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Malaria Prevention and Control Practices Among HIV-infected and HIV-uninfected Women in a Rural Area of Uganda

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Abstract:
We will conduct an ancillary cross-sectional survey as part of an ongoing longitudinal trial of anti-malarial chemoprevention in children. The ongoing trial includes a cohort of 800 HIV-uninfected children who will be enrolled at 4-5 months of age: 400 HIV-exposed infants born to HIV-infected mothers, and 400 HIV-unexposed infants born to HIV-uninfected mothers. At the time of their enrollment in the study, this cross-sectional survey will obtain data from the mothers using a standardized questionnaire in addition to the child's enrollment form that includes descriptive data about the study participants, their parents (especially the mothers), and their households. The objective of the longitudinal trial is to compare the incidence of malaria among infants and children randomized to receive no chemoprevention, daily trimethoprim-sulfamethoxazole, monthly sulfadoxine-pyrimethamine or monthly dihydroartemisinin-piperaquine until the age of 24 months. The questionnaire will provide descriptive data on whether mothers are implementing prevention strategies and help define the impact of HIV status on preventative health behavior by providing a comparison between HIV-uninfected mothers and HIV-infected mothers.

Specific aims:
• To compare the use of ITNs (insecticide treated nets), malaria chemoprophylaxis during and after pregnancy, and fever treatment practices among HIV-infected and HIV-uninfected mothers
• To examine the relationship between HIV status and malaria prevention and control practices
• To determine what other factors (i.e. age, parity, demographics) play a role in malaria prevention and control practices

Significance:
In Sub-Saharan Africa, HIV and malaria are among the leading causes of morbidity during pregnancy. Pregnant women are at increased risk of malaria infection, resulting in maternal anemia, preterm delivery, and intrauterine growth retardation (IUGR). Many women are asymptomatic and consequently remain undetected and untreated. HIV-infected pregnant women are at even greater risk, experiencing more malaria and higher density malaria parasitemia. HIV-infected pregnant women co-infected with malaria have more febrile illnesses, more anemia, and more adverse birth outcomes. Malaria, in turn, increases HIV viral replication and viral load. Currently, the role of malaria in maternal-to-child transmission (MTCT) of HIV is unknown. While data from Malawi have shown that dual exposure to both placental malaria and maternal HIV increased the risk of post-neonatal mortality 3-8 fold compared to infants born to mothers with HIV alone, other data from Kenya and southern Malawi have shown a protective effect. This protective

effect in western Kenya is consistent with the reduced MTCT found in women with dual infection compared with women without placental malaria. Further studies are needed to shed more light on the role of malaria on MTCT. Although much has been learned about the interaction of HIV and malaria during pregnancy, many issues still require elucidation, and there is a clear need to strengthen existing malaria and HIV prevention and intervention programs. The WHO currently recommends a three-pronged approach for malaria control during pregnancy: intermittent preventative treatment (IPT), insecticide-treated bed nets (ITNs), and effective case management of malaria illness. In addition, UNAIDS recommends opportunistic infection prophylaxis with co-trimoxazole for all HIV-infected pregnant women after the first trimester, which in a study in Uganda was associated with a 76% lower malaria rate. Each intervention has been shown to reduce the burden of malaria, and the benefits are additive.

For HIV-infected pregnant women, malaria prevention with ITNs and IPT should be a priority, and for women who are found to be co-infected, appropriate management of both illnesses is a priority for both mother and fetus. There is a need for more data on how to increase access and compliance by a greater number of women. With this aim in mind, the proposed project seeks further insight into the difference in health related behaviors between HIV-infected and HIV-uninfected women, thereby providing a potential area of focus for intervention strategies aimed at malaria prevention in the two groups.

Tororo, the site of the proposed study, is a rural area in Eastern Uganda where malaria is highly endemic and occurs throughout the year. In an area with such high transmission intensity settings, the burden of malaria is concentrated among infants and young children. Tororo provides an ideal epidemiological setting to study the impact of chemopreventative interventions in high risk infants and young children. In addition, Tororo is an excellent site for both the longitudinal study and the questionnaire described above because of existing infrastructure and preliminary work that has been done by the SFGH Infectious Disease research group and the CDC. The CDC has been working in Tororo since 2001, primarily on studies of HIV and co-infections. They have established large cohorts of HIV-infected patients and HIV-uninfected family members and have developed a large infrastructure to support research based at Tororo district hospital. The CDC has also established an extensive program to support the prevention of mother-to-child transmission of HIV. The experience and support provided by the CDC will be critical for assisting in recruitment of study subjects.

Research questions:

• How do the health related behaviors of HIV-infected women differ from those of uninfected women and why?
• Why do some mothers utilize intervention strategies while others don't?
• How can we use this knowledge to increase access to proven malaria prevention and intervention strategies?
• How can we increase compliance with these strategies?

Methods:

***Design*:** A cross-sectional study of 400 HIV-infected mothers and 400 HIV-uninfected mothers living in an area of high malaria transmission intensity (800 total study participants)

Target Population: HIV-infected and HIV-uninfected mothers in Tororo, Uganda
Accessible population: Pregnant women with and without HIV who present to the district hospital

Recruitment strategy and criteria:
Parent Study: PROMOTE-CHEMOPREVENTION
Convenience sampling will be used to enroll a cohort of 800 HIV-uninfected infants between the ages of 4-5 months of age into to the following two strata based on the mothers HIV status: 1) 400 HIV- exposed infants born to HIV-infected mothers, and 2) 400 HIV-unexposed infants born to HIV-uninfected mothers. Potential study participants will be identified from the Tororo District Hospital (TDH) Antenatal Clinic and surrounding clinics providing routine pediatric care. Eligible children will be enrolled when they reach 4-5 months of age and followed until the age of 36 months for all their routine medical care at our designated study clinic. HIV-unexposed children will be randomized to one of four chemoprevention arms when they reach 6 months of age.

Potential study participants less than 6 months of age and their parents/guardians will be identified through the TDH Antenatal Clinic and other clinics within the TDH complex including the TASO (The AIDS Support Organization) clinic. Parents/guardians will be approached about participating in the study and will be provided an information sheet about the requirements of the study. If the parents/guardians are initially agreeable to screening for participation in the study the child and parents will either be escorted to the study clinic or make an appointment to return at a later date. During the screening process, study physicians will assess for initial eligibility criteria. Study participants who pass initial screening will be given an appointment to the study clinic when the child is 4-5 months of age for assessment of final study eligibility. Children who are 4-5 months of age and fulfill all eligibility criteria on the day of initial screening may proceed to enrollment on the same day.

Ancillary study: Malaria Prevention and Control Practices
At the time of enrollment of their children, consenting mothers will verbally complete a standardized questionnaire assessing their malaria prevention and control practices. The survey is modeled after questionnaires used in previous observational studies by the research team and includes information regarding basic demographics of the mother and study participant, health behaviors of the mother, and health-related knowledge and practices of the mother. Prior to the study's onset, physicians will be familiarized with and trained to verbally administer the questionnaire to study participants. The questionnaire will then be administered in the appropriate language. Subsequently, a visit to the participant's home will provide a GPS reading. This information will be used to create a digitalized map of the region. In addition, bed net ownership will be confirmed by direct observation. The ancillary study will be a cross-sectional study comparing a cohort of HIV-infected and a cohort of HIV-uninfected mothers.

Selection Criteria: Inclusion criteria:
- Biological mother of child age 4-5 months enrolled in chemoprophylaxis study
- Confirmed HIV status
- Residency within 30 km of the study clinic

Exclusion criteria:

• Intention of moving more than 30 km from the study clinic during the follow-up period
• Illness too great to answer study questions

Primary Predictor Variable: HIV status

Potential confounders: Age, parity, socio-economic status, urban vs. rural location, distance from clinic, tribe, education

Outcome variables: Use of ITNs, chemoprophylaxis during and after pregnancy, appropriate fever treatment practices

Hypotheses and sample size estimates:
H_0- Null hypothesis: There is no difference in malaria prevention and control practices between HIV-infected and HIV-uninfected mothers.
Alternative hypothesis: HIV-infected mothers are more likely to practice malaria prevention and control behaviors compared to mothers who are HIV-uninfected.

Effect size: A study in Rakai district in Uganda analyzed ITN use amongst HIV-infected women given free bed nets, and follow-up analysis showed that about 90% of women continued to sleep under their nets on a daily basis (CI: 86-96%). We estimate that there are similar retention rates in HIV-infected women in Tororo district. Therefore, the effect size is based on the difference between prevalence of bet net use in HIV-infected women (90%) and HIV-uninfected women (10%)=80%.

Sample size: The sample size has already been calculated for the parent study (800 total participants [400 in each group]).
Standardized effect=0.10/1.96=0.05
Standard deviation=SE*(√400)=1.02
Using appendix 6b, column 2, upper number of 0.10 row: 58 subjects are needed per group

Analysis:
Within 6-9 months, we plan to complete enrollment of the 800 study participants and begin analyzing the data to answer both descriptive questions of interest (e.g. how many study participants were sleeping under an ITN before being enrolled into the study?) using chi-squared tests and t-tests where appropriate, as well test our primary hypothesis using chi-squared tests and bivariate logistic regression analyses. In our analyses, the outcomes will be those variables above (dichotomized) and others we construct. Predictor variables will be assessed for co-linearity. We will use univariate and multivariate logistic regression to look for associations between predictor variables of interest and our outcomes of interest (for each outcome of interest we will perform a separate analysis). For all outcomes we will look for predictor variables including, but not limited to, the HIV status of the mother, such as the age of the mother, measures of socioeconomic status, level of education, location of the household relative to Tororo town, etc. Those characteristics which change the odds associated with HIV status will be considered potential confounders. Within the group of children born to HIV-infected mothers we will examine HIV prevention and treatment practices: What did the mothers use for PMTCT? What proportion of mothers is on ARVs and taking TS prophylaxis? Again, we will try to identify predictor variables for these HIV- related outcomes.

Ethical considerations:

Compensation:

There is no cost to participants to participate in the study, and participants will not be paid for their participation in the study. We will provide all routine medical care, including evaluations, medications available in our clinic, and cost of any transportation free of charge. In addition, we will reimburse the cost of consultation for referrals made by study physicians to other clinics and services within Tororo District Hospital and visits the cost of most diagnostic tests (including laboratory test, X-rays, and ultrasounds) and medications resulting from referrals by the study team, using available funds.

Institutional Review Board (IRB) Review and Informed Consent:

This protocol, all procedures and consent forms, and any subsequent modifications must be reviewed and approved by the IRBs of all the participating institutions in both the U.S. and in Uganda. This includes the UCSF Committee on Human Research (CHR), the MU Faculty of Medicine - Research and Ethics Committee (FOM-REC), and the Uganda National Council of Science and Technology (UNCST).

All consent forms will be translated into the local language (Jopadhola, Teso, Samia, Swahili, Luganda, and English) and back-translated into English to ensure correct use of language. Consent forms will be read aloud to parents by trained study interviewers. The informed consent will describe the purpose of the study, all the procedures involved, and the risks and benefits of participation. Interviewers will ask parents/guardians of study participants to summarize the study and explain the reasons why they want to participate. Either a signature or a thumbprint (for parents/guardians who cannot read) will be acceptable to confirm informed consent for participation in the study.

Administrative Issues:

Personnel-

- MD: Principal investigator, clinical assessment
- MDs/clinic staff: Administer the questionnaire to study participants
- Medical student, clinic staff: Home visit to record GPS reading, verify bed net ownership
- Study coordinator, medical student: Train physicians to administer questionnaire, recruitment, data management
- MD, PhD, medical student: Data management, statistical analysis

Data Management:

The cross-sectional data collected on the enrollment form will be double entered using Epi-info, and stored as a Microsoft Access database.

Time Table:

Physicians will be trained to administer the questionnaire in September. The study is scheduled to begin on October 1st, 2009, and will continue until 800 participants are recruited (the parent study will follow the children for 36 months).

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