

Vanderbilt Tuberculosis Center

VANDERBILT  UNIVERSITY
MEDICAL CENTER

Annual Report

FY 2019
July 2018 – June 2019

About the Vanderbilt TB Center

The global burden of tuberculosis (TB) is enormous; approximately one-third of the world's population is infected with *M. tuberculosis*, and there are approximately 10 million new TB cases each year worldwide. Established in 2012, the Vanderbilt Tuberculosis Center (VTC) is a focal point for collaborative efforts in TB research that contribute to a reduction in the burden of TB and TB/HIV globally, including in Tennessee and Nashville. The VTC facilitates this in three ways:

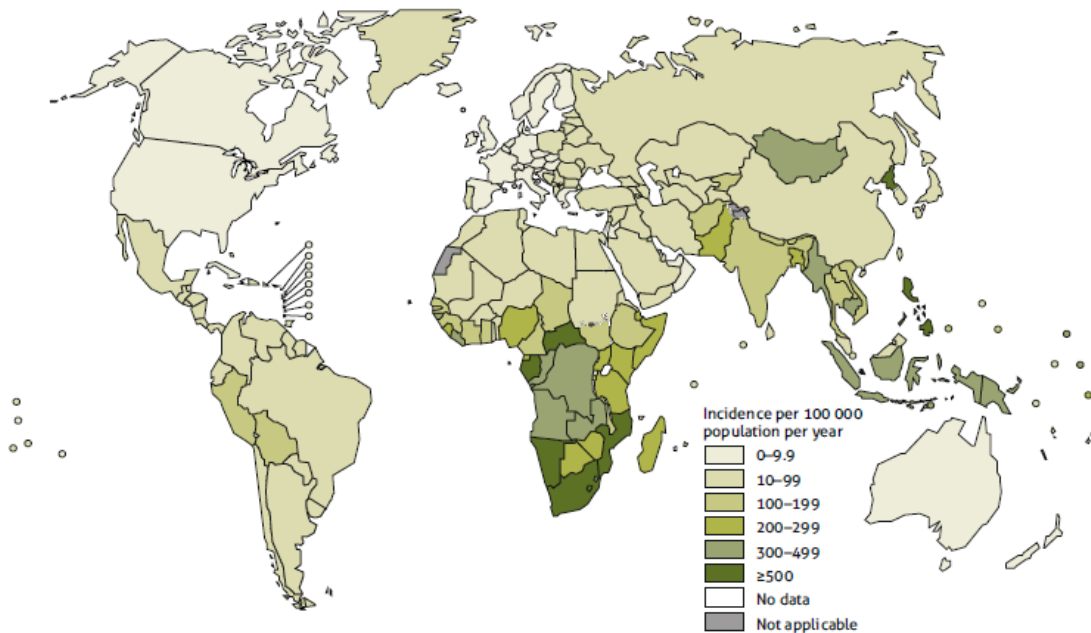
1. **Expand the Vanderbilt global research portfolio** in TB and TB/HIV, with a focus on epidemiology, clinical trials, and translational research.
2. **Develop and mentor junior faculty members, fellows, and students** from Vanderbilt, Meharry, and collaborating health departments and international institutions. Particular attention is paid to investigators who are under-represented minorities and/or women, given the disproportionate burden of TB and HIV in these groups.
3. **Provide technical assistance to the Vanderbilt-linked local and global service programs engaged in TB control:** the Metro Nashville Public Health Department, the Tennessee Department of Health, and PEPFAR/Global Health Initiatives in the Americas, Africa, and Asia.

The VTC builds on the strengths of Vanderbilt University Medical Center and Vanderbilt University in clinical and translational research, and includes the full spectrum of discovery from bench to bedside to outcomes. With expertise in population data management, data quality, and study coordination, our research focuses particularly on epidemiology, host and pathogen factors that predispose to disease, clinical trials, and outcomes and implementation research. We do this in four broad area of research: **Treatment and Prevention, Drug Resistance, TB/HIV, and Transmission and Pathogenesis.**

The Tuberculosis Epidemic

Tuberculosis (TB) is still the **leading cause of death from a single infectious agent** (above HIV/AIDS). In 2018, the World Health Organization (WHO) estimates 10 million people developed TB disease, there were 1.2 million deaths among HIV-seronegative people and an additional 250,000 deaths from TB among HIV-seropositive people. The figure below details incidence by country (WHO Global TB Report 2019).

Estimated TB incidence rates, 2018



FY 2019 Executive Summary

FY 2019 was filled with many grant submissions and much progress on currently active projects.

In September of 2018, the **Regional Prospective Observational Research for Tuberculosis (RePORT)-International meeting** was held in China, and in October 2018 and March 2019 the **RePORT-Brazil** meetings were held in Salvador, Brazil and Manaus, Brazil, respectively. RePORT- International is a global network of research sites in India, Brazil, Indonesia, South Africa, China, and the Philippines dedicated to collaborative tuberculosis research. A standardized research protocol (the



RePORT-Brazil meeting in March 2019 in Manaus, Brazil.

Common Protocol) guides the enrollment of participants with active pulmonary tuberculosis and contacts into prospective observational cohorts. The VTC is the coordinating center for the RePORT-Brazil network and is also a partner with the Durban site of the **RePORT-South Africa network**, together with the **African Health Research Institute (AHRI)**. As of June 2019, RePORT-Brazil completed enrollment, with 3,117 enrolled participants, and RePORT-South Africa AHRI site also completed enrollment and follow-up of 100 participants.

Analyses utilizing RePORT-Brazil data and specimens are ongoing, and the **first publications resulting from RePORT-Brazil funding were published**. **Lauren Peetluk** (Vanderbilt PhD candidate in Epidemiology) published in the *Journal of Infectious Diseases* that unsuccessful TB treatment outcomes in Brazil were associated with lack of weight gain and HIV co-infection during the first two months of TB treatment.

Juan Cubillos-Angulo and Bruno Andrade (Salvador, Brazil) also published two papers investigating genetic polymorphisms and risk of developing *M. tuberculosis* infection and TB disease in Brazilian participants. See our publication list on pg. 9 for the full citations.

Several new RePORT-linked funding opportunities have been submitted and awarded this past year. In February 2019, several supplements were submitted to **CRDF Global's RePORT-CFAR call for proposals**, which required collaboration between RePORT and CFAR (Center for AIDS Research) sites. Both proposals which we participated in were funded. The first was led by Yuri van der Heijden and John Koethe, between the **VUMC CFAR and the RePORT-South Africa AHRI site** and will investigate immune activation and dysglycemia in TB patients with and without HIV. The second was led by Thomas Hawn (University of Washington), Tim Sterling, and Bruno Andrade (Brazil), between the **UW CFAR and the RePORT-Brazil sites** and will investigate macrophage immunogenetics and incipient tuberculosis. Both projects are now in progress.

We also were awarded an R01 in June 2019 that was in response to an NIH RFA to study mechanisms of mycobacterial-induced immunity in HIV-infected and uninfected individuals. This study utilizes RePORT-Brazil specimens. The title of the grant is "**Epidemiologic, immunologic, and genetic predictors and mechanisms of**

The Journal of Infectious Diseases
MAJOR ARTICLE



Lack of Weight Gain During the First 2 Months of Treatment and Human Immunodeficiency Virus Independently Predict Unsuccessful Treatment Outcomes in Tuberculosis

Lauren S. Peetluk,¹ Peter F. Ribeiro,^{1,2} Marcelo Cordeiro-Santos,^{2,4} Afranio Kritski,^{4,5} Bruno B. Andrade,^{2,4,7,8,9} Betina Durovni,¹¹ Solange Calvacante,^{11,12} Maria B. Arriaga,¹³ Megan M. Turner,² Marina C. Figueiredo,² Valeria C. Rolfe,¹² Timothy R. Sterling²; and the Regional Prospective Observational Research in Tuberculosis (RePORT)Brazil network

incipient, sub-clinical, and active TB in HIV-infected and -uninfected close TB contacts” and involves investigators from VUMC, the University of Washington, Brazil, and South Africa.

In August 2018, we submitted a large program grant in collaboration with **Jyothi Rengarajan of Emory University** to NIH’s call for “Immune Mechanisms of Protection Against Mycobacterium Tuberculosis Centers (IMPAC-TB)”. In March 2019, we submitted an R01 to the **U.S.-Brazil Collaborative Biomedical Research Program** focused on extrapulmonary tuberculosis in RePORT-Brazil. And lastly, in July 2019, we submitted a large diagnostic program grant in collaboration with **David Wright of Vanderbilt University** to NIH’s call for “Feasibility of Novel Diagnostics for TB in Endemic Countries (FEND for TB) U01”. These three proposals were not funded, but we anticipate that the work proposed will lead to future grant applications.

Enrollment began in August 2019 on a new CDC-funded trial that will be conducted by the **Tuberculosis Trials Consortium (TBTC)**. **ASTEROID** (Assessment of the Safety, Tolerability, and Effectiveness of Rifapentine given Daily for LTBI; **TBTC Study 37**) will evaluate six weeks of daily rifapentine vs a comparator arm of 12-16 weeks of rifamycin-based treatment for latent *M. tuberculosis* infection. **Tim Sterling** is leading this trial, and 6 study sites are now open for enrollment. Enrollment as of January 2020 was 70.

In July 2018, The Centers for Disease Control and Prevention (CDC) released **updated recommendations for use of once-weekly isoniazid-rifapentine for 12 weeks (3HP)** for treatment of latent tuberculosis (TB) infection. The updated recommendations, published in CDC’s Morbidity and Mortality Weekly Report (MMWR), support expanded use of an effective, shorter, treatment regimen to reach even more people with latent TB infection. **Dr. Timothy Sterling led one of the initial 3HP studies**, funded by the CDC through the Tuberculosis Trials Consortium Study 26.

Our partnerships in **South Africa** continued to flourish this past year. VUMC hosted two Ph.D. students from South Africa as part of the **D43 training grant** with the **University of Cape Town (UCT)**, entitled “**HIV-Associated Tuberculosis Training Program (HATTP)**”. Zinhle Cindi spent January-October 2019 under the mentorship of David Haas; Phuti Choshi is now at Vanderbilt from December 2019-April 2020 under the mentorship of Elizabeth Phillips. This grant’s goal is to develop the next generation of clinician-scientists in HIV-TB at UCT and accelerate the transformation of the demographic composition of researchers at UCT to redress disparities that persist from apartheid.

Yuri van der Heijden continued work on his K08 award on TB drug-resistance in South Africa and submitted an R01 application in July 2019 to the NIH call for U.S.-South Africa Program for Collaborative Biomedical Research, involving partners at UCT and Stellenbosch University. The grant was not funded but had favorable reviews and he is planning re-submission for May 2020. He continues work on his CRDF RePORT-CFAR award, mentioned above.

Collaborator **Larissa Otero** from **Universidad Peruana Cayetano Heredia** was awarded a **K43 grant** in September 2018 from Fogarty International Center (FIC). Her grant is titled “**Patient-centered intervention to prevent TB among children <5 years old**”, and Tim Sterling is one of her faculty advisors. Larissa is the first investigator in Latin America to receive the K43 award.

In October 2018, Bryan Shepherd and Tim Sterling visited Mozambique and Kenya on a **travel grant from the Vanderbilt Institute of Global Health (VIGH)**. The goal for the visit was to develop future collaborations in TB and HIV research and learn more about the sites: AMPATH (Academic Model Providing Access to Healthcare) in Eldoret, Kenya and CISM (Centro de Investigacao em Saude de Manhica) in Manhica, Mozambique. Since their visit, Bryan Shepherd has been working with Lameck Diero of AMPATH on his R01 grant “**Statistical methods for correlated outcome and covariate errors in studies of HIV/AIDS**”. Two investigators from Mozambique participated in the **Vanderbilt Institute of Research Design and Ethics (VIRDE)** course in

October 2019. Tim Sterling is currently mentoring Dinis Nguenha on a manuscript utilizing TB data from CISM, and is developing future grant applications with site PI Alberto Garcia-Basteiro.

A tuberculosis-focused analysis from the Caribbean, Central, and South America network (**CCASAnet**) for HIV Epidemiology was featured and published this past year. An abstract presented at the Conference of Retroviruses and Opportunistic Infections (CROI) 2019 led by Serena Koenig from GHESKIO in Haiti was **featured by NIH News** (below). The abstract, entitled “Mortality after presumed TB treatment completion in

persons with HIV in Latin America”, found that among people with HIV in Latin America, **those diagnosed with TB at an initial clinic visit were about twice as likely to die within 10 years as people not initially diagnosed with TB**. The paper was published in *Clinical Infectious Diseases* in October 2019.

FY 2019 saw many guest speakers and visitors come to the VU/VUMC campus. In October 2018, **Gabardhan Das**, PhD, from Jawaharlal Nehru University in India presented on “Tuberculosis: An Ancient Disease with Modern Outlook”. The Vanderbilt Institute for Infection, Immunology, and Inflammation (VI4) hosted Dr. Das. In January 2019, the Department of Pathology, Microbiology, and Immunology (PMI) hosted faculty candidate **Reuben Barricarte**, PhD, who presented on “Using human genetics to unravel the immunological mechanisms of infectious disease”. Dr. Barricarte has since accepted an offer at VUMC and will start in 2020. In March 2019, the Vanderbilt Institute of Chemical Biology (VICB) hosted **Robert Abramovitch**, PhD, from Michigan State University, who presented on “Targeting Two-Component Regulatory Systems to Inhibit *M. tuberculosis* Pathogenesis”.



Tim Sterling, Bryan Shepherd, and Troy Moon visit the Centro de Investigacao em Saude de Manhica (CISM) in Mozambique to meet with the TB team.



Wednesday, March 6, 2019

Tuberculosis Diagnosis in People with HIV Increases Risk of Death Within 10 Years



Research and Grant Funding

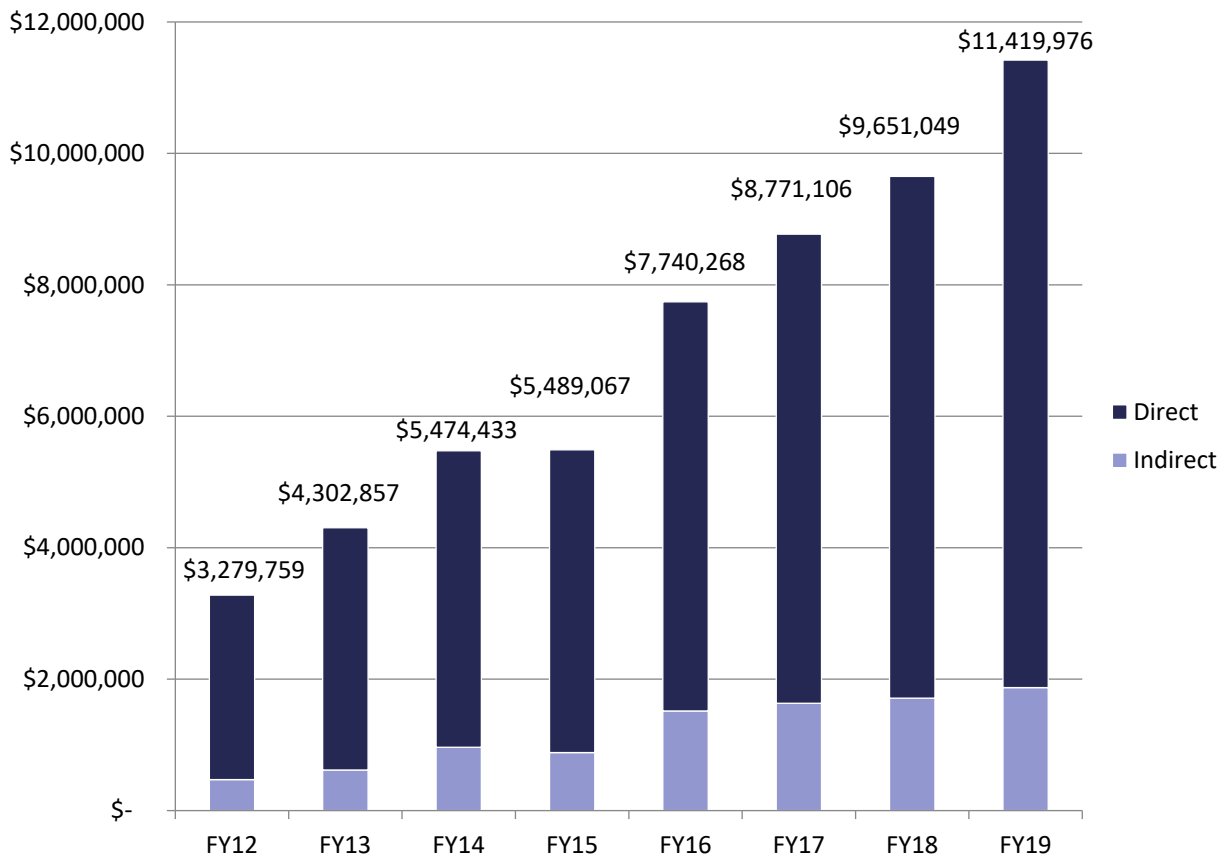
In the previous fiscal year (July 1, 2017 - June 30, 2018), there were 29 TB research projects with total grant funding of \$9,651,049 (\$7,939,452 direct costs, \$1,711,597 indirect costs).

In the current fiscal year (July 1, 2018 – June 30, 2019), there were 28 TB research projects and total grant funding of \$11,419,976 (\$9,548,474 direct costs, \$1,871,503 indirect costs), an 18% increase in total funding from FY2018. Please see the funding table at the end of this document. Not included in the table is the endowed David E. Rogers Professorship, which provided partial support for Dr. Tim Sterling.

We acknowledge research funding from the U.S. National Institutes of Health, Centers for Disease Control and Prevention, Civilian Research and Development Foundation, Brazilian Ministry of Health, and South African Medical Research Council.

The number of submitted and awarded grants has steadily increased. We are pleased to report the amount of grant funding awarded for TB research at Vanderbilt has tripled since the center's inception in 2012, and this past year we exceeded \$10 million in funding. We would like to acknowledge support from the Vanderbilt Institute for Global Health and the Division of Infectious Diseases in the Department of Medicine.

Vanderbilt Tuberculosis Center Grant Funding, FY2012-2019



Education, Training, and Service

The **TB case conference** held monthly in collaboration between the Metro Public Health Department, the Tennessee Department of Health, Meharry Medical College, and Vanderbilt continued for its 16th year, led by Metro TB Medical Director, **Joanna Shaw-KaiKai**. Additional consultation was provided by **Timothy Sterling and Ritu Banerjee** throughout the year. Vanderbilt infectious disease fellows continued to see patients with Drs. Shaw-KaiKai and Sterling on Friday mornings at the Metro Public Health Department TB Clinic.

Tim Sterling also presented at various meetings throughout the year. He gave lectures on treatment of latent *M. tuberculosis* infection at the **7th Brazilian National Workshop of Rede-TB** (Recife; September 2018), the **Tennessee TB Elimination Program Symposium** (Nashville; November 2018), the **XXII Jornadas Internacionales sobre Tuberculosis**. (Barcelona; November 2018), the **University of Washington** (Seattle; March 2019), and the



Tim Sterling presented at the Seminario Amazonico de Pesquisa Clinica em Tuberculose in Manaus, Brazil, in June 2019.

Seminario Amazonico de Pesquisa Clinica em Tuberculose (Manaus, Brazil; June 2019). He also presented updated guidelines for the treatment of latent *M. tuberculosis* infection to the **Advisory Council for the Elimination of Tuberculosis** (ACET; December 2018) and the **National Society of Tuberculosis Clinicians** (April 2019). He moderated a session on TB at the **Conference on Retroviruses and Opportunistic Infections** (CROI; Seattle, March 2019), gave a lecture on biomarkers of extrapulmonary TB at the **NIH and South African Medical Research Council Workshop on TB Biomarkers and Vaccines** (Soweto, South Africa; May 2019) and taught at the **McGill Summer Institute in Infectious Diseases and Global Health** (June 2019). He continued to serve on the **U.S. Department of Health and Human Services Adult HIV Opportunistic Infection Guidelines Committee**.

The **Metro Nashville Public Health Department** hosted a **World TB Day 2019** awareness event on March 22, 2019 that was open to the community at the Lentz Public Health building. The event included presentations on TB statistics, affected populations, patient perspectives, and general awareness activities including TB games!

The VTC continued to host meetings to foster collaboration in TB research at Vanderbilt. In August 2018, **Lauren Saag**, doctoral student in epidemiology, presented data from RePORT-Brazil on early weight change and treatment outcomes of patients with TB and HIV infection. **Tim Sterling** also presented on a recent grant submission to NIAID's call for Immune Mechanisms of Protection Against Mycobacterium Tuberculosis Center (IMPAC-TB).

In September 2018, the VU **Brazilian Studies Department** hosted Brazil Week and had a screening of the movie "Tuberculosis Diaries: A Hidden Epidemic", which was an excellent way to spread awareness of TB to the University community.

In October 2019, the Vanderbilt Institute for Global Health, with leadership from **Holly Cassell**, hosted its annual **VIRDE course** (Vanderbilt Institute of Research Design and Ethics), which provides training to LMIC investigators in grant writing and research design. This year, we had several international investigators attend whose research focused on TB. We held a TB-focused meeting near the end of their course to provide the scholars feedback on their grant proposals and give them an opportunity to ask our investigators questions. Tim Sterling mentored **Marcelo Cordeiro-Santos from Brazil**, April Pettit mentored **Maryam Amour from**



The October 2019 TB Center Meeting, VIRDE scholars presented their TB-research grant projects for feedback from VUMC faculty.

Tanzania, Yuri van der Heijden mentored **Benson Kidenya from Tanzania**, and Troy Moon mentored **Dinis Nguenha and Emilio Valverde from Mozambique**. The scholars' projects included TB clinical trials, diagnostic studies, incidence and risk factors for drug resistance, and DOT feasibility studies. We look forward to their upcoming grant submissions and wish them the best of luck!

VUMC hosted two Ph.D. students from South Africa this past year as part of the **D43 training grant with University of Cape Town**

(UCT), titled "**HIV-Associated Tuberculosis Training Program (HATTP)**". Zinhle Cindi spent January-October 2019 under mentorship of David Haas and Phuti Choshi is now with us from December 2019-April 2020 under mentorship of Elizabeth Phillips. This grant's goal is to develop the next generation of clinician scientists in HIV-TB at UCT and accelerate transformation of the demographic composition of researchers at UCT to redress disparities that persist from apartheid.

Hilary Vansell and Tim Sterling participated in the **VIGH Strategic Planning Initiative** that took place in December 2018. With new leadership from VIGH Director, Ed Trevathan, the Institute is re-imagining its future and the VTC is excited to see new growth and opportunities that may arise from this process.

The VTC welcomed a new Program Manager, **Andressa Scussel**, in January 2020. Andressa earned her Law degree in Brazil and her master's degree in International and Intercultural Education at Florida International University. Andressa will assist with coordinating efforts of the VTC, assist with the research activities of RePORT-Brazil, and work to develop additional research projects, particularly in Portuguese-speaking countries (e.g., Brazil and Mozambique).

The [VTC website](#) continues to highlight VTC research and offer resources related to TB treatment and grant funding. The website is frequently updated with grant opportunities, publications, documents for grants and upcoming conferences and workshops. Please see the [Events](#) section for upcoming meetings and events. To receive VTC newsletters, [sign up here](#).



TB Center members at the August 2018 TB Center Meeting.

Selected Recent Publications (2018-2019)

TB Center-affiliated authors are listed in bold.

1. **Cubillos-Angulo JM**, Arriaga MB, Melo MGM, Silva EC, Alvarado-Arnez LE, de Almeida AS, Moraes MO, Moreira ASR, **Lapa E Silva JR**, Fukutani KF, **Sterling TR**, **Hawn TR**, **Kritski AL**, Oliveira MM, **Andrade BB**. [Polymorphisms in interferon pathway genes and risk of Mycobacterium tuberculosis infection in contacts of tuberculosis cases in Brazil](#). Int J Infect Dis. 2019 Dec 13;92:21-28. [Epub ahead of print] PMID: 31843671
2. **Pettit AC**, Jenkins CA, Blevins Peratikos M, Yotebieng M, Diero L, Do CD, Ross J, **Veloso VG**, Hawerlander D, Marcy O, **Shepherd BE**, Fenner L, **Sterling TR**; [Directly observed therapy and risk of unfavourable tuberculosis treatment outcomes among an international cohort of people living with HIV in low- and middle-income countries](#). International Epidemiology Databases to Evaluate AIDS (IeDEA) Consortium. J Int AIDS Soc. 2019 Dec;22(12):e25423. PMID: 31814312
3. **Peetluk LS**, **Rebeiro PF**, **Cordeiro-Santos M**, **Kritski A**, **Andrade BB**, **Durovni B**, **Calvacante S**, **Arriaga MB**, **Turner MM**, **Figueiredo MC**, **Rolla VC**, **Sterling TR**; [Lack of weight gain during the first two months of treatment and HIV independently predict unsuccessful treatment outcomes in tuberculosis](#). Regional Prospective Observational Research in Tuberculosis (RePORT)-Brazil network. J Infect Dis. 2019 Nov 14. pii: jiz595. [Epub ahead of print] PMID: 31724035
4. Stout JE, Turner NA, Belknap RW, Horsburgh CR, **Sterling TR**, Phillips PPJ. [Optimizing the Design of Latent Tuberculosis Treatment Trials: Insights from Mathematical Modeling](#). Am J Respir Crit Care Med. 2019 Nov 11. [Epub ahead of print] PMID: 31711306
5. Silveira-Mattos PS, Barreto-Duarte B, Vasconcelos B, Fukutani KF, Vinhaes CL, Oliveira-de-Souza D, Ibegbu CC, **Figueiredo MC**, **Sterling TR**, **Rengarajan J**, **Andrade BB**. [Differential expression of activation markers by Mycobacterium tuberculosis-specific CD4+ T-cell distinguishes extrapulmonary from pulmonary tuberculosis and latent infection](#). Clin Infect Dis. 2019 Oct 30. pii: ciz1070. [Epub ahead of print] PMID: 31665254
6. **Koenig SP**, **Kim A**, **Shepherd BE**, **Cesar C**, **Veloso V**, **Cortes CP**, **Padgett D**, **Crabtree-Ramírez B**, **Gotuzzo E**, **McGowan CC**, **Sterling TR**, **Pape JW**; [Increased Mortality after Tuberculosis Treatment Completion in Persons with HIV in Latin America](#). Caribbean, Central and South America Network for HIV Epidemiology (CCASAnet). Clin Infect Dis. 2019 Oct 20. pii: ciz1032. [Epub ahead of print] PMID: 31629369
7. Stout JE, **Sterling TR**, Horsburgh CR Jr. [One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis](#). N Engl J Med. 2019 Sep 12;381(11):e23. PMID: 31509689
8. Reichler MR, Khan A, **Sterling TR**, Zhao H, Chen B, Yuan Y, Moran J, McAuley J, Mangura B; [Risk Factors for Tuberculosis and Effect of Preventive Therapy Among Close Contacts of Persons with Infectious Tuberculosis](#). Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team. Clin Infect Dis. 2019 May 24. pii: ciz438. [Epub ahead of print] PMID: 31127813v
9. **Fiske CT**, **Blackman A**, **Maruri F**, **Rebeiro PF**, **Huaman M**, Kator J, **Scott Algood HM**, **Sterling TR**. [Increased vitamin D receptor expression from macrophages after stimulation with M. tuberculosis among persons who have recovered from extrapulmonary tuberculosis](#). BMC Infect Dis. 2019 Apr 30;19(1):366. PMID: 31039752
10. **Crabtree-Ramírez B**, **Jenkins C**, **Jayathilake K**, **Carriquiry G**, **Veloso V**, **Padgett D**, **Gotuzzo E**, **Cortes C**, **Mejia F**, **McGowan CC**, **Duda S**, **Shepherd BE**, **Sterling TR**. [HIV-related tuberculosis: mortality risk in persons without vs. with culture-confirmed disease](#). Int J Tuberc Lung Dis. 2019 Mar 1;23(3):306-314. PMID: 30871661
11. **Cubillos-Angulo JM**, Arriaga MB, Silva EC, Müller BLA, Ramalho DMP, Fukutani KF, Miranda PFC, Moreira ASR, Ruffino-Netto A, **Lapa E Silva JR**, **Sterling TR**, **Kritski AL**, Oliveira MM, **Andrade BB**. [Polymorphisms in TLR4 and TNFA and Risk of Mycobacterium tuberculosis Infection and Development of Active Disease in Contacts of Tuberculosis Cases in Brazil: A Prospective Cohort Study](#). Clin Infect Dis. 2019 Aug 30;69(6):1027-1035. PMID: 30481307
12. Peters JS, Andrews JR, **Hatherill M**, Hermans S, Martinez L, Schurr E, **van der Heijden Y**, Wood R, Rustomjee R, Kana BD. [Advances in the understanding of Mycobacterium tuberculosis transmission in HIV-endemic settings](#). Lancet Infect Dis. 2019 Mar;19(3):e65-e76. Epub 2018 Dec 13. Review. PMID: 30554995
13. Khan PY, Yates TA, Osman M, **Warren RM**, **van der Heijden Y**, Padayatchi N, Nardell EA, Moore D, Mathema B, Gandhi N, Eldholm V, Dheda K, Hesselting AC, Mizrahi V, Rustomjee R, **Pym A**. [Transmission of drug-resistant](#)

- [tuberculosis in HIV-endemic settings](#). Lancet Infect Dis. 2019 Mar;19(3):e77-e88. Epub 2018 Dec 13. Review. Erratum in: Lancet Infect Dis. 2019 Mar 6. PMID: 30554996
14. **van der Heijden YF**, Hughes J, Dowdy DW, Streicher E, Chihota V, Jacobson KR, Warren R, Theron G. [Overcoming limitations of tuberculosis information systems: researcher and clinician perspectives](#). Public Health Action. 2019 Sep 21;9(3):120-127. PMID: 31803584
 15. Demitto FO, Schmaltz CAS, Sant'Anna FM, Arriaga MB, **Andrade BB**, **Rolla VC**. [Predictors of early mortality and effectiveness of antiretroviral therapy in TB-HIV patients from Brazil](#). PLoS One. 2019 Jun 6;14(6):e0217014. eCollection 2019. PMID: 31170171
 16. Arriaga MB, Torres NMC, Araujo NCN, Caldas SCC, **Andrade BB**, Netto EM. [Impact of the change in the antitubercular regimen from three to four drugs on cure and frequency of adverse reactions in tuberculosis patients from Brazil: A retrospective cohort study](#). PLoS One. 2019 Dec 26;14(12):e0227101. eCollection 2019. PMID: 31877199
 17. **Huaman MA**, **Sterling TR**. [Treatment of Latent Tuberculosis Infection-An Update](#). Clin Chest Med. 2019 Dec;40(4):839-848. Review. PMID: 31731988
 18. **Van der Heijden Y**, Abdullah F, **Andrade BB**, Andrews JR, Christopher DJ, Croda J, Ewing H, **Haas DW**, **Hatherill M**, **Horsburgh CR**, Mave V, Nakaya HI, **Rolla V**, **Srinivasan S**, Sugiyono RI, Ugarte-Gil C, Hamilton C. [Building capacity for advances in tuberculosis research: proceedings of the third RePORT international meeting](#). Tuberculosis (Edinb). 2018 Dec;113:153-162. PMID: 30514497
 19. **Pettit AC**, **Shepherd BE**, **Sterling TR**. [Treatment of drug-susceptible tuberculosis among people living with human immunodeficiency virus infection: an update](#). Curr Opin HIV AIDS. 2018 Nov;13(6):469-477. PMID: 30222609
 20. Stout JE, Wu Y, Ho CS, **Pettit AC**, Feng PJ, Katz DJ, Ghosh S, Venkatappa T, Luo R; Tuberculosis Epidemiologic Studies Consortium. [Evaluating latent tuberculosis infection diagnostics using latent class analysis](#). Thorax. 2018 Nov;73(11):1062-1070. PMID: 29982223
 21. **Huaman MA**, Henson D, Rondan PL, Ticona E, Miranda G, Kryscio RJ, Mugruza R, Aranda E, Ticona C, Abarca S, Heredia P, Aguirre A, **Sterling TR**, Garvy BA, Fichtenbaum CJ. [Latent tuberculosis infection is associated with increased unstimulated levels of interferon-gamma in Lima, Peru](#). PLoS One. 2018 Sep 13;13(9):e0202191. PMID: 30212453, PMCID: PMC6136705
 22. Reichler MR, Khan A, **Sterling TR**, Zhao H, Moran J, McAuley J, Bessler P, Mangura B; Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team. [Risk and Timing of Tuberculosis Among Close Contacts of Persons with Infectious Tuberculosis](#). J Infect Dis. 2018 Aug 14;218(6):1000-1008. PMID: 29767733

Updates on Continuing Projects

Updates are categorized by the VTC's key research areas.

Treatment and Prevention

*Reducing the human reservoir of *M. tuberculosis* infection through early TB detection, treatment and prevention are vital to reducing the global burden of TB.*

Vanderbilt works closely with the **Centers for Disease Control and Prevention**, the **Tennessee Department of Health** and **Metro Nashville Public Health Department** to better treat and prevent TB disease among populations locally and internationally.

Tim Sterling and Program Manager **Hilary Vansell** continued to coordinate efforts of the Executive Affairs Group (EAG) of the **Tuberculosis Trials Consortium (TBTC) of the Centers for Disease Control and Prevention**, of which Tim Sterling serves as the Chair of the TBTC Steering Committee. The TBTC conducts programmatically relevant research that improves the treatment, prevention, and diagnosis of TB. Tim Sterling is leading **TBTC Study 37**, a new trial for latent TB infection. Study 37 will assess six weeks of daily rifapentine vs a comparator arm of 12-16 week rifamycin-based treatment for latent *M. tuberculosis* infection. To date, 6 study sites are now open for enrollment, and as of January 2020, 70 participants have been enrolled. A strength of the TBTC is close collaboration between academic researchers and public health programs. The TBTC has study sites throughout the United States as well as Peru, South Africa, Uganda, Kenya, Vietnam, and Hong Kong.

The Vanderbilt TBTC partner site at the **Universidad Peruana Cayetano Heredia** in Lima, Peru completed enrollment into a TB treatment shortening study (TB Trials Consortium Study 31). Study participants are in follow-up; the results are anticipated in late 2020. This project is being led by **Eduardo Gotuzzo, Alvaro Schwalb, Rodrigo Cachay, and Tatiana Caceres**.

Drug Resistance

Multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid and rifampin, and extensively drug-resistant TB (XDR-TB), defined as MDR-TB strains that are also resistant to fluoroquinolones and second-line injectable agents, are a growing concern. Researchers at Vanderbilt, with collaborators in Tennessee as well as Lima, Peru and Cape Town and Durban, South Africa, study resistance to TB drugs, with a particular focus on the fluoroquinolones. These agents are widely used to treat other bacterial infections, which can increase the risk of drug resistance in TB, and also affect the diagnosis and treatment of TB.

Work has continued on the **PRE-EMPT study** (Predictors of Resistance Emergence Evaluation in MDR-TB Patients on Treatment, R01AI134430), which is led by **Robert Horsburgh** at Boston University. This is an observational study of multi-drug resistant TB in which patients are being enrolled through RePORT-Brazil and RePORT-India. To date, more than 100 participants have been enrolled. Results of the OptiQ study of levofloxacin dose-ranging, conducted at the Cayetano site in Peru and in South Africa are expected in late 2020.

Neil Osheroff continued work on a VA grant, which was renewed in 2018 for an additional four years. This research focuses on interactions between fluoroquinolones (and related compounds) with DNA gyrase from wild-type and mutant *M. tuberculosis* strains. Understanding the basis of drug-gyrase interactions is a key concept in designing novel drugs that display greater activity against the enzyme and can overcome resistance. Recent findings have shown promising results, by **making a slight chemical change to the drug moxifloxacin, it has much better activity against the wild-type gyrase enzyme**; it maintains activity against resistant enzymes; and in all cases, it forms more stable DNA strand breaks. In addition, the **laboratory is working on a group of gyrase-targeted drugs** called "novel bacterial topoisomerase inhibitors" as well as other drug classes that are showing excellent activity against wild-

type and fluoroquinolone-resistant *M. tuberculosis* gyrase. This exciting work could have important therapeutic implications.

Yuri van der Heijden continued work on a K08 Career Development Award from the National Institutes of Health. He and his partners at **Stellenbosch University (Rob Warren)** and the **University of Cape Town (Keertan Dheda, Helen Cox)** in Cape Town, South Africa will continue to examine the acquisition of fluoroquinolone-resistant tuberculosis in a setting with high rates of MDR-TB and HIV. Yuri is also investigating drug resistance related to TB/HIV/Diabetes Mellitus. In May 2019 he became a Senior Researcher of the Aurum Institute in Johannesburg. He remains on the Vanderbilt faculty, and will split his time between South Africa and the United States.

Work is nearing completion on an NIH-funded R56 grant, “Fluoroquinolones and Efflux-Mediated Cross Resistance in HIV-related TB”, which builds on work done by **Brandon Eilertson, Fernanda Maruri, and Amondrea Blackman** on the role of DNA gyrase mutations and efflux pumps in fluoroquinolone resistance. This project is in collaboration with **David Sherman** and **Tige Rustad** from the Center for Infectious Disease Research (CIDR) in Seattle.

TB/HIV

TB is closely linked to HIV; HIV has been a key contributor to the TB epidemic. People with living with M. tuberculosis and HIV infection are significantly more likely to develop TB than persons who are HIV-negative. To control TB in high HIV-prevalence settings, it is imperative to coordinate efforts for TB and HIV control. Vanderbilt collaborates with international organizations and performs studies in population-based cohorts to identify ways to reduce the burden of TB among persons living with HIV.

Work continued on the R01 project, “**Predictors of treatment toxicity, failure, and relapse in HIV-related tuberculosis**” (R01 AI120790), which began in August 2016. This study builds on the existing **RePORT-Brazil Cohort**, for which Vanderbilt serves as the coordinating center. The over-arching goal of this project is to optimize the treatment of HIV-related tuberculosis in a large, genetically diverse cohort in Brazil, by characterizing the relationship between human genetic single nucleotide polymorphisms (SNPs), tuberculosis and HIV drug levels, and tuberculosis treatment outcomes. The project involves colleagues at all RePORT-Brazil sites (including **Adalberto Santos**) as well as Vanderbilt investigators **Tim Sterling, David Haas, Digna Velez Edwards, Richard Caprioli, Bryan Shepherd** and **Stephany Duda** and **Ed Acosta** from the University of Alabama-Birmingham. Participant enrollment is complete, and laboratory assays will be performed in the coming year.

In the past year, the **Caribbean, Central, and South America Network (CCASAnet) for HIV epidemiology**, headed by **Catherine McGowan** has continued to collect and synthesize data through the **Vanderbilt Data Coordinating Center (VDCC)**. CCASAnet has created a shared repository of HIV patient data that has been merged from 10 sites throughout Latin America. This dataset has allowed high-quality analyses of HIV and TB. The most recent analyses are being led by **Serena Koenig (GHESKIO), Bryan Shepherd, and Tim Sterling**, exploring mortality after presumed TB treatment completion in persons with HIV, and time to ART initiation regardless of TB status. An abstract presented at CROI 2019 was featured by NIH News! The abstract, titled “**Mortality after presumed TB treatment completion in persons with HIV in Latin America**”, found that among people with HIV in Latin America, those diagnosed with TB at an initial clinic visit were about twice as likely to die within 10 years as people not initially diagnosed with TB. The paper was published in *Clinical Infectious Diseases* in October 2019.

Work has continued on **Bryan Shepherd’s R01** grant titled “Statistical methods for correlated outcome and covariate errors in studies of HIV/AIDS”. This project involves two sites from CCASAnet in Peru and Mexico, and two sites from IeDEA-East Africa in Uganda and Kenya. The goal of this project is to create novel statistical methods, study design, and tools to assist with the validation of patient records and improve the estimation of outcomes for HIV/TB studies. The group is currently developing a study on the timing and type of test for bacteriologically confirmed TB and associated outcomes and will compare the validated and non-validated datasets.

April Pettit studies the epidemiology and outcomes of those co-infected with TB and HIV via datasets from large HIV cohort collaborations including **NA-ACCORD**, **CCASAnet**, **ART-CC**, and **leDEA**. A recently published paper in *Journal of the International AIDS Society* investigated directly observed therapy (DOT) and the risk of unfavorable TB treatment outcomes among an international cohort of people living with HIV in low- and middle-income countries (the leDEA cohort). Additionally, Dr. Pettit is involved in clinical studies of TB infection and disease via the **Tuberculosis Epidemiologic Studies Consortium** and the **Tuberculosis Trials Consortium**, funded by the Centers for Disease Control and Prevention. She is part of the protocol team of Study 31 which is investigating high-dose rifapentine with or without moxifloxacin for shortening treatment of pulmonary TB. She is also conducting studies of social and behavioral determinants of HIV care with the support of NIH R01 funding.

Yuri van der Heijden and John Koethe have a newly funded grant from CRDF Global to **explore immune activation and dysglycemia in TB patients with and without HIV**. This project is a collaboration between the VUMC CFAR site and the RePORT-South Africa AHRI site.

VUMC hosted two Ph.D. students from South Africa this past year as part of the **D43 training grant with University of Cape Town (UCT)**, titled “**HIV-Associated Tuberculosis Training Program (HATTP)**”. Zinhle Cindi spent January-October 2019 under mentorship of David Haas and Phuti Choshi is now with us from December 2019-April 2020 under mentorship of Elizabeth Phillips. This grant’s goal is to develop the next generation of clinician scientists in HIV-TB at UCT and accelerate transformation of the demographic composition of researchers at UCT to redress disparities that persist from apartheid.

C. William Wester leads a large **CDC-PEPFAR**-funded initiative in Mozambique entitled, “**Avante: Towards Epidemic Control**” where the Vanderbilt University Medical Center (VUMC)/Friends in Global Health (FGH) team provides technical assistance supporting the scale-up of comprehensive HIV and TB services, including the provision of combination antiretroviral therapy (ART). This 5-year grant allows VUMC/FGH to become the lead clinical partner within the province, expanding its scope of work and now being responsible for all 22 districts within the province. The VUMC/FGH team is making great strides in numerous areas, as they now provide extensive support to 144 sites that are providing potentially life-saving ART, a marked increase from 18 ART sites when the initiative began in late 2012. Within the last CDC grant year (September 30th, 2018 – September 29th, 2019), **> 95,000 patients were screened for TB (including contacts of persons with TB) in VUMC/FGH supported sites; with > 13,000 new TB patients being registered in the program and > 95% of eligible HIV/TB co-infected persons initiating ART**. An impressive 99% of eligible HIV/TB co-infected persons initiated cotrimoxazole prophylaxis as recommended by existing national guidelines. During this current CDC funding year (September 30th, 2019 – September 30th, 2020), the VUMC/FGH team plans to specifically focus on improving TB case identification among persons newly identified as being HIV-positive in the supported districts having the largest dual HIV & TB burdens, namely the districts of Quelimane, Inhassunge, Nicoadala, and Namacurra, while also focusing on improving the absolute number and proportion of eligible (active TB screen negative) placed on TB preventive therapy (TPT).

Transmission and Pathogenesis

A better understanding of the pathogenesis of TB is key to developing novel approaches to combatting this disease. Researchers at Vanderbilt along with international collaborators have been working to improve our understanding of the mechanisms behind M. tuberculosis transmission and pathogenesis.

Tim Sterling, Bruno Andrade (Brazil), and Thomas Hawn (UW) were awarded a **new R01** this year titled “Epidemiologic, immunologic, and genetic predictors and mechanisms of incipient, sub-clinical, and active TB in HIV-infected and -uninfected close TB contacts” (R01AI147765). This project **seeks to understand the protective and predisposing factors for progression from M. tuberculosis infection to TB disease**. The group will evaluate innate immune responses in macrophages and their correlates with human genetic polymorphisms, acquired

immunity to *M. tuberculosis*, and epidemiologic factors associated with the risk of incipient and active TB. These studies will be performed in the Regional Prospective Observational Research in Tuberculosis (**RePORT**)-Brazil cohort. This work may identify host pathways associated with protection against TB (for future host-directed therapies and vaccines), and to identify persons infected with *M. tuberculosis* who would benefit most from TB preventive therapy. Collaborators include **Spyros Kalams, Simon Mallal, and Peter Rebeiro at Vanderbilt; Bruno Andrade, Valeria Rolla, Afranio Kritski, Marcelo Cordeiro Santos, Solange Cavalcante, Cristina Lourenco, and Ricardo Khouri in Brazil; Thomas Hawn and Javeed Shah at the University of Washington; and Mark Hatherill, Thomas Scriba, and Stanley Kimbung at the University of Cape Town.**

The **Regional Prospective Observational Research for TB (RePORT)-Brazil** cohort is co-funded by the NIH and the Brazilian Ministry of Health. This multi-year observational cohort has been established to perform translational studies of the pathogenesis of *M. tuberculosis* infection and TB disease. The cohort consists of approximately 1200 TB cases and 2000 of their close contacts across 5 sites in three cities in Brazil (Rio de Janeiro, Salvador, and Manaus) and will lay the groundwork for many important future studies and funding opportunities for VTC members. It is coordinated with similar networks in India, South Africa, China, Indonesia, and the Philippines. Enrollment began in June 2015 in Rio de Janeiro, in January 2016 in Manaus, and in Salvador in June 2016. The first phase of enrollment ended June 30, 2019; follow-up will continue through June 30, 2021. There have been > 200,000 specimens collected, processed and stored in the biorepository.

The Vanderbilt-funded **Trans-Institutional Programs (TIPS)** award, “**Building a multi-disciplinary approach to assess the quality of healthcare in Brazil**” has been completed. **Heather Ewing** presented her MPH thesis on data on TB and stigma from the **Latin America Public Opinion Project (LAPOP)** survey that was conducted in Brazil as part of this grant. Peter Rebeiro is the first author on the manuscript that has been submitted for publication.

The VTC is also a partner site for the **Regional Prospective Observational Research for Tuberculosis (RePORT)-South Africa** with the **African Health Research Institute (AHRI, formerly KwaZulu-Natal Research Institute for TB and HIV)**. VUMC and AHRI were jointly awarded 3 years of funding from NIH and CRDF Global to enroll into the RePORT-South Africa network. **Tim Sterling, Yuri van der Heijden, and Fernanda Maruri** work alongside AHRI investigators **Adrie Steyn and Al Leslie; Farina Karim** and Khadija Khan serve as study coordinators. As of December 2019, enrollment and follow-up has been completed for all 100 participants. An application for renewal of the RePORT-South Africa funding is in progress, which will utilize previously collected specimens and propose new data collection and synthesis.

Spyros Kalams continued work on an R21 project investigating T-cells and the adaptive immune response to TB. This project is using single-cell sorting to evaluate T-cell receptors and peptide-specific human immune responses to *M. tuberculosis* to gain insights into potentially novel TB vaccine strategies. This work builds on an administrative supplement investigating biomarkers for TB infection and disease funded by National Institutes of Health (NIH) and the Brazilian Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). **Alexandre de Almeida, Chris Fiske, Spyros Kalams, Amondrea Blackman** worked on this project, studying a previously established cohort of TB patients and their close contacts. They seek to identify relevant biomarkers of two key TB outcomes: acquisition of *M. tuberculosis* infection and progression from infection to TB disease.

Bruno Andrade, Salvador site-PI for the RePORT-Brazil network and an adjunct faculty member at Vanderbilt, studies biomarkers for susceptibility to TB disease. Through a CRDF Global supplement, he and **John Koethe, Henrique Serezani, and Tim Sterling** are investigating prospective profiling of eicosanoid and inflammatory balance in TB-diabetes. This study will evaluate participants from RePORT-Brazil and RePORT-South Africa and will also utilize the Eicosanoid Core at Vanderbilt.

A new CRDF Global grant was awarded to **Thomas Hawn, Bruno Andrade, and Tim Sterling** investigating **macrophage immunogenetics and incipient tuberculosis in Brazil**. This project involves the RePORT-Brazil sites and the UW CFAR site and builds on work on latent infection already happening in the cohort.

Tools and Diagnostics

Rapid and accurate diagnosis is critical for timely initiation of TB treatment, but many people with TB (or TB symptoms) do not have access to adequate initial diagnosis. New tools and diagnostics are needed that can accurately diagnosis TB disease and be utilized in settings across the globe.

David Wright and Rick Haselton continue work on their R01, “**A 100-fold more sensitive TB diagnostic based on magnetic concentration and "coffee ring" formation**”. In many settings, inspection of a stained sputum sample under a microscope remains the primary diagnostic tool for tuberculosis. This project proposes a simple modification of this well-established procedure to increase its sensitivity and extend its capabilities to detect drug resistant strains. The approach is based on a magnetic gathering of tuberculosis bacilli from the total sputum volume and, using the microfluidics of “coffee ring” formation, concentrate any tuberculosis present into a pre-selected region of a slide for inspection by standard bright field microscopy.

There are two additional diagnostic projects in Brazil. The first is an evaluation of a **novel urine lipoarabinomannan (LAM) test** developed by **David Wright** that his doctoral student **Megan van der Horst** will evaluate in RePORT-Brazil specimens, in collaboration with Valeria Rolla and Adriano Gomes. The second is a **sputum PCR-based test (Truenat)** for the diagnosis of TB that is similar to the current GeneXpert test. This study is being led by Afranio Kritski in Brazil, in collaboration with other RePORT-Brazil investigators.

Next Steps and New Submissions

There are currently several NIH grants in development or under review. Program Managers Hilary Vansell and Andressa Scussel will continue to seek out and announce TB funding opportunities as they are posted and offer support in developing the necessary components. All TB-related grants can be found in the “Grants Progress” Table, as well as any recent submissions.

We also wish to add a laboratory-based investigator with strengths in latent *M. tuberculosis* infection, including methods to improve its detection, and factors associated with progression to tuberculosis disease. A background in host and/or pathogen genomics would be beneficial for both the VTC and the Division of Infectious Diseases. Such a scientist would provide synergy with the current strengths of the VTC, including expertise in population-based work, and access to large, well-characterized cohorts.

VTC Collaborators



Local and International Collaborators

The VTC is a joint effort of the Division of Infectious Diseases within the Department of Medicine and the Vanderbilt Institute for Global Health. In addition to other partners at Vanderbilt, local and international collaborators include:

- Metro Nashville Public Health Department
- Tennessee Department of Health
- Meharry Medical College
- Friends in Global Health, LLC
- Vanderbilt Center for Latin American Studies
- Latin American Public Opinion Project (LAPOP)
- The Tuberculosis Trials Consortium (TBTC) of the Centers for Disease Control and Prevention (CDC)
- The Tuberculosis Epidemiologic Studies Consortium (TBESC) of the CDC
- Southeastern National Tuberculosis Center
- International Epidemiologic Databases to Evaluate AIDS (leDEA)—NIH
- The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of leDEA
- The Antiretroviral Therapy Cohort Collaboration
- The Caribbean, Central and South America Network (CCASAnet) for HIV Epidemiology-leDEA
- Regional Prospective Observational Research for Tuberculosis- Brazil (RePORT Brazil)
- Fundacao Oswaldo Cruz (Fiocruz), Instituto Nacional de Infectologia, Rio de Janeiro, Brazil
- Universidad Peruana Cayetano Heredia, Peru
- Regional Prospective Observational Research for Tuberculosis- South Africa (RePORT SA)
- The Africa Health Research Institute, South Africa
- The Aurum Institute, South Africa
- Stellenbosch University, South Africa
- University of Cape Town, South Africa
- University of Witwatersrand, South Africa