To Members of the Review Committee:

1. Background and Hypothesis:

As the HIV prevention of maternal to child transmission programs become more successful and widespread, the number of children who are exposed to HIV in utero but remain uninfected (HEU) is increasing dramatically. Among all children, accelerated progression from latent MTB infection to active TB disease is associated with immunosuppression and younger age. HEU infants, specifically, have an increased risk of developing life-threatening TB disease compared to the general population. Isoniazid (INH) is known to prevent progression of MTB infection to TB disease in the adult population, including those who are HIV-infected. However, data regarding INH for the prevention of TB disease in infants is mixed, with very little data for using INH as prevention of MTB infection in HEU infants who are at high risk for developing TB.

Adherence to INH is important for its efficacy in preventing TB disease. Multiple studies have reported INH adherence in children is very low but there is little data regarding the risk factors that contribute to this poor adherence. Poor adherence is an important barrier for the wider implementation of INH as a TB prevention measure for children.

The Infant TB Infection Prevention Study ("iTIPS") is a RCT designed to investigate whether isoniazid (INH) reduces the risk of MTB infection in HEU children in western Kenya (an area of high HIV and TB burden). Given the importance of adherence for INH efficacy, and potential issues with INH adherence in children, I have designed an observational study nested within the iTIPS RCT to evaluate INH adherence within HEU infants in the treatment arm of the iTIPS study. Prior studies evaluating INH adherence have focussed primarily on HIV infected children or children above the age of 1 year. This study is especially novel because it examines INH use as a prevention measure instead of as a TB treatment. In addition, determining INH adherence using an accurate, cost-effective urine test will improve the validity of the study results as previous research on INH adherence has used less reliable proxies for adherence, such as maternal reports or pill counts. With the rising global burden of TB and an expanding, high risk population of HEU infants, this study is needed to determine the efficacy and challenges with using INH as a prevention of TB disease for HEU infants in low-resource settings.

In the INH adherence study we will use a (POC) urine test for INH (The Arkansas Urine Test) to evaluate adherence. The Arkansas Urine test is inexpensive, easy to use, and accurate for measuring INH adherence. The test has been well-tested in adolescents and adults and found to have results well-correlated with self-reported adherence to INH for treatment of latent tuberculosis infection over several months of follow-up. However, this test has rarely been used with infants so this study's use of a urine test as a measure of INH adherence in infants is novel within INH prophylaxis interventions.

Both the parent iTIPS RCT and proposed nested observational adherence study are feasible. Pregnant HIV-infected and uninfected women and their infants have been enrolled in other longitudinal studies (both observational and interventional studies) at these sites for more than 4 years, with high rates of retention.

The Infant INH Adherence Study Hypotheses and Aims:

Aim 1: Evaluate maternal report and pill count vs. urine POC test for INH adherence. Hypothesis: Maternal report and pill count will be less accurate compared to urine testing.

Aim 2: Investigate correlates of infant INH adherence for the prevention of MTB infection. Hypothesis: Maternal (age, socio-economic level, education level, antiretroviral status, other chronic disease status, HIV status of partner, household size, etc.) and infant characteristics (growth measures, intercurrent...
illness, birth complications, etc.) will be associated with improved adherence as measured by positive POC INH urine test.

Exploratory Aim: Investigate barriers and challenges of INH adherence for the prevention of MTB infection.
Hypothesis: Poor INH adherence is a result of lack of access to proper healthcare services and medications, lack of finances for transport to collect medication, cultural and community stigmas regarding medications, and misunderstanding and lack of knowledge about INH prophylaxis.

2. Experimental Design & Methods, including Sample Size:

Design: Prospective observational cohort study to evaluate adherence of INH for prevention of MTB infection in HEU infants nested within parent RCT. Infants in the parent RCT are enrolled at 6 weeks of age randomized to receive 12 months of INH for the prevention of MTB infection. Adherence assessment including maternal report, pill count, and POC urine INH testing will occur throughout the 12 months of study follow up. Myself and other research staff will give the mothers adherence questionnaires to obtain the maternal report of adherence at their monthly medication pick-up appointments. We will ask mothers to bring their pill bottles with them to every appointment so that we can conduct pill counts at their monthly appointments as well. We will collect urine from the infants at their monthly appointments to conduct the urine test to assess INH adherence. At the 3 month visit, we will administer a questionnaire about adherence in order to better explore the qualitative aims regarding IHN adherence. Inclusion criteria: HEU infants randomized to receive INH in parent RCT. Exclusion criteria: HIV positive or premature infants will be excluded. Sample size: Aim 1 & 2: 150 HEU infants randomized to receive INH in parent RCT. Exploratory Aim: 50 HIV-infected mothers of the HEU infants. This is an appropriate sample size for the research study because with only 125 infants in each arm, the study will have the power to detect at least a 65% decrease in MTB infection in the INH arm vs. control. We have increased the sample size by 20% to account for loss to follow-up, non-adherence, and isoniazid resistance, enrolling 300 mother-infant pairs (150 per arm). Outcomes and statistical methods: Aim 1: Sensitivity and specificity of maternal report of adherence based on discussion with mother during INH collection visits and pill count based on number of pills remaining at each visit compared to POC urine INH test. Aim 2: Potential correlates will be evaluated for their association with poor adherence (previous INH dose >48 hours ago or stop collecting INH after < 4 months) using chi2, Student's t-test, or Wilcoxon rank sum tests as appropriate and their relationship to adherence will be assessed using a multivariate logistic regression model. Exploratory Aim: Use questionnaires to assess adherence from mother at 3 month appointment and quantitatively code and qualitatively analyze common themes and significant differences between mothers’ challenges with INH adherence for their infants.

In the upcoming months, I will meet with Dr. [Name] and Dr. [Name] at least monthly to prepare the adherence questionnaires, obtain the urine tests and prepare other related research materials before I arrive for data collection this summer. I also will write an in-depth research literature review regarding INH adherence in HEU children and infants in Africa to further inform my research methods development and data analysis. While in Kenya, I will be working closely with Dr. [Name], who has a wealth of experience working with medical students and student researchers at this Kenyan site. I have scheduled weekly phone/Skype calls with Dr. [Name] and Dr. [Name] in order to assess my research progress and results. With support for data analysis from weekly meetings with Dr. [Name] and Dr. [Name] in [City], I plan to finish my data analysis and research paper write-up once I return to [City].

3. Expected Significance of Results:

Adherence research is critical for confirming the the iTIPS RCT results and could contribute important information regarding issues of adherence for INH as a TB prevention measure. Although the RCT will be using an intention to treat measure for the primary efficacy endpoint, additional information regarding adherence by using a less subjective measure of adherence, will allow us to more accurately perform per protocol analyses. A better understanding of issues with INH adherence for TB prevention in children, and specifically among HEU children could inform TB prevention efforts in resource limited settings. A urine-
based test could offer an easy, accessible and cost-effective method of testing and potentially improving INH prophylaxis adherence in future prevention interventions for HEU infants.

4. Reasons for Applying for the Scholarship

I am applying for this scholarship in order to fund the purchase of Arkansas urine tests and other relevant research materials, and to cover the costs of my travel and living expenses for my 10 week stay in Kenya this summer.

5. List of Relevant References: