

SUMMARY STATEMENT

PROGRAM CONTACT:
SUDHA SRINIVASAN
240-627-3062
sudha.srinivasan@nih.gov

(Privileged Communication)

Release Date: 09/14/2018

Revised Date:

Application Number: 1 K01 AI138620-01A1

Principal Investigator

ROSS, JENNIFER M

Applicant Organization: UNIVERSITY OF WASHINGTON

Review Group: **AIDS**
Acquired Immunodeficiency Syndrome Research Review Committee
AIDS - EXP. REV.

Meeting Date: **08/30/2018** *RFA/PA:* **PA18-369**
Council: **OCT 2018** *PCC:* **A11A**
Requested Start: **09/01/2018**

Project Title: **Modeling approaches to prioritize TB prevention among people with HIV in Uganda**

SRG Action: **Impact Score: [REDACTED]**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **3A-No children included, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
1	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]
3	[REDACTED]	[REDACTED]
4	[REDACTED]	[REDACTED]
TOTAL	[REDACTED]	[REDACTED]

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the **COMMITTEE BUDGET RECOMMENDATIONS** section.

Text from the application is copyrighted. The awardee provided express permission for NIAID to post the grant application and summary statement for educational purposes. The awardee allows you to use the material (e.g., data, writing, graphics) they shared in the applications for nonprofit educational purposes only, provided the material remains unchanged and the principal investigators, awardee organizations, and NIH NIAID are credited.

Freedom of Information Act (FOIA). NIAID is strongly committed to protecting the integrity and confidentiality of the peer review process. When NIH responds to FOIA requests for grant applications and summary statements, the material will be subject to FOIA exemptions and include substantial redactions. NIH must protect all confidential commercial or financial information, reviewer comments and deliberations, and personal privacy information.

Contact Information. Email NIAID's Office of Knowledge and Educational Resources at deaweb@niaid.nih.gov

RESUME AND SUMMARY OF DISCUSSION: This exceptional resubmission application for a Mentored Research Scientist Development Award (K01) entitled “Modeling approaches to prioritize TB prevention among people with HIV in Uganda” was submitted by the University of Washington, Seattle, WA and supported by Dr. Ruanne Barnabas (Primary Mentor, University of Washington), Dr. David Dowdy (Johns Hopkins University, co-mentor) and Drs. Simon Hay and Judith Wasserheit (University of Washington, co-mentors). This research goal of this K01 application seeks to maximize the public health impact of preventive therapy (PT), for TB in HIV-infected individuals using geospatial models integrating available epidemiologic information in Uganda. Three Specific Aims are planned and results from this work have the potential to introduce novel tools for PT implementation.

The review committee identified many strengths in this K01 application. This is a very strong candidate with a well-described plan for integration of TB and HIV surveillance, incidence and prevalence to enhance the efficiency and effectiveness of public health programs for both infections. The candidate is supported by strong a strong mentoring team and there is confidence that this entire research group can lead the candidate to success. The candidate has been largely responsive to prior critiques, and the minor weaknesses of the application and approach can be easily addressed.

There were minor weaknesses identified by the review committee the did not affect the score. There are minor concerns about the amount of planned didactic work in Year 1 and its effect on planned field work. Reviewers were unclear if differences in Urban and rural incidence and migration patterns were fully considered and if these were included in the district level mapping. There are minor concerns that local and national political and economic issues have not been fully considered. There are also minor concerns that the candidate has not addressed the conditionality of Aims 2 and 3 on the validation of the model in Aim 1, and the availability of molecular epidemiology data

Based upon the evaluation of scientific and technical merit, this application received an Overall Impact/Priority score of [REDACTED]

DESCRIPTION (provided by applicant):

The goal of this proposed K01 mentored career development award is to support Dr. Jennifer Ross’s research training in the advanced epidemiologic methods of geospatial and mathematical modeling of HIV and tuberculosis (TB) to further her goal of developing targeting strategies for prevention of TB among people living with HIV (PLHIV). Dr. Ross is currently an Acting Instructor/Senior Fellow in infectious diseases at the University of Washington. This award will support her development in modeling methods and implementation science to facilitate her transition to becoming an independent investigator. She will receive mentorship from Dr. Ruanne Barnabas, Professor Simon Hay, Dr. David Dowdy, and Dr. Judith Wasserheit for this award. The research goal of the award is to maximize the public health impact of preventive therapy (PT), either with isoniazid alone or with rifapentine, for TB prevention in HIV-infected individuals using cutting-edge geospatial models that integrate existing epidemiologic information. TB is the leading cause of death among PLHIV in sub-Saharan Africa, including those recently started on antiretroviral (ART) therapy in Uganda. PT prevents tuberculosis and TB-associated mortality among PLHIV, but fewer than 5% of eligible Ugandans receive it due to limited resources to successfully implement PT programs. This award will marry the expanding sources of TB and HIV surveillance data in Uganda with the expertise at UW and the Institute for Health Metrics and Evaluation in spatiotemporal and mathematical modeling to produce novel tools that guide PT implementation. This K01 proposal will inform the prioritization of PT through three research aims. In the first aim, Dr. Ross will examine the relationship between ART coverage and geographic predictors of TB with TB prevalence, incidence, and mortality among PLHIV using geospatial and mathematical models. In the second aim, Dr. Ross will estimate the impact of PT implementation on HIV-TB mortality

using mathematical models of a regionally- targeted implementation strategy versus uniform roll-out. Finally, in the third aim, Dr. Ross will engage stakeholders to inform model development, evaluate the effect of engagement with the model on stakeholder support of modeling, and facilitate implementation of targeted TB prevention. This award will support Dr. Ross to dedicate more than 75% of her effort to research as she furthers her learning in the methods and application of state-of-the-art geospatial and mathematical modeling techniques. Acquiring these advanced skills will facilitate her future R01 proposals. With her clinical training in infectious disease, her outstanding mentorship, and the support of this award to further develop her expertise, Dr. Ross will be well-positioned to contribute to the control of TB and HIV epidemics in sub-Saharan Africa.

PUBLIC HEALTH RELEVANCE

This study will develop mapping and modeling tools to guide use of the antibiotic isoniazid for preventing tuberculosis (TB) among people with HIV infection. This study takes place in Uganda, where TB is the leading cause of death among people with HIV, and is important for global health because TB is among the leading causes of death for the more than 35 million people living with HIV worldwide. The tools developed may help to stretch limited health resources by identifying the places where prioritizing isoniazid use could have the greatest health impact.

CRITIQUE 1

Candidate:

Career Development Plan/Career Goals /Plan
to Provide Mentoring:

Research Plan:

Mentor(s), Co-Mentor(s), Consultant(s),
Collaborator(s):

Environment/Commitment to the Candidate:

Overall Impact:

Training in advanced epidemiologic methods of geospatial and mathematical modeling of HIV and tuberculosis (TB) to develop targeting strategies for prevention of TB (best use of IPT) among people living with HIV (PLHIV). Integration of TB and HIV surveillance, incidence and prevalence in the context of ART and TB treatment programs is critical to the efficiency and effectiveness of public health programs to treat both infections and prevent the re-activation and transmission of TB. The plans now include a modification of the schedule as for a 4-year assessment. The proposed modeling is an extension of the Global burden of disease and dynamic transmission models which have been developed by her mentors. Adding the exquisite granularity of district-level data collected by the MOH and DHS. The candidate will produce implementation data obtained through interviews and “gamification” of the dynamic model. The creation and sustainability of an HIV/TB “Dashboard”, the uptake of modeling outcomes by policy makers and the application of modeling to other African countries is a daunting task. But the experience of her mentors, the years she has invested in GIS and dynamic modeling will pay off. There are no better groups positioned to implement these IT solutions than UW, IHM and Professor Hay. Strong mentorship from Dr. Barnabas and a well-constructed team means that the project will have full support of modelers and economists interested in optimizing TB prevention.

1. Candidate Strengths

- The candidate spent 11 months in Uganda (2015-2016) as a Fogarty Global Health Research Fellow, using GIS mapping and statistical modeling to estimate the impact of cotrimoxazole scale up for PLHIV on population malaria burden and is preparing a manuscript on that project. She also developed collaborations with the Uganda National TB and Leprosy Program, US CDC and local universities.
- As a resident, she traveled to Uganda to interview patients about TB symptoms and care and learned to use GIS mapping software to develop a geospatial model of access to TB care/travel time in the program's TB surveillance network. She published a first author manuscript from that work. She also began working with Dr. Barnabas on a study of modeling the impact of valacyclovir on HIV disease progression and transmission at population level (manuscript under review).
- The candidate has 2 first (or co-first) author publications directly relevant to the proposed study.
- The candidate is currently leading the development of the Institute for Health Metrics and Evaluation's first geospatial TB incidence and mortality model in Brazil with Professor Hay. This serves as a test case for a high TB burden country with excellent mortality and TB notification data that will allow development of techniques for areas with more limited data. She is also working with Dr. Barnabas on a patient-level meta-analysis of the impact of IPT plus ART for the WHO.
- The candidate has a CFAR award to determine contributing causes of death in persons with HIV in Brazil using novel machine learning algorithms.
- Mentor letters speak to her leadership ability and creativity in addition to her strong quantitative training and skills.

Weaknesses

- None noted.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring

Strengths

- Training Aims align well with scientific Aims.
- Team members relevant expertise and roles for mentorship are clearly articulated.
- Coursework reflects needed skills in data management, statistical methods in spatial epidemiology, disease modeling and data visualization.
- Plan for taking a course specifically about writing research applications during Year 2 in addition to the scientific courses is a strength.

Weaknesses

- There are minor concerns that didactic work is very heavy in Year 1 and it may be difficult to accomplish considering planned field work.
- Weekly meetings with Hay and Dowdy for 4 years may be unrealistic.

3. Research Plan

Strengths

- Use of vital registration data, DNS and surveillance data and experience of the PI as Fogarty fellow included mapping the scale-up of ART by district from 2010 to 2015 using data from PEPFAR and Uganda's national electronic health surveillance database, DHIS-2.
- The model developed by Dr. David Dowdy, mentor for this proposal, to estimate the impact of IPT on the HIV-TB co-infection epidemic in Rio de Janeiro, Brazil, provides a good starting point. This deterministic compartmental model has compartments for people who are TB-uninfected, have latent TB infection (with or without IPT), active TB, and are recovered.
- The 3rd aim, assessing the response of policy and stake-holders to the presentation of data as either a passive lecture with question/answers or the "gamification" of TB prevention/intervention with the ability to input variables and observe predictions is a very interesting social-science, marketing and media experiment.

Weaknesses

- The anticipated roll-out of INSTIs as first-line therapy is likely to impact on viral suppression and transmission and the reactivation and acquisition of TB.
- Five-fold differences in Urban and rural incidence findings begs the question of rural urban and migration patterns. Is this included in the district level disease mapping?
- It is unclear if there are sending and receiving sites in rural and urban communities.
- It is unclear if local and national political and economic issues been considered. Do regional and local differences in surveillance, health care delivery and data quality inform measurement and response to prevalence/incidence? Community vs clinic-based ART is mentioned which is presumably a different mix in each district.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s)

- The support team for this work is strong. Dr. Ruanne Barnabas as Primary mentor will offer intensive mentoring for all aims. Mathematical modeling of the impact of HIV co-infections and care interventions.
- Cost-effectiveness analysis is a strength. implementation of HIV care in Uganda weekly in person with Prof. Simon Hay Co-mentor, Aims 1.
- Geospatial modeling of infectious disease burden data visualization and communication of modeling analyses Weekly in person with Dr. David Dowdy Co-mentor Aims 1 and 2.
- Mathematical modeling of HIV-TB co-infection Monthly via Skype with Dr. Judith Wasserheit Co-mentor Aim 3.
- Evaluation of stakeholder engagement Monthly in-person Dr. Yukari Manabe Advisor Aims 2 and 3.
- Assessment of TB prevention interventions in Uganda Engagement with TB stakeholders in Uganda Monthly via Skype Dr. Stella Zawedde-Muyanja Advisor Aims 1 and 3.
- Interpretation of TB surveillance data Engagement with TB stakeholders in Uganda.
- Monthly meetings via skype.

Weaknesses

- How much programming from IHME?
- Will it be possible to take the courses in year 1-3 and accomplish field work in Uganda and conduct weekly meetings with Dowdy and Hay?

5. Environment and Institutional Commitment to the Candidate

Strengths

- The UW Department of Global Health, ICRC and affiliated Institute for Health Metrics and Evaluation provide an exemplary environment to support the candidate.
- Strong connections with relevant groups in Uganda such as the National TB and Leprosy Program and CDC will assist with feasibility of obtaining appropriate datasets. There is a letter of support from the Minister of Science, Technology, and Innovation from Uganda.

Weaknesses

- None noted

CRITIQUE 2

Candidate:

Career Development Plan/Career Goals /Plan
to Provide Mentoring:

Research Plan:

Mentor(s), Co-Mentor(s), Consultant(s),
Collaborator(s):

Environment/Commitment to the Candidate:

Overall Impact:

This is a resubmission application from Dr. Jennifer Ross, an infectious disease fellow at University of Washington, who received her MD and MPH in Epi/Biostatistics from Oregon Health and Science University and completed residency at University of California, San Francisco. The purpose of this K01 is to support her research training in advanced epidemiological methods of geospatial and mathematical modeling of HIV and TB to further her goal of developing targeted strategies for TB prevention. The application seeks to inform the prioritization of TB preventive therapy (INH alone or with rifapentine) through 3 specific aims. The research Aims are 1) to examine the relationship between ART coverage and geographic predictors of TB with TB prevalence, incidence and mortality among PLHIV using geospatial and mathematical models with inputs from surveillance datasets using geospatial and mathematical models; 2) to estimate the impact of TB preventive therapy implementation on HIV-TB mortality using mathematical models of a regionally-targeted implementation strategy versus uniform roll-out; and 3) to engage stakeholders to inform model development, evaluate the effect of engagement with the model on stakeholder support of modeling and facilitate implementation of targeted TB prevention.

The candidate has been responsive to the prior critiques. Namely, she is now requesting 4 years of support, given her prior training in GIS and modeling. She has decreased the number of didactic coursework in year 1, when field work in Uganda would also be needed. The candidate has clarified her career goals, to work at the intersection of mathematical modeling and implementation science. She has now added information regarding prior K mentorship for the mentors; Dr. Barnabas has had two prior 2 K awardees, as has Dr. Dowdy (though this is not stated in their letters of support). The

candidate has added specific deliverables to each aim. Aim 1 now considers the impact of migration on geographic notification patterns. More detailed is provided on model validation. Aim 2 now considers INH plus rifapentine and additional sources of micro-costing data are provided. Aim 3 has been revised to consider an evaluation framework focusing on acceptability and feasibility of modeled strategies, which aligns better with the stated goal of the aim. While largely quite responsive to prior comments, the candidate does not address the conditionality of Aims 2 and 3 on the validation of the model in Aim 1, nor the availability of molecular epidemiology data. Her mentorship team is large and may be difficult to manage. Generally, these are minor concerns in an otherwise extremely strong application.

1. Candidate:

Strengths

- Very strong candidate – Infectious disease trained, former EIS fellow, MPH in epidemiology and biostatistics, and has already completed coursework in mathematical modeling and GIS.
- Spent 11 months in Uganda as a Fogarty Research Fellow and developing relevant collaborations with investigators at the Ugandan National TB and Leprosy Program and US CDC which will facilitate the proposed work.
- Already works with Dr Barnabas of the International Clinical Research Center and Dr Hay at the Institute for Health Metrics and Evaluation (Global Burden of Disease Study). She has published 3 manuscripts with Dr. Barnabas (one as first-author) and one with Dr. Hay (as part of Global Burden of Disease report) with another 2 pending.
- She is currently leading the development of the Institute for Health Metrics and Evaluation's first geospatial TB incidence and mortality model in Brazil with Professor Hay. This serves as a test case for a high TB burden country with excellent mortality and TB notification data that will allow development of techniques for areas with more limited data (first manuscript under review).
- Strong letters of recommendation speaking to the high likelihood of Dr. Ross becoming an independent investigator and creating her own research niche in using geospatial methods and dynamic disease models to prioritize and evaluate TB prevention interventions. She is described as smart, hard-working, enthusiastic and organized, with strong relationships with Ugandan partners.

Weaknesses

- None noted.

2. Career Development Plan/ Career Goals & Objectives:

Strengths

- Training aims map well with scientific aims, with coursework in spatial epidemiology, cost-effectiveness and data visualization and build on her prior training.
- Team members relevant expertise and roles for mentorship are clearly articulated.
- A course in writing research proposals and a manuscript preparation short-course are strengths in terms of professional development.

Weaknesses

- If she is ultimately wanting to implement interventions (and not only model them), it is not clear if this a single course on implementation science is adequate. However, the candidate has now stated that her goal with an R01 may including modeling and evaluating implementation of geographically-specific strategies for HIV and TB prevention. This is somewhat tempered language and suggests a strong modeling component for future work, appropriate to the current training plan.

3. Research Plan:

Strengths

- TB preventive therapy is an underused modality, and ways to inform its use could have high public health impact. Using geospatial modeling to integrate heterogeneous, granular HIV and TB prevalence routine data to identify focused resource investment in TB preventive therapy at the district level may be a promising strategy. These methods may be generalizable to other settings.
- She will develop modeling tools to guide implementation of preventive therapy at a sub-national scale, which fits well with the “right intervention at the right place at the right time” philosophy of targeted now espoused in the HIV community.
- Map of ART scale up by district in Uganda that she developed as a Fogarty Fellow will be incorporated into the model developed in Aim 1 to help account for the impact of ART on developing incident TB in the model.
- The candidate has refined the Aims based on prior reviewer feedback.
 - In Aim 1, she has incorporated travel for care seeking into the model, included parameter inputs for the dynamic transmission model of HIV-TB co-infection, and provided more detail about how HIV and TB interact in the model.
 - In Aim 2, she has added reduced efficacy of TB preventive therapy in the context of drug-resistant TB. She has added 3HP to the prevention strategies. She has also added more details about the costing approach and sources of costing data.
 - In Aim 3, she has now focused on feasibility and acceptability of incorporating model results into practice based on presentation format (interactive versus passive format).

Weaknesses

- While largely quite responsive to prior comments, the candidate does not appear to address the conditionality of Aims 2 and 3 on the validation of the model in Aim 1, nor the availability of molecular epidemiology data.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- Mentorship for this award will be from Dr. Ruanne Barnabas (primary mentor, infectious disease, mathematical modeling, clinical trials of models of HIV care), Professor Simon Hay (co-mentor at Institute for Health Metrics and Evaluation, where candidate is currently based, and expert in geospatial science), Dr. David Dowdy (co-mentor at JHU, expertise in TB transmission modeling and economic evaluations of interventions, as well as clinical trials involving TB case finding) and Dr. Judith Wasserheit (co-mentor implementation science). All are excellent and well-funded.

- Dr. Dowdy has served as mentor or co-mentor for over 35 trainees and won an excellence in mentoring award from JHU School of Medicine.
- Dr. Zawedde-Muyanja is a Ugandan physician based at the IDI at Makerere University and will advise Dr Ross on accessing an interpreting program data for TB to input into the models and facilitate introduction to key TB stakeholders. Dr. Frank Mugabe is also a physician specializing in TB who is Program Manager of the Ugandan TB and Leprosy Program and will advise on assembly of TB surveillance and prevalence survey data and engagement of stakeholders.
- Dr. Manabe is a new addition to the team with extensive mentorship experience; she was previously seconded from JHU to IDI at Makerere University. She will advise on project implementation in Uganda.

Weaknesses

- Large mentorship team. Size is justified by multi-disciplinary and international nature of work, but how will all of these meetings and inputs from mentors/advisors be coordinated (2 weekly, 1 bi-weekly, 4 monthly)?

5. Environment and Institutional Commitment to the Candidate:


Strengths


- University of Washington, and specifically the ICRC and the CFAR, have an excellent track record in the development of early stage investigators.
- Strong connections with relevant bodies in Uganda such as the National TB and Leprosy Program and CDC will assist with feasibility of obtaining appropriate datasets. She has a letter of support from the Ministry of Science, Technology and Innovation.
- Dr. Wasserheit, Department of Global Health Chair, notes that they plan to hire Dr. Ross to a full-time faculty position at the completion of her fellowship.


Weaknesses


- None noted.


CRITIQUE 3

Candidate: 

Career Development Plan/Career Goals /Plan to Provide Mentoring: 

Research Plan: 

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 

Environment/Commitment to the Candidate: 

Overall Impact:

This K01 resubmission proposes development of modeling and mapping approaches to guide the implementation of INH use among HIV – TB co-infected persons living in Uganda. Still a primary cause of death among people living with HIV, TB may be relatively easily treated yet identification of those

with or at risk for HIV – TB coinfection remains a significant public health challenge. The candidate proposes development of new mathematical and geospatial models to identify predictors of TB as well as collection of stakeholder data to inform the impact of the approach when applied in Uganda. Overall enthusiasm was high for both the candidate and proposal. Minimal weaknesses in the research plan would be easily addressed.

1. Candidate:

Strengths

- The applicant has considerable experience in infectious disease research combined with modeling and public health expertise. Her training at OHSU allowed her to expand her skillset to include mapping analysis, a skill of particular use in the proposed study. She has also worked in the Emerging Infectious Disease Laboratory as a Training Fellow at CDC where she focused on molecular epidemiology and furthered her experience in that regard. Each of these skills is integral to the proposed work.
- Dr. Ross has spent time in East Africa and in Uganda where the proposed program will take place. She appears to have several longstanding collaborators from Uganda on this project who will be able to support her work and mentor her with regard to unique features of the data and eventual implementation.
- Her interest in reducing HIV – TB coinfection is an eventual long-term career goal; each of the proposed aims and the training activities will support this long-term goal.

Weaknesses

- None noted.

2. Career Development Plan/ Career Goals & Objectives:

Strengths

- The courses are suitably advanced and build upon Dr. Ross' existing education as well as filling educational gaps that the proposal intends to fill.
- The timeline and plans for direct training with the mentors and co-mentors are well-articulated and thoughtfully planned.
- The EPI 588 *Writing Research Proposals* course will support her R01 development.
- The proposed didactic courses and scheduled conferences are appropriate in content.

Weaknesses

- This is a very ambitious training program with many courses intermixed with a full research plan and a lot of international travel. Along with her clinical practice (which is <6% FTE) and teaching activities (which are <6% FTE), one concern is that there could be too much work proposed to be reasonably achieved.

3. Research Plan:

Strengths

- The specific aims are well considered and laid out and have been revised in concert with the earlier critiques.

- Dr. Ross has developed similar models for TB and HIV epidemics in Brazil and Uganda, as well as working on the Global Burden of Disease study. Her prior experience will provide an excellent foundation to adapt and validate the proposed co-infection mathematical model yet expands upon rather than simply replicating prior models.
- Models (ART and TB in Aim 1 and PT and TB in Aim 2) proposed are feasible based on existing TB data. For example, in Aim 1, ART coverage, geographic predictors of TB and HIV (e.g., incidence, prevalence, mortality, etc.) are available. This is important as the existence of measures on which to parameterize the models will make them that much more accurate and with fewer biases.
- Characterizing co-infection and modeling it as proposed has promise as a method to target prevention efforts and engage a larger population into treatment.
- The implementation science aim is novel and can address some of the real-world implementation struggles that use of mathematical/geospatial models as a way to focus treatment/prevention efforts may likely encounter.

Weaknesses

- The plan is highly ambitious, even without the implementation science aim which involves recruiting 30 senior program leaders for a trial (this is a very busy and often hard to engage population). The proposal seems to have been scaled back from a 5-year program and there is the concern that not all of the activities and training can feasibly be accomplished in the new 4-year time frame. This is particularly true of this last stakeholder aim, which requires primary data collection, full IRB review, and enrollment of program leaders.
- There are concerns that a great deal is planned for Year 1 to enable Year 4 evaluation of the impact of approaches in Aim 3. Slow accrual, secular changes, barriers to enrollment are all potential challenges to being able to complete this Aim.
- One concern about Aim 3 is whether participation in this RCT will in any way negatively affect people in their jobs. This seems unlikely but should be disclosed as a potential risk if there is any potential negative employment outcome.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- The mentorship team is outstanding and appropriate to the proposed activities. Dr. Barnabas is well published in the specific field of study in mathematical models specific to East Africa (including Uganda where the study takes place) and also has mentored numerous junior faculty and trainees in the past.
- Co-mentors Dr. Hay and Dr. Wasserheit are similarly well known and experienced in the field Dr. Ross is proposing to work in, thus will be able to address methodological issues immediately as they emerge. Both are located at UW.
- Dr. Dowdy has considerable experience in modeling HIV – TB co-infection and will be similarly helpful. Although at JHU, specific bi-weekly skype sessions to address Aims 1 and 2 are proposed.
- The Scientific Advisor team is multidisciplinary in nature and selected to provide expertise in HIV and TB modeling.
- Taken together, the mentorship team is very strong and will be able to support the implementation and analysis of Dr. Ross' aims.

Weaknesses

- None noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- UW offers outstanding resources sufficient to support the aims of the study and the training of Dr. Ross.
- The CFAR and other centers and institutes at UW are exemplary and will be able to provide specialized services should they become required. The mentoring team can link to these as needed.
- The Ugandan Ministry of Health is clearly supportive (narrative, LOS) of this activity and the applicant indicates that they have specifically requested that this work be performed in order to focus their public health efforts in TB. Similarly, personnel from the TB Prevention Program are a part of the mentorship team and thus integrally involved in the proposed activities.

Weaknesses

- None noted.

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): **Code 30 ACCEPTABLE**

Projects to be undertaken with support of this training grant, which involve human subjects, must conform to the NIH policies on the protection of human subjects. Guidance can be found in PHS398 application materials and the NIH Office of Extramural Research web site <http://grants.nih.gov/grants/policy/hs/index.htm>.

Comment: Aims 1 and 2 will use estimates from existing models and other data to develop the models. Aim 3 will be an implementation science RCT of program leaders to evaluate optimal approaches to incorporate models into program planning, where the effect of presentation of model results will be evaluated. The information provided regarding risks to participants is well considered and appropriate in its approach to reducing risk.

DATA AND SAFETY MONITORING PLAN: **NOT APPLICABLE**

INCLUSION OF WOMEN PLAN (Resume): **Code 1A ACCEPTABLE**

Projects to be undertaken with support from this training grant, which involve clinical research studies, must conform to the NIH policies on the inclusion of women in study populations. See http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Details of such studies, including a description of the population and rationale for inclusion/exclusion, must be provided to the NIH program administrator of this training grant prior to undertaking the studies.

INCLUSION OF MINORITIES PLAN (Resume): **Code 1A ACCEPTABLE**

Projects to be undertaken with support from this training grant, which involve clinical research studies, must conform to the NIH policies on the inclusion of minorities in study populations. See http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Details of such studies, including a description of the population and rationale for inclusion/exclusion, must be provided to the NIH program administrator of this training grant prior to undertaking the studies.

Comment: Inclusion of Minorities: The majority of participants will be black/African appropriate to the setting. Parameters are being derived from underlying population data and will reflect the population structure. No one will be excluded on the basis of race or ethnicity.

INCLUSION OF CHILDREN PLAN (Resume): **Code 3A NOT APPLICABLE**

Projects to be undertaken with support from this training grant, which involve clinical research studies, must conform to the NIH policies on the inclusion of children in study populations. See <http://grants.nih.gov/grants/funding/children/children.htm>. Details of such studies, including a description of the population and rationale for inclusion/exclusion, must be provided to the NIH program administrator of this training grant prior to undertaking the studies.

VERTEBRATE ANIMALS (Resume): **Code 10 NOT APPLICABLE**

Projects to be undertaken with support from this training grant, which involve vertebrate animals, must conform to the NIH policies on the humane care and use of laboratory animals. Guidance can be found

in PHS398 application materials and the NIH Office of Extramural Research web site
<http://grants.nih.gov/grants/olaw/olaw.htm>.

BIOHAZARD COMMENT: **NOT APPLICABLE**

RESUBMISSION:

Comments: The candidate has been largely responsive to the reviews. Weaknesses from the prior submission appear to have been thoughtfully considered overall and addressed in this resubmission.

**TRAINING IN THE RESPONSIBLE CONDUCT
OF RESEARCH:** **ACCEPTABLE**

Format: **Acceptable**
Subject Matter: **Acceptable**
Faculty Participation: **Acceptable**
Duration: **Acceptable**
Frequency: **Acceptable**

FOREIGN INSTITUTION: **JUSTIFIED**
The challenge of HIV- TB co-infection is greatest in Sub-Saharan Africa. The selected region is appropriate for this study and it could not be conducted in the US.

SELECT AGENTS: **NOT APPLICABLE**

RESOURCE SHARING PLANS: **ACCEPTABLE**
Data Sharing Plan Comments (if >\$500,000/year): **NOT APPLICABLE**
Sharing Model Organisms Comments: **NOT APPLICABLE**
Genomic Data Sharing (GDS) Comments: **NOT APPLICABLE**

**AUTHENTICATION OF KEY BIOLOGICAL
AND/OR CHEMICAL RESOURCES:** **NOT APPLICABLE**

BUDGET AND PERIOD OF SUPPORT: **ACCEPTABLE**
The budget was recommended as requested

Footnotes for 1 K01 AI138620-01A1; PI Name: Ross, Jennifer M

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html>. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting

or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.