Tuberculosis (TB) is a leading cause of death among women and children globally.[1] HIV-infected women with TB during pregnancy or postpartum have 2-fold increased risk of mortality, and their infants have >3-fold risk of death.[2] In TB-endemic countries, the risk TB disease in HIV-infected pregnant women is increased up to 10-fold, due to changes in a woman's immune system both from HIV and pregnancy and the early postpartum period.[3-5] Isoniazid preventive therapy (IPT) reduces the risk of TB disease by up to 80% when combined with antiretroviral therapy (ART). In 2015, Kenya rolled out IPT guidelines for people living with HIV and AIDS (PLWHA) and efforts to scale-up therapy across the country have continued, with an estimated 800,000 PLWHA initiated on IPT as of 2018.[6,7] The Kenyan national IPT guidelines, which mirror World Health Organization (WHO) guidelines, state that IPT can be initiated at any time during pregnancy and should be continued if a woman becomes pregnant while on therapy.[8,9]

Although administration of IPT during pregnancy to prevent TB may benefit both mothers and infants, there is a paucity of data on the effect of maternal IPT on infant safety outcomes. Preliminary data from the multi-center IMPAACT P1078/TB APPRISE clinical trial found higher proportion of poor infant outcomes (low birthweight, fetal demise, prematurity and congenital anomalies measured as a composite outcome) among women who started IPT during pregnancy compared to IPT administered postpartum (23% vs 17%, p=0.009).[10] Conversely, the TSHEPISO study in South Africa found a trend of lower rates of prematurity among infants born to women using IPT during pregnancy (10 vs 22%, p=0.06) and no differences in other infant outcomes.[11] Additional data on the potential risks and benefits of IPT use during pregnancy are urgently needed to inform global public health policy. We propose to evaluate whether maternal IPT in pregnancy is associated with poorer infant outcomes including preterm delivery, low birth weight, congenital anomalies, and perinatal death (Aim 1) and assess maternal considerations of IPT acceptability and completion (Aim 2).

With strong mentorship and collaborators who are well-poised to support me in this endeavor, including Dr. Lisa Cranmer, who has worked in Kenya for >5 years and who is a published expert in TB immunity with ongoing NIH-funded research, and Dr. Dickens Onyango, a leader in medical epidemiology with the Kenyan Ministry of Health who has vast research experience with TB and HIV, I will investigate the following aims:

Aim 1: Determine if maternal IPT exposure during pregnancy is associated with poor infant birth outcomes in HIV-infected pregnant woman in a programmatic setting.
Hypothesis: Maternal IPT exposure in pregnancy will not have a negative impact on birth outcomes.

Approach: We will perform a retrospective chart review of antenatal, birth and HIV care records at 3 health care facilities in Kisumu, Kenya between 2015-2018. We will compare the rate of poor obstetric outcomes (prematurity, low birth weight, congenital anomalies, stillbirth, neonatal death, and any other reported infant adverse event) among women who initiated IPT during pregnancy and women who took IPT outside of pregnancy (prior to pregnancy or during the postpartum period).

Aim 2: Explore factors related to the maternal decision-making process surrounding IPT initiation during pregnancy.
Hypothesis: Mothers weigh a number of factors when determining to initiate and complete IPT during pregnancy which are likely related to their understanding of HIV, TB, IPT and perception of impact to their unborn child.

Approach: We will collect survey data and perform structured interviews to assess maternal acceptability of IPT and determine factors that influence their decision to initiate and complete IPT during pregnancy.

The proposed research will generate data to better understand the risks, benefits and patient determinants of IPT use during pregnancy. Our data will provide evidence to inform both national policies in Kenya as well as WHO guidelines on the timing of IPT in HIV-infected women to provide optimal benefit for both mother and child.

A. Study Population

The study will be conducted in Kisumu, Kenya, where there is high prevalence of HIV and TB. TB disease prevalence is estimated at 502 per 100,000 with 63% of TB cases among HIV-infected individuals.[12,13] Antenatal HIV prevalence is 26%.[14] IPT was rolled out in Kenya in 2015 in PLWHA with intensified case finding using a TB symptom screen to identify those eligible.[6] Since that time, efforts to scale up IPT have resulted in high uptake of IPT, with many HIV-infected women initiating during pregnancy (Table 1).[15] Estimates suggest approximately 42% of women initiate IPT prior to pregnancy, 49% started during pregnancy, and the remainder initiated in the postpartum period.[15]

IPT initiation timing and pregnancy	
Pre-conception initiation	95/224 (42.4)
Pregnancy initiation	110/224 (49.1)
Postpartum initiation	19/224 (8.5)

Table 1: Timing of IPT initiation in 224 HIV-infected mothers in Kenya

B. Study Design

Aim 1: Determine if maternal IPT exposure during pregnancy is associated with poor infant birth outcomes in HIV-infected pregnant woman in a programmatic setting.

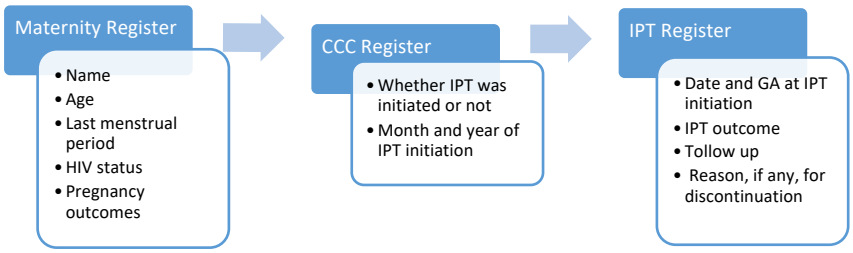

Figure 1: Overview of chart review for data collection with relevant information from each

Design: Retrospective chart review

Approach: We will conduct medical record review at 3 healthcare facilities in Kisumu, Kenya including Kisumu County Hospital, Lumumba Sub-County Hospital, and Jaramogi Odinga Oginga Teaching and Referral Hospital. Data will be collected from the following medical chart registers: maternity, comprehensive care clinic (CCC), and IPT register (Figure 1).

a) Screening: A woman's maternity register will be used to identify her HIV status and timing of pregnancy. For HIV-infected patients, we will use the patient identification number to link with the CCC register and determine whether IPT was initiated. Using the CCC identification number, we will then link to the IPT register to determine the duration of IPT and timing relative to the patient's pregnancy (during or outside pregnancy). Inclusion criteria will include women of known HIV-positive status at the time of pregnancy who have initiated IPT and completion of at least 3 months of IPT. Exclusion criteria include known HIV-negative status or unknown HIV-status at time of pregnancy.

b) Data Collection: Abstracted maternal data will include maternal age, date and timing of IPT initiation, including weeks gestational age, date of IPT completion or discontinuation and reason, if any, stated for discontinuation, ART regimen, CD4 count and maternal side effects or adverse events. Abstracted infant data will include gestational age, birth weight, congenital anomalies, stillbirth, neonatal death, and any other reported infant adverse event (Appendix 1).

Statistical Methods: Statistical analyses will be conducted by Dr. Elizabeth Quincer with assistance from the Emory + Children's Biostatistics Core. Descriptive statistics will be calculated for all variables of interest and include means and standard deviations, medians and ranges or counts and percentages, as appropriate. Effect of maternal IPT exposure during pregnancy on infant outcomes (prematurity, low birth weight, death and congenital anomaly evaluated individually and as a composite endpoint) will be determined using chi square or Fisher's exact test, as appropriate and multivariable logistic regression, adjusting for maternal age, ART and CD4 count.

Sample size: Assuming a 15% baseline rate of a poor infant outcomes, we will include at least 250 mother-infant dyads per group in order to detect a 10% difference between women who completed IPT during pregnancy and women who completed IPT outside of the peripartum period (Figure 2). Sample size calculations are based on the following assumptions: α = 0.05,

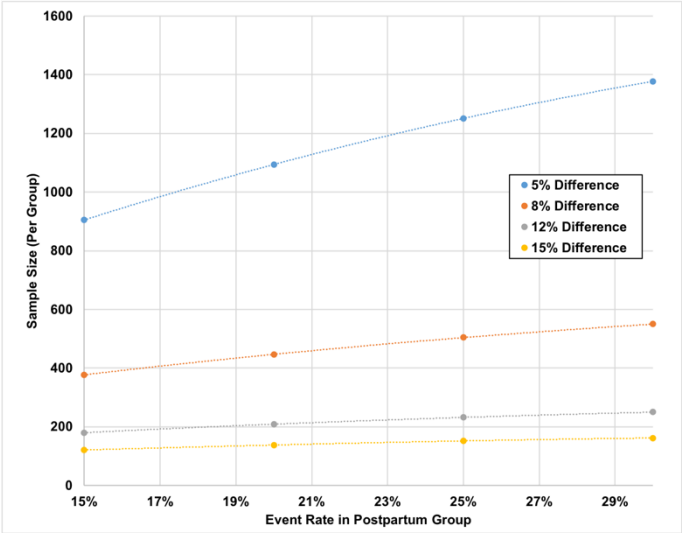

Figure 2: Sample size calculations based on event rate and difference per group

β = 0.20 (power = 0.80), and sample size ratio 1:1. We estimate that we will need to review registry data for between 800-1000 women in order to obtain at least 250 women enrolled per group (IPT during pregnancy and IPT outside of pregnancy). Using estimates from ongoing research through the Kenyan Ministry of Health, which found approximately 355 HIV-positive women enrolled in IPT during pregnancy over a one-year time period, an estimated 1065 women can be expected to be initiated during a three-year time period. Estimates of up to ~90% of women have been found to complete the full 6-month course of therapy.[12]

Aim 2: Explore factors related to the maternal decision-making process surrounding IPT initiation during pregnancy.
Design: Structured interview and survey
Approach: Individuals will be recruited from each of the three-health facilities. Patients will be eligible for enrollment if they are over the age of 18 years, newly diagnosed with HIV in the preceding 6 months and currently pregnant. Study team members will be utilized to administer surveys and conduct interviews in the preferred language of the participant (Kiswahili, English, or Dholuo). We will administer a short survey to collect demographic information and questions to assess motivation for initiating IPT using a Likert scale. A structured interview will then be conducted to further explore maternal motivation and understanding of IPT. We will perform 30 individual interviews across the three health facilities, for an average of 10 individuals per facility. Demographic data and information regarding maternal motivation will be summarized using descriptve statistics. Interviews will be recorded and we will perform inductive thematic content analysis using MAXQDA software.

C. Mentorship and Research Team
Dr. Lisa Cranmer (Mentor, Emory) has conducted research in Kenya for >5 years and lived in Kisumu, Kenya where the study will be conducted for 2 contiguous years. She has led numerous research studies on HIV and TB and currently is PI of an NIH K23 award to investigate the role of maternal antibodies on infant TB acquisition. In addition, she is co-investigator of an RO1 evaluating the effect of maternal HIV on infant trained immunity. Dr. Dickens Onyango (Co-Mentor, Kenya Ministry of Health) is the County Director of Health for Kisumu County. He has conducted research studies within the public health sector on the epidemiology of TB and HIV and is currently involved in work to evaluate the uptake of IPT in Kisumu. He serves as a field supervisor for residents in epidemiology and is currently mentoring a post-doctoral fellow, Dr. Albert Odhiambo, on a complementary study evaluating maternal safety outcomes for IPT in pregnancy and post-partum. Dr. Odhiambo is a co-investigator on the proposed study and will provide in-country collaboration.

D. Timeline
As a resident on the Pediatric Residency Training Program's Global Health Track, I will be completing this research as my scholarly project for the track. Data collection is planned for July and August 2019. Subsequent statistical analyses and preparation of results for dissemination will then occur. We are targeting submitting an abstract to the TB Union meeting in April 2020 and planning to present our findings at the World TB Union conference in the fall of 2020. We will also plan to submit at least 2 manuscripts as a result of this work within 1 year after grant completion.

E. Potential Challenges/Limitations
Although cited research to date has suggested that we will have significant numbers of subjects to enroll, it is possible that we will find lower than expected numbers of women who have completed IPT, which will decrease our study's power. As mentioned above, our Kenyan colleagues have an ongoing retrospective chart review, and have documented 355 women using IPT during pregnancy over a one-year time period, which we believe makes our study feasible. We anticipate sufficient numbers to complete our analysis over a 2 year review period 2016-2018, but will extend our chart review to additional years if needed.

F. Future Directions
These data will provide important insights into the safety of IPT during pregnancy. As IPT use in pregnancy represents a global health policy, a thorough understanding of infant safety is paramount, and these data will add to the growing body of literature informing this topic. This project will also provide a rich environment to expose me to field research in global health. I will gain new research skills in data collection, analysis and gain a better understanding of conducting field research in global settings. In addition to my proposed project, I will have the opportunity to interact with key individuals to form partnerships with the potential for future collaboration. This research will directly add to my repertoire of growing skills, serving as a foundation for my chosen career path in global health and pediatric infectious disease.

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Appendix 1: Comprehensive data obtainable from select registers

Register	Data
Antenatal Care Register	Date of visit; ANC number; First visit; Number of visits; Full name; Village/Estate; Phone number; Data of birth; Age; Marital status; Parity; Gravidae; Date of LMP; Estimated date of child birth; Gestation in weeks; Weight; Height; Blood pressure; Breast exam; Counseled on; RPR/VDRL; HIV status before 1st ANC; HIV testing; WHO stage; Viral load; On ARV before 1st ANC visit; Started HAART in ANC; CTX; AZT for baby; NVP for baby; TB; Cervical cancer; Other conditions; Deworming; IPT 1-3; TT dose; Given supplementation; Received ITN; Exercises given in ANC; Partner HIV testing; Partner HIV result; Referrals; Date of next visit; Remarks
Antiretroviral Register	Serial counter; ART start date; Unique patient number; Patient name; Sex; Date of birth; Address; Patient type at starting; Stage at start ART; CTX start; INH start; TB treatment; PMTCT; 1st line regimen
Isoniazid Preventive Therapy Register	IPT start date; Serial No.; District IPT No.; CCC No.; Patient name; Physical Address; Cell phone No.; Sex; Age; Weight; Height; BMI; Indication for IPT; IPT HIV status; IPT dose; Reason for discontinuation of IPT; Date of outcome; Month at follow up/TB status/Date
Maternity Register	Admission number; Date of admission; No. of ANC visits; Full name; Village/Estate; Age, Marital status; Parity; Gravidae; Date of LMP; Expected date of delivery; Diagnosis; Duration of labor; Date of delivery; Time of delivery; Gestation at birth; Mode of delivery; Placenta complete; Blood loss; Condition at delivery; Baby sex; Baby weight; Live birth; FSB; MSB; APGAR score; VDRL/RPR results; HIV status at ANC; HIV status at maternity; ARV prophylaxis at ANC; ARV prophylaxis at maternity; ARV prophylaxis to baby; CTX to mother; Vitamin A; Partner HIV test; Delivery conducted by; Birth notification number; Date of discharge; Status of baby; Comments

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Quincer, Elizabeth Mary

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Pediatric Resident

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
Concordia College	BA	08/2009	06/2013	Biology
Chicago Medical School	MD	08/2013	06/2017	Medicine
Emory University	Resident	07/2017	Present	Pediatrics

A. Personal Statement

My career goal is to become a clinician-scientist in global pediatric infectious diseases. My training to date has included undergraduate and medical school study in the fields of biology and medicine, respectively, and I am currently completing my medical residency training in the field of pediatrics. As I have progressed throughout my career, I have developed a desire to work in a global setting. During medical school, I was able to integrate this desire with my interests in public health and policy, by engaging in research in Rwanda aimed at assessing the system-wide changes made to the health care system following the Rwandan genocide. This opened my eyes to the many ways that research can be integrated into medicine. After deciding on pediatrics as my chosen specialty for my residency training, I continued to look for opportunities to further myself in global child research, and Emory's pediatric residency program has given me a number of opportunities. In the proposed project , I will investigate the safety of isoniazid therapy to prevent TB in HIV-infected pregnant women in Kenya, and our data will influence both national Kenyan and global health policy. Through implementing this project, I will gain valuable experience that will serve as foundation to advance my career goal of becoming a clinician scientist in global pediatric infectious disease.

B. Positions and Honors

Positions and Employment

2017-present Pediatric Resident, Emory School of Medicine

Other Experience and Professional Membership

2011-present Member, Beta Beta Beta, National Biological Honor Society
2012-present Member, Omicron Delta Kappa, National Leadership Honor Society

2012-present	Member, Nu Rho Psi, National Honor Society in Neuroscience
2013-present	Member, American Medical Association
2013-present	Member, Organization of Student Representatives, Association of American Medical Colleges
2017-present	Member, Gold Humanism in Medicine Honor Society
2013-present	Resident Member, American Academy of Pediatrics

Honors/Awards

2009-2013	Presidential Distinction Scholarship, Concordia College
2013-2015	Alumni Association Scholarship, Chicago Medical School
2014	Board of Trustees Scholarship, Chicago Medical School
2014	Global Health Scholarship, Chicago Medical School

C. Contributions to Science

1. During my undergraduate career, I worked on research in the field of neuroscience aimed at studying two clinically important neurological conditions, multiple sclerosis and systemic lupus erythematosus (SLE). Together with my undergraduate lab, we evaluated the effect that music therapy, in the form of Mozart's music, may have on the progression of multiple sclerosis, specifically through gene expression of proteins involved in the synthesis of myelin in a murine model. We found increase in expression of key genes, implying a potentially positive effect of music therapy. Additionally, using a behavioral testing analysis in a murine model of SLE, we conducted research to better characterize the progression of neuropsychiatric symptoms in SLE, knowledge which is beneficial for a better understanding of the disease process itself.
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    3. **Quincer, E,** Quinlan, C, Kempfert, M, Twedell, K. Project title limited by contract. Mayo Innovation Scholars Program Research Project. 2013. Rochester, MN

2. I took an interest in medical education during medical school and participated in the development and evaluation of a community clinic operated by an interprofessional group of students from my university. This model not only allowed students to learn from those in other disciplines, but it also provided a valuable asset to the community. Additionally, I helped to develop a learning community model that was implemented by the medical school and used to augment the curriculum as well as to foster a culture of mentorship and support within the medical school. Both of these innovations in medical education were presented to the greater scientific community at national meetings of the Association of American Medical Colleges.
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3. I have been involved in ongoing research in global health and pediatric infectious diseases. My initial introduction to global health came when I worked as a research assistant to Dr. Agnes Binagwaho with the Rwandan Ministry of Health, working on a public health project aimed at documenting the progress made in the health sector since the time of the Rwandan genocide. The product was developed into a didactic curriculum, which is currently in use at the University of Global Health Equity in Rwanda. I am also involved in ongoing NIAID-sponsored research evaluating the effectiveness of the influenza vaccine in a pediatric population with Emory University's Vaccine and Treatment Evaluation Unit. Additionally, I am working with the Child Health and Mortality Prevention Surveillance (CHAMPS) Network through Emory's Global Health Institute studying the global implications of misclassification of stillbirths and neonatal deaths in CHAMPS' data on the causes of death in global child mortality. Finally, I have completed a case study in the field of pediatric infectious diseases, which has been accepted for and is pending publication in the Journal of Pediatrics. I plan to continue my research endeavors in global health and pediatric infectious diseases throughout the remainder of my pediatric residency and beyond.
    1. **Quincer, E**, Jaggi, P. Nicolau syndrome: A rare complication following intramuscular injection. The Journal of Pediatrics. Forthcoming.

D. Research Support

None.

The effect of isoniazid preventive therapy in pregnancy on infant outcomes
PI: Dr. Elizabeth Quincer
Co-Mentors: Dr. Lisa Cranmer, Dr. Dickens Onyango

1. Study Population Characteristics

   a. *Study Population*
   Approximately 1,000 women will be screened, and 500 eligible HIV-positive, pregnant women and their infants will be enrolled (250 women with IPT use during pregnancy and 250 with IPT use outside of pregnancy). Inclusion criteria include: known HIV-positive status at time of pregnancy, isoniazid preventive therapy (IPT) initiation and completion of at least 3 months of IPT. Exclusion criteria include known HIV-negative status or unknown HIV-status at time of pregnancy. Chart review of records dating September 2015 to present time will be included. Interview data will also be collected on a subset of individuals.

   b. *Enrollment Table*

Racial Category	**Ethnic Categories**				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native					
Asian					
Native Hawaiian or Other Pacific Islander					
Black or African American	500				
White					
More than One Race					
Total					500

2. Protection and Monitoring Plans

   a. *Protection of Human Subjects*
   Human subject data will be included in order to assess the safety of this therapy in human populations. IPT initiation in HIV-positive individuals and pregnant women is the recommendation of many national and global guidelines, and therefore, the determination of the safety for infants is warranted. Aim 1: As national guidelines have been rolled out in Kisumu, Kenya, that directly impact the populations living there, 3 health facilities in the region were chosen for data collection. Abstracted data from these human subjects' charts will include maternal age, date and timing of IPT initiation, including weeks gestational age, date of IPT completion or discontinuation and reason, if any, stated for discontinuation, ART status, CD4 count and maternal side effects or AE. Abstracted infant data will include pregnancy outcome, gestational age, birth weight, congenital anomalies, stillbirth, neonatal death, and any other reported infant adverse events. Identifiable information (Medical record numbers and date of birth) will be obtained to link participant data in the chart review; these data will be recorded in a link log that will maintained in a locked study cabinet and will be destroyed after data collection is complete. All de-information will be stored on password-protected electronic device. Aim 2: Pregnant women will be recruited from antenatal care clinics at the same 3 health care facilities, and informed consent will be obtained from women interested in the study. Interviews will occur in a private location with members

of the research team present. Risks to the individuals participating in the study include breach of confidentiality, and all measures will be taken to minimize this risk (see below).

b. *Protection Against Risks*
Aim 1: Subjects will initially be recruited for chart review based on inclusion and exclusion criteria, as described above from 3 health care facilities in Kisumu County, Kenya. Informed consent for the retrospective chart review will be waived, pending final review from both Kenyan and Emory IRB committees. Study team members involved in data abstraction are trained in human subjects research and protection of confidentiality. Any identifiable information (medical record number, date of birth) will be collected on a link log that will be stored in a locked study cabinet within a locked study room only accessible to study team members. Link logs will be destroyed after data collection is complete. De-identified data will be stored in a password-protected database. Aim 2: Approximately 10 women from each of the 3 health facilities will be recruited and will be eligible for enrollment if they are older than age 18, newly diagnosed with HIV in the preceding 6 months, and currently pregnant. In-person informed consent will be obtained for all in-person interviews in the language preferred by the participant (English, Dholuo, or Kiswahili). All reasonable measures will be taken to safeguard the confidentiality and privacy of the data abstracted in order to protect these populations. It is expected that no identifiable information will be collected for Aim 2; this non-identifiable data will stored on a password protected device. It will only be shared with individuals directly associated with the research.

c. *Potential Benefits of Proposed Research to Human Subjects and Others*
While there will be no direct benefit to participants in this study, the results of the study will be useful in understanding the safety of IPT for pregnant women and their infants for future populations. In addition, interview data may help clinicians understand the considerations that women make when they decide to initiate IPT, would be useful for allowing clinicians to relate to and motivate these patients in a shared decision-making process. As IPT-use during in HIV-infected individuals during pregnancy is currently a guideline in a number of countries, including Kenya, this information will be valuable in further understanding the safety of this therapy in infants born to these mothers.

d. *Importance of the Knowledge to be Gained*
Potential knowledge to be gained includes information on the safety of IPT and effect on infant outcomes. Knowledge of the consideration's women make when they determine to initiate IPT will also be gained. Both of these areas have limited information to date.

e. *Data and Safety Monitoring Plan*
Not applicable as proposed study is not a clinical trial.

3. Protocol Synopsis

a. Statistical Design and Power
A retrospective cohort study using chart review will be utilized. Sample size calculations are based on the following assumptions: $\alpha = 0.05$, $\beta = 0.20$ (power = 0.80), and sample size ratio 1:1. Assuming a 15% baseline rate of a poor infant outcome, we must sample 250 mother-infant dyads per group in order to detect a 10% difference between women who completed IPT antepartum and women who completed IPT prior to pregnancy. We will aim to screen 1000 women in order to ensure enough women (500) will meet inclusion criteria. Further details can be found in the Methods/Experimental Design section of the application.

b. *Will the study use FDA-regulated intervention?* No

EMORY UNIVERSITY SCHOOL OF MEDICINE

Department of Pediatrics
Division of Pediatric Infectious Diseases

April 15, 2019

Department of Pediatrics
Division of Pediatric Infectious Diseases

To: Fellow Research Fund Re: Mentor Letter of Support

This letter is in enthusiastic support of Dr. Elizabeth Quincer's application for the Resident Research Fund pilot grant. Dr. Quincer is a second-year pediatric resident who is hoping to pursue a long-term academic career in global pediatric infectious diseases. She is a well-qualified candidate who has developed skills in research and global health throughout her clinical and pre-clinical career. Dr. Quincer completed a Bachelor's degree at Concordia College and an MD degree from Chicago Medical School. Her commitment to excellence is underscored by several awards throughout her career to date, including the National Honor Society in Neuroscience and a Global Health Scholarship at Chicago Medical School. Dr. Quincer has worked in the field of neuroscience as an undergraduate and as a medical student she investigated health systems in Rwanda; she has presented her research at national conferences and has submitted a case report to the Journal of Pediatrics. Currently, she is a pediatric resident on the Global Health Scholars Track at Emory, and has contributed to several projects in the field of global pediatric infectious disease, including research on the effectiveness of influenza vaccination and work through the Child Health and Mortality Prevention Surveillance (CHAMPS) Network.

For her Resident Research Fund application, Dr. Quincer he has focused on understanding the effect of maternal isoniazid preventive therapy (IPT) during pregnancy on infant health outcomes. While IPT reduces the rate of TB in HIV-infected populations and is recommended for use regardless of pregnancy status, there are few data to inform the safety of this approach. Preliminary data from the IMPAACT 1078/TB APPRISE randomized clinical trial demonstrated poorer infant outcomes when IPT was used during pregnancy compared to postpartum (Gupta et al. CROI 2018), but analysis of a prospective cohort in South Africa found IPT was associated with reduced rates of infant prematurity (Salazar et al. CROI 2019). No programmatic data have been published to date, yet Kenya has rolled out wide-scale implementation of IPT, with high uptake among antenatal programs where many women are diagnosed with HIV for the first time. Along with my collaborators at University of Washington, we recently found nearly 50% of IPT was initiated during pregnancy among HIV-infected peripartum women at health care facilities in Kisumu, Kenya (LaCourse et al. JAIDS in press). The proposal that Dr. Quincer suggests is ideal to determine IPT safety and evaluate maternal acceptability of IPT use in pregnancy, and either positive or negative results of this study will be important. Dr. Quincer's co-mentor Dr. Onyango at the Kenya Ministry of Health has conducted research on pediatric IPT and is currently mentoring a postdoctoral fellow Dr. Odhiambo on a complementary study to investigate the effect of IPT in the peripartum on maternal outcomes. Drs. Onyango and Odhiambo will provide in-country support to Dr. Quincer to facilitate her research and trouble-shoot any potential challenges that arise. The pilot grant from the Fellow Research Fund will support research assistants to help with data collection through collaboration with SWAP, an NGO with local experience in conducting maternal and child health research, who have an existing collaboration with Drs. Onyango and Odhiambo. Dr. Quincer's proposal leverages existing resources and provides an efficient approach that is possible within the scope of the research grant.

Emory University School of Medicine
2015 Uppergate Drive
Atlanta, Georgia 30322

Tel 404-727-5642
Fax 404-727-9223

The Robert W. Woodruff Health Sciences Center

EMORY UNIVERSITY SCHOOL OF MEDICINE

Department of Pediatrics
Division of Pediatric Infectious Diseases

I am committed to providing mentorship for the proposal, with input at least weekly. I will provide training and mentorship on study design, data analysis and manuscript preparation. I am a junior faculty mentor and currently funded through an NIH K23 award with dedicated time for research. I have led a randomized clinical trial and 2 cohort studies while based in Kisumu, Kenya where Dr. Quincer's study will take place, and have published 20 manuscripts in the field of maternal and child TB/HIV. My substantive experience conducting TB/HIV research in Kenya for the past 7 years has provided me with the foundational skills needed to mentor Dr. Quincer on her proposed project, and I envision that Dr. Quincer's experience conducting the proposed study will serve as a rich opportunity to guide her future research endeavors in pediatric infectious disease.

In summary, Dr. Quincer is a superb candidate, the proposal is unique and innovative and has potential to yield important new insights in the field of maternal and child health, and I am committed to providing careful mentorship and collaborations. I believe that Dr. Quincer would be an ideal recipient for the Resident Research Fund grant.

Sincerely,

Lisa M. Cranmer, MD, MPH
Assistant Professor
Division of Pediatric Infectious Disease Emory University School of Medicine

Emory University School of Medicine
2015 Uppergate Drive
Atlanta, Georgia 30322

Tel 404-727-5642
Fax 404-727-9223

COUNTY GOVERNMENT OF KISUMU

Telegrams: "PRO.(MED)"
Tel: 254-057-2020105
Fax: 254-057-2023176
E-mail: kisumucdh@gmail.com

When replying please quote:

County Director of Health,
Kisumu.
P. O. Box 721-40100,
KISUMU.

DEPARTMENT OF HEALTH

RE: GN 133 VOL. IX (415) **Date: 11th April 2019**

Dear Pediatric Research Alliance Resident Research Fund Committee,

RE: LETTER OF SUPPORT FOR DR ELIZABETH QUINCER

I am pleased to collaborate with Dr. Elizabeth Quincer and other co-investigators from Emory University, Kenya Ministry of Health, Centers for Disease Control and Prevention, and University of Washington on the proposed project "The effect of isoniazid preventive therapy use in pregnancy on infant outcomes" I will support Dr. Elizabeth Quincer as a co-mentor along with Dr. Lisa Cranmer on this study. I have expertise working in various areas of the public health sector in Kenya and am currently involved in research investigating maternal uptake of IPT. I will provide field-site mentorship, logistical support, and clinical expertise for successful execution of the proposed work.

Tuberculosis remains a major cause of mortality and mortality globally. HIV-infected pregnant women and their infants represent two populations who are particularly impacted. HIV-infected women with TB disease during pregnancy have higher rates of poor maternal outcomes, and their infants similarly experience increased mortality and worse outcomes. Isoniazid preventive therapy (IPT) decreases the risk of TB disease in HIV-infected individuals when combined with antiretroviral therapy. Guidelines surrounding IPT administration have been released in many global and national contexts. Kenya rolled out IPT guidelines in September of 2015, which mirror World Health Organization guidelines and state that IPT can be initiated at any time during pregnancy. Although IPT administration during pregnancy to prevent TB may benefit both mothers and infants, to date, there is limited data on the effect of maternal IPT on infant safety outcomes. This project aims to contribute to the understanding of infant safety outcomes of IPT use in pregnancy in order to inform national Kenyan guidelines and global health public policy.

The proposed study will advance the data on infant safety of IPT administration in pregnancy. At least 2 studies to date have completed research in this area and found differing results. Therefore, further research is needed, and Dr. Quincer's proposed project will be an important addition to the growing body

of knowledge. Our research team in Kisumu is excited to participate in this important project. The Kenyan Ministry of Health has completed evaluations surrounding IPT initiation and is currently performing research surrounding maternal uptake of IPT, which will compliment Dr. Quincer's proposed research. We are committed to support Dr. Quincer to liase with local health facilities, obtain local ethical approval for her study, and guidance as she collects and analyzes the data. Given our ongoing work on maternal IPT using similar research methods, we are well-suited to support the execution of this project in Kenya.

Dr. Quincer is well qualified to engage in this important research endeavor. Her clinical training in pediatrics and interests in clinical infectious disease and epidemiology will serve her well. With the support of myself and Dr. Lisa Cranmer, she will have a strong foundation for successful execution of the proposed study.

Sincerely,

Dr. Onyango D.
County Director of health
Kisumu County.

Off Aga Khan Rd
Milimani Estate
P.O. Box 3323-40100
KISUMU, KENYA
Tel: 0202030712
Website : www.swapkenya.org

11th April 2019

Dear Dr. Quincer,

RE: Resident Research Grant submission, "The effect of maternal isoniazid preventive therapy in pregnancy on infant outcomes"

I am pleased to offer the support and assistance of the Safe Water and AIDS Project (SWAP) to provide research staff assistance to your proposed project, "The effect of maternal isoniazid preventive therapy in pregnancy on infant outcomes."

SWAP has worked in Western Kenya since 2005 on various public health research and implementation projects, in the areas of water and sanitation as well as projects involving maternal and child health and HIV. We have strong experience in research data collection and collaboration with the Ministry of Health and local health facilities where you will conduct this research.

Your proposal addresses an important question affecting HIV-infected mothers and their children. Given the rapid roll-out of isoniazid preventive therapy (IPT) in Kisumu, it is of utmost importance to determine whether IPT used during pregnancy will affect infant birth outcomes. We are excited to contribute to this endeavor and will be able to provide two research staff assistants to work with you for 1 month to execute your project at a rate of 10 USD per day per research assistant. We are available to provide ongoing advice, training and supervision for your staff as they collect data and cope with any challenges that may arise.

I wish you well in your application and am enthusiastic about the opportunity to assist your studies.

Yours sincerely,

Alex Mwaki
Country Director

Spring 2019 Resident Research Fund
Budget Template

Title:
PI: Elizabeth Quincer
Budget Prepared By: Elizabeth Quincer
Project Start Date: 7/1/2019
Project End Date: 6/30/2020
Length of Project (months): 12
Maximum budget $2,500

Personnel	**Role**	**Days**	**Salary per Day**	**Total**
TBA Research Assistant	Research Assistant	30.00	$ 10	$ 300
TBA Research Assistant	Research Assistant	30.00	$ 10	$ 300
Subtotal				**$ 600**

Non-Personnel
Laboratory/Office Supplies
Clinical Research Costs

Other Expenses	**Months**	**Rate**	
Monthly International Phone Travel Plan	2	$ 130	$ 260
Housing in Kenya	2	$ 445	$ 890

Pediatric Cores	**Hours**	**Salary per Hour**	
Biostatistics Core	15	$ 50	$ 750
Children's Clinical & Translational Discovery Core			
Biomarkers Core			
Flow Cytometry Core			
Animal Physiology Core			
Integrated Cellular Imaging Core			
Other Core(s), as needed			**$ 1,900**
Total Costs			**$ 2,500**

Resident Research Fund

Research Plan

Are you a previous Resident Research Fund awardee who is applying for a second year of funding for your original project?

No

Project Title

If you are a previous awardee applying for a second year of funding, please ensure your project title is exactly the same as your original project title.

The effect of maternal isoniazid preventive therapy in pregnancy on infant outcomes

Abstract

Global and national guidelines recommend the use of isoniazid preventive therapy (IPT) to reduce tuberculosis (TB) disease in people living with HIV and AIDS (PLWHA), as these individuals are at increased risk of TB acquisition in endemic countries. HIV-infected mothers and their infants have higher rates of TB infection, disease progression, and mortality and may benefit from IPT; however, there is a paucity of data on the safety of IPT in pregnancy and its impact on infant outcomes. Preliminary data from the IMPAACT P1078/TB APPRISE Study Team and the Tshepiso study found differing results with poorer infant outcomes and no impact on infant outcomes in the setting of IPT administration in the peripartum period, respectively. Given these findings and the fact that, to date, no programmatic data have been published, additional research is needed. National guidelines recommending universal implementation of IPT in PLWHA were established in Kenya in 2015, and Kenya has had rapid uptake of IPT in antenatal care among HIV-infected pregnant women to date. We propose to evaluate whether maternal IPT during pregnancy is associated with poorer infant outcomes and assess maternal considerations leading to the decision to initiate and complete IPT during pregnancy. A retrospective chart review of antenatal and birth records of mother-infant dyads between 2015-2018 and interview data from 3 health care facilities in Kisumu, Kenya will be utilized. These findings have implications not only for informing Kenyan national and global policies on the use of IPT during pregnancy but also on sociocultural considerations surrounding IPT acceptability and completion in women of childbearing age.

Hypothesis/Detailed Specific Aims/Research Goals

Maximum one page

**.pdf*

Specific AimsResearch Goals_EQRRF_1.3.pdf

Methods/Experimental Design

Maximum two pages

Must include expected results and conclusions. Please also include a brief description of any critical co-investigators or collaborators who will be necessary and involved in this research project.

**.pdf*

MethodsExperimental Design_EQRRF_1.4.pdf

Progress Report for Second Year

Maximum one page. The progress report is required only for previous awardees who are applying for a second year of funding.

This report should include a brief update on your project and an explanation of why additional funding is needed (e.g. additional funding is needed to complete the original project due to unforeseen circumstances, additional specific aims or hypotheses will be tested, etc.). Be sure to specifically address how a second year of funding would enhance your project.

**.pdf*

Impact and Relevance to Child Health (2-4 sentences)

Globally, TB remains the leading cause of death due to a single infectious agent, and it is known that both HIV and pregnancy increase the risk of TB disease. Isoniazid preventive therapy (IPT) reduces the risk of TB; however, more research is needed in order to determine the safety of IPT to the infant when used during pregnancy. This research will shed light on this area in not only assessing the impact of IPT on infant birth outcomes, but also evaluating maternal considerations on the acceptability of IPT in pregnancy. Given programmatic guidelines on IPT from a number of countries worldwide and the World Health Organization, additional research surrounding infant outcomes on the implementation of IPT during pregnancy is necessary and timely.

Please provide a brief statement explaining how these funds will facilitate your research objectives.

In brief, funds from the resident research grant will be utilized to pay in-country personnel to assist in data collection, conduct of interviews, and translate interview material. Additional allocation of funds will be used for international telephone services. A portion of the funds will also be dedicated to aid with statistical analyses through the Emory + Children's Biostatistics Core. Finally, remaining funds will be used to augment the pediatric residency program's contribution for lodging while in Kisumu, Kenya for the resident investigator in order for this individual to complete data collection. Please refer to detailed description in budget.

How will you communicate the results of this project (e.g. present an abstract at a regional or national meeting in your field, publish a manuscript, submit a grant application to further the research project, etc.)?

We will plan to submit an abstract of our findings in April 2020 to the International Union Against Tuberculosis and Lung Disease World Conference in the fall of 2020 and will publish 2 manuscripts within a year of grant completion.

Please select all pediatric cores that will be used by this project.

Biostatistics

Please enter any other cores used by this project that are not listed above (such as the Winship Biostatistics Core, RSPH Biostatistics Core, etc.).

Principal Investigator & Mentor

Please note: When uploading attachments in this application, you must click "Upload" after selecting your file.

Principal Investigator

Prefix

Dr.

First Name

Elizabeth

Last Name

Quincer

Suffix

Degrees

MD

Current Work Email Address

elizabeth.quincer@emory.edu

Personal Email Address

equincer@gmail.com

Mobile Phone

218-639-1570

Primary Academic Institution

Emory University

Primary Academic Department

Emory University-School of Medicine-Department of Pediatrics

What is the end date of your pediatric residency training program?

June 30, 2020

PI Biosketch

Instructions for Required NIH Format

Example Biosketch for Postdoctoral Researchers

It is not necessary to include a "Scholastic Performance" section in your biosketch.

**.pdf*

EMQ Biosketch_EQRRF_1.1.pdf

Primary Academic Position Title

Resident

Primary Mentor

Prefix

Dr.

First Name

Lisa

Last Name

Cranmer

Suffix

Degrees

MD, MPH

Email

lisa.cranmer@emory.edu

Mobile Phone

303-842-7777

Primary Academic Institution

Emory University

If your mentor's primary academic institution is not listed, please enter it here.

Primary Academic Department

Emory University-School of Medicine-Department of Pediatrics

If your mentor's primary department is not listed, please enter it here.

Mentor Biosketch

NIH Format Required

*.pdf

LMC Biosketch_EQRRF_1.1.pdf

Co-Mentor (if applicable)

Prefix

Dr.

First Name

Dickens

Last Name

Onyango

Suffix

Degrees

MD, MS

E-mail

macdickens2002@gmail.com

Mobile Phone

Primary Academic Institution

Institution Not Listed

If your co-mentor's primary academic institution is not listed, please enter it here.

Ministry of Health, Kenya

Primary Academic Department

Department Not Listed

If your co-mentor's primary department is not listed, please enter it here.

County Director of Health

Co-Mentor Biosketch

NIH Format Required

*.pdf

DOO Biosketch_EQRRF_1.0.pdf

Human Subjects & Vertebrate Animals

Human Subjects Research

Please direct all IRB-related questions to the appropriate IRB.

Is this project a clinical trial?

No

Does this project involve human subjects research?

Yes

The following upload and IRB status question are required ONLY for projects involving human subjects research:

Human Subjects Information

Please follow the Human Subjects Research and Clinical Trials Information outline provided in the RFA.

*.pdf

Human Subjects Research and Clinical Trials Information Form_EQRRF_1.3.pdf

IRB Status

Not Yet Submitted

If your IRB protocol has been approved, please enter your IRB number and expiration date and upload your IRB approval or determination letter.

IRB Number

IRB Expiration Date

IRB Approval/Determination Letter

*.pdf

Vertebrate Research

Does this project involve vertebrate animals?

No

The following upload and IACUC status question are required ONLY for projects involving vertebrate animal research:

Vertebrate Animals Section

NIH Format Required

*.pdf

IACUC Status

If your IACUC protocol has been approved, please enter your protocol number and expiration date and upload your IACUC approval letter.

IACUC Project Number

IACUC Expiration Date

IACUC Approval Letter

**.pdf*

Letters of Support

Please upload a letter of support from your mentor and any co-mentors or collaborators whose involvement is critical to the proposed research project.

Mentor Letter of Support

**.pdf*

Cranmer LOS_Quincer_RRG.pdf

Co-Mentor Letter of Support

**.pdf*

Onyango LOS_EQRRP_1.0.pdf

Other Letter of Support 1

**.pdf*

SWAP LOS_EQRRF_1.0.pdf

Other Letter of Support 2

**.pdf*

Other Letter of Support 3

**.pdf*

Budget

Project Period

Project Start Date

July 01, 2019

Project End Date

June 30, 2020

Budget

Total Amount Requested

Max: $2,500

2500

Line Item Budget

You must use the budget template included on the website. Please see the website for budget requirements and restrictions. Reminder: These are not travel awards; funds may not be used for travel.

**.xls, *.xlsx*
Line Item Budget_EQRRF_1.1.xlsx

Detailed Budget Justification

An example of an adequately detailed budget justification is available on the website.

PERSONNEL
TBA Research Assistant
The research assistants provided through SWAP-Kenya will assist with data collection, interviews, and translation services. The assistants have been working with the in-country Ministry of Health team on data collection for a related study by Dr. Odhiambo and are familiar with the health care registers and have received human subjects training. These individuals will be paid through a fee-for-service mechanism through SWAP-Kenya. This individual's daily rate is 1000 Kenyan schillings (~10 USD)/day x 30 business days x 2 research assistants = $600

OTHER EXPENSES
International Phone Travel Plan
Verizon's international travel plan is $130/month x 2 months = $260. An in-country phone will be necessary to make calls to the team and for interviews.

Housing in Kenya
As the resident applying for this research will be doing a majority of the data collection during the in-country time, assistance with housing costs is necessary. Other travel expenses (airfare, per diem) will be subsidized through the Pediatric Residency Global Health Program. Housing cost is estimated at $445/month x 2 months = $890.

PEDIATRIC CORE COSTS
Biostatistics expertise: 15 hours x $50 = $750 is requested for assistance in study design and analytical expertise required to analyze the proposed aims of this study.

Final Step

Suggested Reviewers (Optional)

Please use the following space to suggest a potential expert reviewer(s) for this grant who would not have a conflict of interest in serving as a reviewer.

Please note: For the purposes of these awards, a potential reviewer is considered to be in conflict if she/he:

- *Has an active role in the project.*
- *Is in the same laboratory.*
- *Has a formal mentor/mentee relationship with the applicant or his/her mentor.*
- *Is the applicant's director, supervisor or division director.*

- *Has another personal, professional, or financial relationship/interest in the applicant, mentor or project.*

Dr. Martha Rogers

Signature

Please type your full name as an electronic signature that you attest that this application is true and complete to the best of your knowledge.

Elizabeth Mary Quincer

Program Area

Resident Research Fund