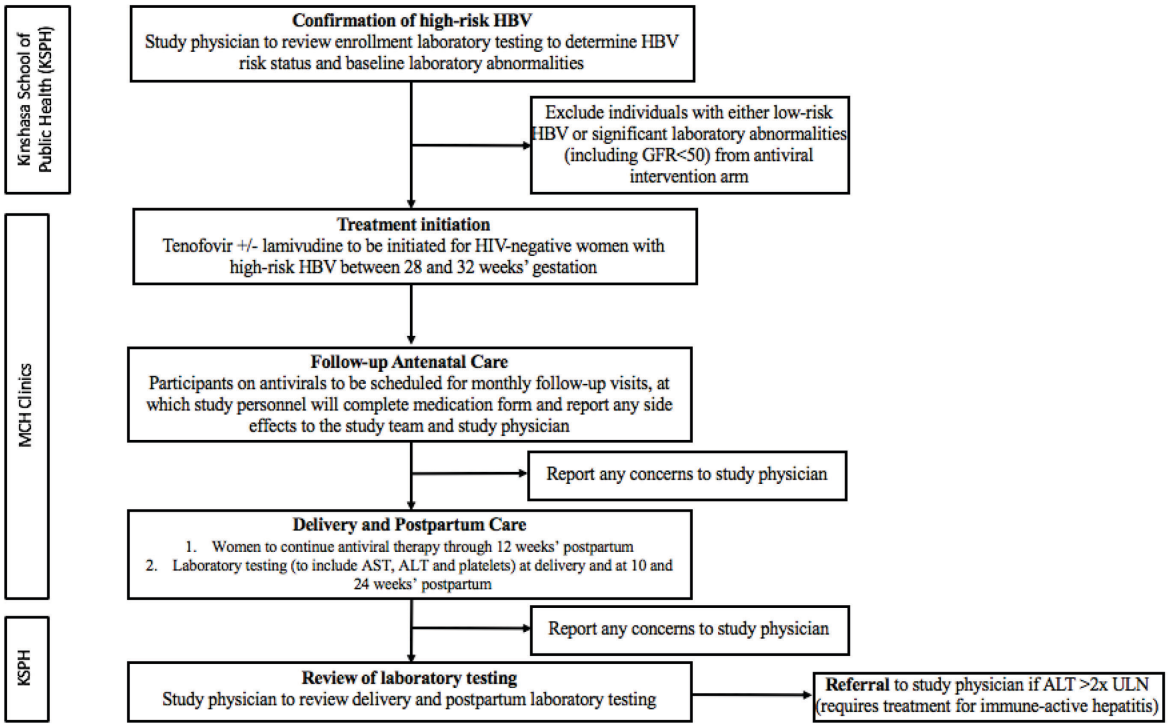


Appendix B:

Part 1: General Study Screening and Management Algorithm



Part 2: Management of HIV-negative Women with High-risk HBV on Antiviral Therapy



Appendix C: Screening and Enrollment Sheet

Instructions: *Use this table to record all women contacted who were (a) ineligible to participate in the study, (b) refused to participate after hearing about the study, (c) who were not interested in hearing about the study or (d) who were eligible and enrolled into the stud. Do not record the name of the woman. If the woman was ineligible or refused to participate, please record reason for ineligibility or for refusal. If she was eligible and enrolled into the study, record her participant ID number*

Number	Date	Is the woman 1-ineligible OR did the woman 2-refuse OR was the woman 3-not interested in hearing about the study OR was she 4-Eligible? ***Write below the number of the answer***	Reason for ineligibility ***(enter the code*)***	Reason for refusal *Write below the number of reason the woman refused to participate* *1– don't want to participate* *2 – don't have husband's permission* *3 – don't have time* *4 – others (specify)*	For women ELIGIBLE: ***Write below the Participant ID number***
0001					
0002					
0003					
0004					
0005					
0006					
0007					
0008					
0009					
0010					

**1 – Presented after 24 weeks' gestation*

2- Does not intend to stay in Kinshasa until delivery and 6 weeks post-partum

3- Is severely ill and require hospitalization

Appendix D: Eligibility Checklist for Participants

ELIGIBILITY CHECKLIST FOR PARTICIPANTS		
	YES	**NO**
1. The gestational age is ≤24 weeks completed	□	□
2. The participant intends to stay in Kinshasa through delivery and six weeks postpartum	□	□
3. The participant is NOT severely sick and does NOT require extended hospitalization	□	□

IF THE ANSWER OF ONE OF THESE QUESTIONS IS **NO**, THE PARTICIPANT IS **NOT ELIGIBLE**

Appendix E: Master Appointment Sheet for Interviewers

Site number _____

Participant ID#	Current visit date	Next follow-up visit date	Observation

Appendix F: Master Withdrawal or Termination Sheet

Instructions: *Use this table to record all participants who refuse to continue their participation in the study. Do not record the name of the woman. Please record reason for withdrawal.*

Participant ID#	Date	Visit	Reason for withdrawal *Write below the number of reason the mother is ineligible:* *1*– No reason 2 – Husband's request 3 – Don't have time 3 – Loss of pregnancy 4 – Baby died 5 – others (specify)

Appendix G: Medication Documentation Form

Instructions: *Use this table to record all information pertaining to medication administration.*

Participant ID#	Date of Visit	Pill Count (# out of 30)	Side Effects Reported (if any)	Date Antiviral Course Initiated	Date Antiviral Course Completed	Reason for Premature Termination (if any)

Appendix H: Vaccine Log

Instructions: *Use this table to record information about infant vaccination. Timing is very important – all infants should receive the vaccine* ***within 24 hours of life!***

Participant ID#	Date of Birth	Time of Birth	Birth Weight (kg)	Date of Vaccination	Time of Vaccination	Adverse Reaction (if any)

Appendix I: Dried-Blood Spot (DBS) Collection and Handling

This SOP describes the procedures of collecting and handling whole blood on filter paper (DBS) for storage

I. Material storage

The Kit can be stored at room temperature (22 - 25 °C)

II.Required supplies for DBS

1) Permanent marker (pointe fine)Filter paper collection devices
2) Gloves without talcum
3) Sterile lancetsAlcohol 70°Cotton wool
4) Sealable plastic bags
5) Humidity cards
6) Dessicant packs
7) Glycine weighing paper
8) Eau de javel (concentration
9) Sample rack for drying process
10) Sharp container

Steps prior to sample collection

Well lighted room

III. DBS sample collection

Use universal safety precautions while handling biological fluids and tissues

Clearly label the card with the participant ID number

Do not touch circles

The sample collection is an essential part of the testing :

1) Wear gloves
2) Position the patient.
3) Cleanse the 3rd or 4th finger (or heel) with alcohol and wait for 30 second to allow it to dry.
4) Puncture finger or heel with sterile, disposable lancet. **Do not "milk" blood from the finger.**
5) Wipe away first drop of blood with dry cotton wool
6) When next large drop of blood appears, touch filter paper circle to blood. Do not touch paper to skin
7) Completely fill the circle with the blood Fill at least three circles with blood drops for adults and at least two circles with blood for children.
   Dry the DBS sample using the sample rack with slots where the filter paper specimen should be inserted

IV. Drying DBS

- Avoid touching or smearing the blood spots
- Allow the specimen to fully air dry horizontally at least 3hours or all night at room temperature
- Keep away from direct sunlight , dust and insects
- Do not heat, stack or allow DBS to touch other surfaces during the drying process

Allow the DBS sample to completely dry before packaging.

V. Package of DBS for storage

At the end of each day, package the dried samples (wait until next day if some samples are not dried yet after 3 hours)Store the samples and ship them every week (Contact the lab coordinator to organize the shipping process) Place each filter paper between sheets of weighing paper to prevent cross contamination.

1) Insert the dried filter papers in plastic bags : one plastic bag may contain up to 10 samples.
2) Add 2 to 4 dessicant packet
3) Add humidity cards
4) Seal the plastic bag after driving out residual air .
5) Label the bag

Appendix J: Participant Enrollment Interview

When to give the interview: At the first encounter during pregnancy

Objective of the interview: To collect demographic, economic, and psychosocial information and measure perception of PMTCT risk

---

A. GENERAL INFORMATION (*PLEASE PRINT CLEARLY*)

A1. Facility Name:

_____

A2. Last name: _____

A3. First name: _____

A4. Address: _____

Use the following space to note the major landmarks for this address: _____

_____

_____

A5. Telephone Number: _____

A6. Who can we contact in case we are unable to reach you directly?

Last and First Name of the contact: _____

Telephone Number of the contact: _____

(REMOVE THIS PAGE BEFORE SENDING FOR DATA ENTRY)

B. Confirmation of HIV and Hepatitis B status

1	HAS THE PARTICIPANT HAD A POSITIVE HEPATITIS B TEST?	☐ YES (1) ☐ NO (2) **STOP THE INTERVIEW**
2	Has the participant ever been told that she has hepatitis B in the past (before today)?	☐ YES (1) ☐ NO (2)
3	HAS THE PARTICIPANT HAD A POSITIVE HIV TEST?	☐ YES (1) ☐ NO (2)

C. Obstetrical history

1	Date of Last Menstrual Period	__/__/____DD/MM/YYYY ☐ Don't Know	
2	Gestational age in weeks IF LMP UNKNOWN USE THE CLINICAL ESTIMATION FROM ANC REGISTER	____weeks	
3	Including this pregnancy, how many times have you been pregnant (even if the pregnancy did not result in the birth of a live child)?	_____ ☐ FIRST PREGNANCY (1) →	**6**
4	When was the last delivery?	☐ 1 YEAR OR LESS (1) ☐ 2 YEARS (2) ☐ 3 YEARS (3) ☐ 4 YEARS (4) ☐ 5 YEARS OR MORE (5)	
5	How many children are still alive?	_____	
a	How old is/are he/she/they?	*1st* _____ *2nd* _____ *3rd* _____ *4th* _____ *5th* _____	*6th* _____ *7th* _____ *8th* _____ *9th* _____ *10th* _____
6	Do you have an antenatal care card/book with you today? IF YES: ASK TO SEE THE CARD/BOOK.	☐ Yes (1) ☐ No, CARD KEPT WITH FACILIT(2) **SKIP TO D** ☐ NO CARD/BOOK USED (3) **SKIP TO D**	
a	How many weeks pregnant is the client, according to the ANC card?	# of weeks _____ NOT AVAILABLE (99)	
b	Has the mother received hepatitis B vaccine according to the book? If so, please note the # of doses.	☐ YES, _____ doses (1) ☐ NO (2) ☐ UNKNOWN (8)	

D. Disclosure of Hepatitis B status

1	Have you told anyone that you have Hepatitis B?	☐ No (2) → **2** ☐ Yes (1)	
a	Who did you disclose to?	☐ PARTNER/FATHER OF MY BABY (1) ☐ MY MOTHER (2) ☐ MY SISTER (3) ☐ OTHER _____ (6) (SPECIFY)	
2	Do you know the Hepatitis B status of your partner?	☐ NO (2) → **3** ☐ YES (1)	
a	What is his status	☐ POSITIVE (1) ☐ NEGATIVE (2)	
3	During this visit (or previous visits) has a provider discussed with you about inviting your partner to come to the clinic with you?	☐ YES, THIS VISIT ONLY (1) ☐ YES, THIS & PREVIOUS VISIT (2) ☐ YES, PREVIOUS VISIT ONLY (3) ☐ NO (4) ☐ DON'T KNOW (8)	
4	Have you ever received a hepatitis B vaccine? If so, how many doses?	☐ YES, _____ doses (1) ☐ NO (2) ☐ DON'T KNOW (8)	

E. Patient satisfaction with care received

Now I am going to ask you some questions about the services you received today. I would like to have your honest opinion about the things that we will talk about. This information will help improve services in general.

1	How long did you wait between the time you arrived at this facility and the time you were able to see a provider for the consultation?	___H___MINUTES SAW PROVIDER☐ IMMEDIATELY….0000 ☐ DON'T KNOW…..9898				
2	*Now I am going to ask about some common problems clients have at health facilities. As I mention each one, please tell me whether any of these were problems for you today, and if so, whether they were major or minor problems for you.*					
		MAJOR	MINOR	NO PROBLEM	DK	
a	Time you waited to see a provider	☐ (1)	☐ (2)	☐ (3)	☐(8)	
b	Ability to discuss problems or concerns about your pregnancy	☐ (1)	☐ (2)	☐ (3)	☐(8)	
c	Amount of explanation you received about the problem or treatment	☐ (1)	☐ (2)	☐ (3)	☐(8)	
d	Privacy from having others see the examination	☐ (1)	☐ (2)	☐ (3)	☐(8)	
e	Privacy from having others hear your consultation discussion	☐ (1)	☐ (2)	☐ (3)	☐(8)	
f	Availability of medicines at this facility	☐ (1)	☐ (2)	☐ (3)	☐(8)	
g	The hours of service at this facility, i.e., when they open and close	☐ (1)	☐ (2)	☐ (3)	☐(8)	
h	The number of days services are available to you	☐ (1)	☐ (2)	☐ (3)	☐(8)	

i	The cleanliness of the facility	☐ (1) ☐ (2) ☐ (3) ☐(8)	
j	How the staff treated you	☐ (1) ☐ (2) ☐ (3) ☐(8)	
k	Cost for services or treatments	☐ (1) ☐ (2) ☐ (3) ☐(8)	
3	Are you a part of any prepayment plan (such as worker insurance or a similar program) or institutional arrangement that pays for some or all of the services you receive at this or any other facility?	☐ YES (1) ☐ NO (2) ☐ DON'T KNOW (8)	
4	Were you charged, or did you pay fees for any services you received or were provided today?	☐ YES (1) ☐ NO (2) **GO TO 5**	
a	What is the total amount you paid for all services or treatments you received at this facility today?	Total amount_____ FC ☐ DON'T KNOW (98)	
5	Is this the closest health facility to your home?	☐ YES (1) → ☐ NO (2) ☐ DON'T KNOW (8)	**6**
a	What was the main reason you did not go to the facility nearest to your home? IF CLIENT MENTIONS SEVERAL REASONS, PROBE FOR THE MOST IMPORTANT, OR MAIN REASON. CHECK ONLY ONE RESPONSE	☐ INCONVENIENT OPERATING HOURS (01) ☐ BAD REPUTATION (02) ☐ DON'T LIKE PERSONNEL (03) ☐ NO MEDICINE (04) ☐ PREFERS TO REMAIN ANONYMOUS (05) ☐ IT IS MORE EXPENSIVE (06) ☐ WAS REFERRED (07) ☐ OTHER_____ (96) ☐ DON'T KNOW (98)	
6	In general, which of the following statements best describes your opinion of the services you either received or were provided at this facility today READ ALL STATEMENTS, CHECK ONLY ONE a) I AM **VERY SATISFIED** WITH THE SERVICES I RECEIVED IN FACILITY ☐ (1) b) I AM **MORE OR LESS SATISFIED** WITH THE SERVICES I RECEIVED ☐ (2) *c)* I AM **NOT SATISFIED** WITH THE SERVICED I RECEIVED ☐ (3)		
7	Will you recommend this health facility to a friend or family member?	☐ YES (1) ☐ NO (2) ☐ DON'T KNOW (8)	

F.Travel Distance

Read: ***Now I am going to ask you a couple of questions about transportation.***			
1	How long does it take for you to come to this maternity (one-way)	_____ min	
2	How will you usually come to the maternity?	☐ Walk (1) → ☐ Taxi (2) ☐ Other_____ (3)	**G**

a	If taxi or paid transportation, what is the cost for one-way travel?	_____FC

G. Perception of Hepatitis B and MTCT Risk

Read: ***Now I am going to ask you some questions about your understanding of Hepatitis B and the risk of passing it on to your baby during pregnancy or childbirth.***

1. In your opinion, how serious a disease is hepatitis B?

- ☐ Very serious (1)
- ☐ Somewhat serious (2)
- ☐ Not very serious, (3)
- ☐ Not at all serious? (4)
- ☐ Don't Know (8)
- ☐ Refuse to answer (9)

2. What are the signs and symptoms of hepatitis B (check all that apply)?

- ☐ No symptoms (1)
- ☐ Jaundice (yellowing of skin) (2)
- ☐ Abdominal pain (3)
- ☐ Rash (4)
- ☐ Don't Know (8)
- ☐ Refuse to answer (9)

3. How can a person get hepatitis B (check all that apply)?

- ☐ Through handshakes (1)
- ☐ Through contact with blood from an infected person (2)
- ☐ Through sharing dishes (3)
- ☐ Mother-to-child transmission (4)
- ☐ Sexual transmission (5)
- ☐ Through breastfeeding (6)
- ☐ Don't Know (8)
- ☐ Refuse to answer (9)

4. How can mother-to-child transmission of hepatitis B be prevented (check all that apply)?

- ☐ Infant vaccination at birth (1)
- ☐ Antiviral treatment during pregnancy (2)
- ☐ Don't Know (8)
- ☐ Refuse to answer (9)

5. How difficult or easy will it be for you to come to the clinic for follow-up appointments for hepatitis B? Would it be:

- ☐ Very difficult (1)
- ☐ Somewhat difficult (2)
- ☐ Somewhat easy (3)
- ☐ Very easy? (4)
- ☐ Don't Know (8)
- ☐ Refuse to answer (9)

6. What makes it difficult for you to come to the clinic to receive your treatment? *(check all that apply*)

- ☐ Transportation (A)
- ☐ No Childcare (B)
- ☐ Takes too much time (C)
- ☐ Husband/partner won't allow (D)
- ☐ Other_____

H. Demographic characteristics

Now I am going to ask you some questions about yourself. I would like to have your honest responses as this information will help to improve services in general.		
1	How old were you at your last birthday? PROBE TO DETERMINE THE AGE IF THE PARTICIPANT DOES NOT KNOW HER AGE	AGE IN YEARS __/__/
2	In what day, month, and year were you born? PROBE TO DETERMINE AT LEAST THE YEAR	__/__/____
3	Are you currently married, separated, divorced, widowed or never married?	☐ MARRIED (1) → 4 ☐ SEPARATED (2) ☐ DIVORCED (3) ☐ WIDOWED (4) ☐ NEVER MARRIED (5)
a	Are you currently living with someone in a marriage-like relationship?	☐ Yes (1) ☐ No (2)
4	Have you ever attended school?	☐ Yes (1) ☐ No (2) **SKIP TO I**
a	What is the highest level of school you attended: primary, secondary, or higher?	☐ Primary (1) ☐ Secondary (2) ☐ Higher education (3)
b	What is the highest (grade/form/year) you completed at that level?	HIGHEST GRADE __/__/ IF <1YEAR, ENTER "00"

I. Mother's Socio-economic Information

Now I am going to ask you questions regarding your home, where you have been living since you learned that you were pregnant with this baby. If you have not been living consistently in a single home, think about where you will be living most of the time during this pregnancy.		
1	How long have you lived at your current address?	_____Years _____ months *DON'T KNOW = "98" REFUSED = "99*
2	How many adults (people 18 and older) are living with you at home?	_____
3	How many children under 18 are living with you at home?	_____
4	How many rooms do you have in your house?	_____
5	Do you have electricity at your house?	☐ Yes (1) ☐ No (2)
6	How many of the following, if any, do you have at your house: (ENTER "00" IF THE PATIENT DOES NOT HAVE THE ITEM OR IF THE ITEM IN QUESTION IS NOT WORKING)	Beds _____ Radios_____ TVs_____ Mobile phones_____

		Refrigerators_____ Bicycles_____ Motorcycles_____ Car _____
7	With what do you cook at home? (*check all that apply)*	☐ Wood/Charcoal (1) ☐ Gas (2) ☐ Electric Stove (3)
8	What kind of water do you drink? (Check only one)	☐ Private piped water (1) ☐ Piped water from the Neighbors (2) ☐ Communal tap (3) ☐ Protected well (4) ☐ Spring/source water (5) ☐ Other (*specify*)_____ (6)
9	Aside from your own housework, have you done any work in the last seven days?	☐ Yes (1) [**SKIP TO 13**] ☐ No (2)
10	As you know, some women take up jobs for which they are paid in cash or kind. Others sell things, have a small business or work on the family farm or in the family business. In the last seven days, have you done any of these things or any other work?	☐ Yes (1) [**SKIP TO 13**] ☐ No (2)
11	Although you did not work in the last seven days, do you have any job or business from which you were absent for leave, illness, vacation, maternity leave, or any other such reason?	☐ Yes (1) [**SKIP TO 13**] ☐ No (2)
12	Have you done any work in the last 12 months?	☐ Yes (1) ☐ No (2) [**SKIP TO THE END]**
13	What is your occupation, that is, what kind of work do you mainly do?	☐ Market or street trader (1) ☐ Seamstress (2) ☐ Hairdresser (3) ☐ salaried (4) ☐ Other _____ (6)
14	Do you do this work for a member of your family, for someone else, or are you self-employed?	☐ Family member (1) ☐ Someone else (2) ☐ Self-employed (3) ☐ Government (4)

Check the questionnaire to make sure all question were asked and answers recorded appropriately. Thank the participant for taking her time to answer to your question and make sure she has received her compensation before letting her go.

Date_____/_____/_____

Initials of person completing form_____

Appendix K: Participant Exit Interview

When to give the interview: *Six months post-partum or six months after the end of pregnancy*

Objective of the interview: *To collect information on satisfaction with care received.*

J. GENERAL INFORMATION (*PLEASE PRINT CLEARLY*)

A1. Facility Name:

_____

A2. Last name: _____

A3. First name: _____

A4. Address: _____

Use the following space to note the major landmarks for this address: _____

_____

_____

A5. Telephone Number: _____

A6. Who can we contact in case we are unable to reach you directly?

Last and First Name of the contact: _____

Telephone Number of the contact: _____

PREGNANCY OUTCOME: ☐ SINGLE BIRTH ☐ TWIN ☐ STILLBIRTH ☐ MISCARIAGE/ABORTION

Infant PID #_____; Status: ☐ ALIVE ☐ DEAD, DATE OF DEATH __/__/____

Twin 1 PID# _____; Status: ☐ ALIVE ☐ DEAD DATE OF DEATH __/__/____

Twin 2 PID# _____; Status: ☐ ALIVE ☐ DEAD DATE OF DEATH __/__/____

(REMOVE THIS PAGE BEFORE SENDING FOR DATA ENTRY)

K. Infant Status

	CLINICAL PARAMETERS		
1	CHECK THE VACCINATION CARD OR THE APPROPRIATE REGISTER TO COLLECT THE FOLLOWING INFORMATION		
a	WEIGHT	___.__ __ __ KG; NOT RECORDED ☐ (99999)	
b	LENGTH	__ __ __ CENTIMERS; NOT RECORDED ☐ (999)	
c	HEAD CIRCUMFERENCE	__ __ __ CENTIMERS; NOT RECORDED ☐ (999)	
d	HBsAg RESULTS	☐ POSITIVE (1) ☐ NEGATIVE (2) ☐ NOT AVAILABLE (8)	
2	VACCINATION	☐ BCG ; DATE __/__/__ DD/MM/YY ☐ POLIO O; DATE __/__/__ DD/MM/YY ☐ POLIO I ; DATE __/__/___ DD/MM/YY ☐ POLIO II ; DATE __/__/___ DD/MM/YY ☐ POLIO III; DATE __/__/___ DD/MM/YY ☐ DPT HepB Hib I ; DATE __/__/___ DD/MM/YY ☐ DPT HepB Hib II ; DATE __/__/___ DD/MM/YY ☐ DPT HepB Hib III ; DATE __/__/___ DD/MM/YY ☐ PCV I ; DATE __/__/__ DD/MM/YY ☐ PCV II ; DATE __/__/__ DD/MM/YY ☐ PCV III ; DATE __/__/__ DD/MM/YY ☐ VPI; DATE __/__/__ DD/MM/YY	

L. Mother's status and Disclosure of HBV Status

1	CHECK THAT THE CAREGIVER IS THE RECORDED PARTICIPANT (MOTHER) IN THE STUDY	☐ YES, (1) → **2** ☐ NO, NOT THE BILOGICAL MOTHER OF THE CHILD (2)	
a	Where is the biological mother who was enrolled in the study?	☐ DEAD (1) DATE __/__/__ DD/MM/YY ☐ SICK, IN HOSPITAL (2) ☐ SICK, AT HOME (3) ☐ OTHER (6) SPECIFY _____	
b	What is your relation with the baby	☐ GRAND MOTHER (1) ☐ AUNT (2) ☐ SISTER (3) ☐ OTHER _____ (6)	
	DISCLOSURE OF HBV STATUS AND PARTNER INVOLVEMENT		
2	Have you told anyone you have HBV?	☐ No (2) → **3** ☐ Yes (1)	
a	Who did you disclose to	☐ PARTNER/FATHER OF MY BABY (1) ☐ MY MOTHER (2) ☐ MY SISTER (3) ☐ OTHER _____ (6)	

		(SPECIFY)	
3	Do you know the HBV status of your partner	☐ YES (1) ☐ NO (2) ☐ NOT TOGETHER ANY MORE (8)	
a	What is his status	☐ POSITIVE (1) ☐ NEGATIVE (2)	

M. Visit and Medication Adherence

When taking your daily Hepatitis B medications, it is normal that you might forget to take your medications, or not do so as directed by your nurse/doctor, and you may have your own reasons for taking your medication like you did. Please answer the following questions honestly so that the hospital staff will be able to help you ensure that you or other patients take their medications correctly in the future.

1	Since being diagnosed with Hepatitis B, have you missed or were you late for a scheduled visit?	☐ No	**Go to #4**
		☐ Yes	
2	How many visits did you miss?	☐ 1	
		☐ 2	
		☐ 3 or more	
3	People may miss clinic visits for various reasons. Here is a list of possible reasons why you may have missed a visit. Think about the visit you missed, did you miss the visits because …(Check all applicable responses) ☐ you did not have money for consultation fees ☐ you did not have money for transportation ☐ the distance is too far ☐ your partner/husband prevented you ☐ you didn't want people to know about your HBV status ☐ you didn't understand why you needed to go to the visit ☐ you didn't take your pills ☐ you had other commitments ☐ you didn't feel good/ you were in poor health ☐ Other (specify): _____		
4	Were you instructed to take antiviral medication **during pregnancy**? ☐ Yes ☐ No ☐ Not sure		
5	How often **during pregnancy** did you take your Hepatitis B medication in the dose and scheduling that your doctor told you to? (CHECK ONE) ☐ None of the time ☐ A little of the time ☐ Some of the time ☐ A good bit of the time		

	☐ Most of the time ☐ All of the time ☐ Did not take any medication
6	How often **after delivery** did you take your Hepatitis B-related medications in the dose and scheduling that your doctor told you to? (CHECK ONE) ☐ None of the time ☐ A little of the time ☐ Some of the time ☐ A good bit of the time ☐ Most of the time ☐ All of the time ☐ Did not take any medication
7	Did you take any other medications during pregnancy? If so, please list the medications below. _____ _____

N. Patient satisfaction with care received

Now I am going to ask you some questions about the services you or your baby received today. I would like to have your honest opinion about the things that we will talk about. This information will help improve services in general.

1	How long did you wait between the time you arrived at this facility and the time you were able to see a provider for the consultation?	____ hours / ____ minutes SAW PROVIDER IMMEDIATELY(00/00) DON'T KNOW (98/98)	

2	*Now I am going to ask about some common problems clients have at health facilities. As I mention each one, please tell me whether any of these has been a problem starting when you arrived in this facility for the delivery, and if so, whether they were major or minor problems for you.*				
		MAJOR	MINOR	NO PROBLEM	DK
a	Time you waited to see a provider	☐ (1)	☐ (2)	☐ (3)	☐(8)
b	Ability to discuss problems or concerns about your child's health	☐ (1)	☐ (2)	☐ (3)	☐(8)
c	Ability to discuss problems or concerns about your own health [IF RESPONDENT IS ENROLLED]	☐ (1)	☐ (2)	☐ (3)	☐(8)
d	Amount of explanation you received about the problem or treatment	☐ (1)	☐ (2)	☐ (3)	☐(8)
e	Privacy from having others see the examination	☐ (1)	☐ (2)	☐ (3)	☐(8)
f	Privacy from having others hear your consultation discussion	☐ (1)	☐ (2)	☐ (3)	☐(8)
g	Availability of medicines at this facility	☐ (1)	☐ (2)	☐ (3)	☐(8)
h	The hours of service at this facility, i.e., when they open and close	☐ (1)	☐ (2)	☐ (3)	☐(8)
i	The number of days services are available to you	☐ (1)	☐ (2)	☐ (3)	☐(8)
j	The cleanliness of the facility	☐ (1)	☐ (2)	☐ (3)	☐(8)

k	How the staff treated you	☐ (1) ☐ (2) ☐ (3) ☐ (8)	
l	Cost for services or treatments	☐ (1) ☐ (2) ☐ (3) ☐ (8)	
3	Is this the closest delivery facility to your home?	☐ YES (1) ☐ NO (2) ☐ DON'T KNOW (8)	
a	What is the main reason you did not go to the facility nearest to your home? IF CLIENT MENTIONS SEVERAL REASONS, PROBE FOR THE MOST IMPORTANT, OR MAIN REASON.	☐ INCONVENIENT OPERATING HOURS (1) ☐ SEEKING BETTER QUALITY SERVICES (2) ☐ NOT LIKE THE WAY IN WHICH I WAS TREATED IN OTHER FACILITY (3) ☐ THIS FACILITY IS CLOSE TO MY HOUSE (4) ☐ THIS FACILITY IS LESS EXPENSIVE (5) ☐ WAS REFERRED (6) ☐ OTHER_____ (7)	
4	In general, which of the following statements best describes your opinion of the services you received at this facility since arriving here for delivery READ ALL STATEMENTS, CIRCLE ONLY ONE d) I AM **VERY SATISFIED** WITH THE SERVICES I RECEIVED IN FACILITY (1) e) I AM **MORE OR LESS SATISFIED** WITH THE SERVICES I RECEIVED (2) f) I AM **NOT SATISFIED** WITH THE SERVICED I RECEIVED (3)		
5	Will you recommend this health facility to a friend or family member?	☐ YES (1) ☐ NO (2) ☐ DON'T KNOW (8)	

O. Acceptability of study

Now I am going to ask you some questions about your feeling or what you think of the study that you participated in. I would like to have your honest opinion about the things we will discuss.

1	How was your experience of having *your* (the mother's) blood drawn? (CHECK ONE) ☐ Very unacceptable ☐ Somewhat unacceptable ☐ No opinion ☐ Somewhat acceptable ☐ Very acceptable ☐ Did not allow study personnel to take my blood
2	How was your experience with having *your infant's* blood drawn? (CHECK ONE) ☐ Very unacceptable ☐ Somewhat unacceptable ☐ No opinion ☐ Somewhat acceptable ☐ Very acceptable ☐ Did not allow study personnel to take my child's blood
3	How was the experience of having your infant vaccinated at birth? (CHECK ONE) ☐ Very unacceptable ☐ Somewhat unacceptable

	☐ No opinion ☐ Somewhat acceptable ☐ Very acceptable ☐ Did not allow study personnel to vaccinate my infant
4	What is your opinion about taking a drug (tenofovir +/- lamivudine) during and after pregnancy to prevent transmission of the virus to the baby? (CHECK ONE) ☐ Very unacceptable ☐ Somewhat unacceptable ☐ No opinion ☐ Somewhat acceptable ☐ Very acceptable ☐ Did not allow study personnel to vaccinate my infant

Check the questionnaire to make sure all question were asked and answers recorded appropriately. Thank the participant for taking her time to answer to your question and make sure she has received her compensation before letting her go.

Date_____/_____/_____

Initials of person completing form_____