

# Vanderbilt Tuberculosis Center

VANDERBILT  UNIVERSITY  
MEDICAL CENTER

## Annual Report

FY 2018

July 2017 – June 2018

## 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 more than 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:

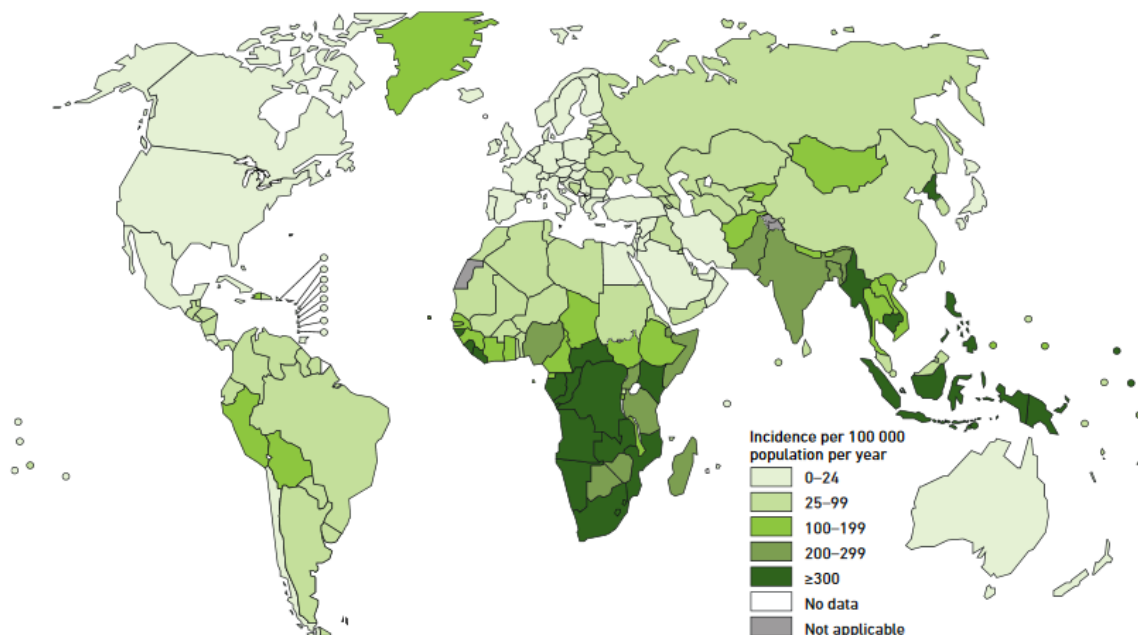
1. **Expand the Vanderbilt global research portfolio** in TB and TB/HIV, with a focus on epidemiology, clinical trials, and translational research.
2. **Develop and mentor junior faculty members, fellows, and students** from Vanderbilt, Meharry, and collaborating health departments and international 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 2017, the World Health Organization (WHO) estimates 10 million people developed TB disease, there were 1.3 million deaths among HIV-negative people and an additional 300,000 deaths from TB among HIV-positive people. The figure below details incidence by country (WHO Global TB Report 2018).

**Estimated TB incidence rates, 2017**



## FY 2018 Executive Summary

FY 2018 was filled with many grant submissions and much progress on currently active projects.

In September of 2017, the **Regional Prospective Observational Research for Tuberculosis (RePORT)-Brazil** and **RePORT-International** meeting was held in Rio de Janeiro, Brazil. 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 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 2018, RePORT-Brazil had enrolled 1,906 participants, and RePORT-South Africa AHRI site has enrolled 100 participants.



Bruno Andrade and Valeria Rolla, RePORT-Brazil principal investigators, visit VUMC

Several RePORT-linked funding opportunities have been submitted and awarded this past year. In January 2018, several supplements were submitted to **CRDF Global's** RePORT supplemental funding RFA which requires cross-collaboration between RePORT regions. RePORT-Brazil and RePORT-South Africa were awarded a supplement entitled "**Towards a global TB biomarker: Comparison of small transcriptomic signatures to predict, diagnose and monitor TB disease**", which is currently in progress. VUMC investigators also continue work on a supplement funded in the previous cycle titled, "**Prospective profiling of eicosanoid and inflammatory balance in TB-diabetes**". An R01 application was also submitted in January 2018 in response to the NIH RFA calling for proposals to study mechanisms of mycobacterial-induced immunity in HIV-infected and uninfected individuals. This study will utilize RePORT-Brazil specimens and the application will be re-submitted in January 2019. Finally, in August 2018 a large program grant was submitted in collaboration with **Jyothi Rengarajan of Emory University** to NIH's call for "Immune Mechanisms of Protection Against Mycobacterium Tuberculosis Centers (IMPAC-TB)". Review of this application is pending.



VUMC investigators, staff, and guest visitors at the April 2018 "Cutting-Edge Translation Research in TB Symposium"

The VTC hosted many collaborators on campus in April 2018 for the "**Cutting-Edge Translational Research in Tuberculosis Symposium**". Guest speakers **Thomas Hawn (University of Washington)** presented on macrophages and resistance to M.tb infection, **Bruno Andrade (Brazil)** spoke about immune profiling in TB patients using biomarkers, and **Moises Human (University of Cincinnati)** described his recent work on M.tb infection and cardiovascular disease. VUMC investigators **Spyros Kalams** and **Simon Mallal** also

presented on single cell analyses to elucidate adaptive immune responses to pathogens for applications for vaccines. It was a very productive meeting and enhanced collaborations for submission of the IMPACTB application mentioned above.

Significant progress has been made on a new CDC-funded trial that will be conducted by the **Tuberculosis Trials Consortium (TBTC)**, the **Tuberculosis Epidemiologic Studies Consortium (TBESC)** and the **British**

**Medical Research Council (BMRC).** 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 the development of this trial, and study sites are currently completing start-up activities. Enrollment is expected to begin in early 2019. Results were published in November 2017 for another trial funded through the TBTC, **Study 33**, of which Vanderbilt/Metro Public Health TB Clinic was an enrolling site. The results of this study support using self-administered, once-weekly isoniazid and rifapentine to treat latent TB infection in the United States, and such treatment could be considered in similar settings when directly-observed therapy (DOT) is not feasible.

Our partnerships in **South Africa** continued to flourish this past year. A new **D43 training grant** was awarded to the **University of Cape Town (UCT)**, with VUMC as a partner and mentor site. The program, titled “**HIV-Associated Tuberculosis Training Program (HATTP)**” will work 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. **Yuri van der Heijden** continues work on his K08 award on drug-resistance in South Africa and presented an abstract at the IWHOD conference in April 2018 entitled, “**Differences in ascertainment of tuberculosis resistance according to four patient-matching strategies using programmatic laboratory data in South Africa**”. He also submitted an R01 application in September 2018 involving partners at UCT and Stellenbosch University for further exploration of drug-resistance in TB; the review is pending.



Kate Clouse, Yuri van der Heijden, and Fernanda Maruri meet up in Cape Town, South Africa

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.

**Bryan Shepherd** and **Tim Sterling** submitted an R34 clinical trial planning grant in May 2018 entitled “**Planning Grant for the TuLHIP Trial (Tuberculosis Treatment Length and Adherence in HIV-Positive Persons)**”. If funded, this grant will involve three sites that are currently part of the **leDEA Network (International epidemiology Databases to Evaluate AIDS)** in Kenya, Haiti, and Peru, and a new partner site in Mozambique. This pragmatic randomized controlled trial seeks to test the effectiveness of extending TB treatment duration to improve clinical outcomes among persons with HIV and TB. It will also test the effect of an electronic medication adherence reminder to improve adherence.

FY 2018 saw many guest speakers and visitors come to the VU/VUMC campus. In October 2017, **Charles Daley (National Jewish Hospital)** presented Medicine Grand Rounds on nontuberculous mycobacteria. **Clare Smith (University of Massachusetts)** presented in November 2017 on the underlying genetics of tuberculosis susceptibility. In February 2018,



Paul Farmer and VUMC investigators and ID fellows in February 2018

Vanderbilt University School of Medicine (VUSM) hosted **Paul Farmer** on campus. The VTC and the ID Division faculty and staff were able to spend some time with Dr. Farmer, hearing his advice for new faculty and detailing our current work in Haiti and Peru. Finally, in June 2018, **Kelly Chibale (University of Cape Town)** visited campus. Dr. Chibale gave several talks, focusing on his role in pioneering translational medicine in Africa in malaria and tuberculosis. The VTC was thrilled about the establishment of the **Vanderbilt Institute for Infection, Immunology, and Inflammation (VI4)** in July 2017, and are grateful for their partnership in promoting guest speakers in TB research.

## Research and Grant Funding

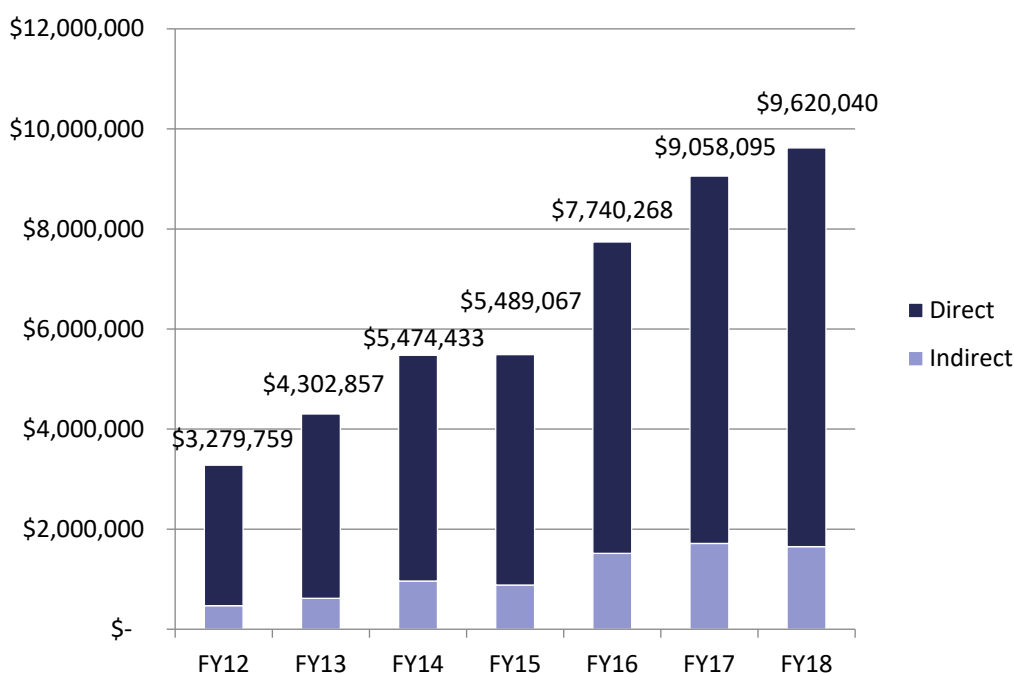
In the previous fiscal year (July 1, 2016 - June 30, 2017), there were 26 TB research projects with total grant funding of \$9,058,095 (\$7,345,091 direct costs, \$1,713,004 indirect costs).

**In the current fiscal year (July 1 2017 – June 30 2018), there are 29 TB research projects and total grant funding of \$9,620,040 (\$7,968,619 direct costs, \$1,651,421 indirect costs), a 6.2% increase in total funding from FY2017.** Please see the table at the end of this document. Not included in the table is the endowed David E. Rogers Professorship, which provided 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. 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, 2012-2018**



## Education, Training, and Service

The **weekly TB case conference** held in collaboration between the Metro Public Health Department, the Tennessee Department of Health, Meharry Medical College, and Vanderbilt continued for its 15<sup>th</sup> year, led by 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 Dr. Sterling on Friday mornings at the Metro Public Health Department TB Clinic.

Tim Sterling also presented at various meetings throughout the year. He gave a lecture on treatment of latent *M. tuberculosis* infection at **IDWeek** (October 2017), the **London School of Hygiene and Tropical Medicine** (November 2017), the **International Consortium for Trials of Chemotherapeutic Agents in TB** (INTERTB; November 2017), and the **American Thoracic Society** (May 2018). He also gave an update on the diagnosis and treatment of TB at the **American Society for Microbiology Microbe** meeting (June 2018). He served on the **World Health Organization Task Force on Latent Tuberculosis Infection** and contributed to the **U.S. Department of Health and Human Services Adult HIV Opportunistic Infection Guidelines**.

The **Metro Nashville Public Health Department** hosted a **World TB Day 2018** awareness event 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. They also premiered a video they created featuring “Tubercules”, which was led by Amber Coyne. The video is a virtual clinical tour guided by a TB superhero and combines humor and action to walk patients through the TB evaluation and treatment initiation process, breaking down the fear that can sometimes accompany TB testing and treatment. The video also won the **CDC’s TB ETN 2018 Project Excellence Award**. [Link to video](#).



Metro Nashville TB Clinic staff on World TB Day 2018 and Amber Coyne as “Tubercules”!



Lauren Saag, PhD Candidate, joined the VTC in August 2017

The VTC was pleased to welcome **Lauren Saag, PhD candidate** to the group in August 2017. Lauren is completing her PhD in epidemiology and is working closely with Tim Sterling and the RePORT-Brazil cohort. The **Vanderbilt Comprehensive Care Clinic (VCCC)** also hosted two Vanderbilt undergraduate students, Trisha Pahawa and Kamaria Wilson, in Summer 2018 to work with Megan Turner on the HIV Epidemiology Outcomes project.

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. In July 2017 the VTC launched an updated newsletter platform. To receive VTC newsletters, [sign up here](#).

The VTC continued to host **quarterly meetings** to foster collaboration in TB research at Vanderbilt. In August 2017, **Heather Ewing**, MPH student, presented on research originating from a Vanderbilt TIPS project on TB stigma in Brazil. During her presentation, entitled “Stigma and Social Determinants of *M. tuberculosis* transmission and TB control”, she discussed the results of a survey conducted through LAPOP, which asked

questions to participants about TB and associated stigma. **Tim Sterling** also gave an update of ongoing grants and projects and discussed future directions of the TB Center.

In January 2018, **Jason Cummins**, TB Control Program Manager for the TN State Department of Health, presented on TB epidemiology for the state of Tennessee in 2017. **Stephanie Pearlman**, a doctoral student in the Haselton Lab also presented on a new R01 grant awarded to their lab, titled “A 100-fold more sensitive diagnostic based on magnetic ring concentration and “coffee ring” formation”.

In August 2018, **Lauren Saag**, doctoral student, 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).

### **Selected Recent Publications (2017-2018)**

1. 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
2. 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. 2018 Nov 24. [Epub ahead of print]. PMID: 30481307
3. 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
4. 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
5. 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
6. 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
7. Gibson EG, Blower TR, Cacho M, Bax B, Berger JM, Osheroff N. [Mechanism of Action of Mycobacterium tuberculosis Gyrase Inhibitors: A Novel Class of Gyrase Poisons](#). ACS Infect Dis. 2018 Aug 10;4(8):1211-1222. PMID:29746087
8. van der Heijden YF, Karim F, Chinappa T, Mufamadi G, Zako L, Shepherd BE, Maruri F, Moosa MS, Sterling TR, Pym AS. [Older age at first tuberculosis diagnosis is associated with tuberculosis recurrence in HIV-negative persons](#). Int J Tuberc Lung Dis. 2018 Aug 1;22(8):871-877. PMID: 29991395, PMCID: PMC6064608
9. Amaral EP, Riteau N, Moayeri M, Maier N, Mayer-Barber KD, Pereira RM, Lage SL, Kubler A, Bishai WR, D'Império-Lima MR, Sher A, Andrade BB. [Lysosomal Cathepsin Release Is Required for NLRP3-Inflammasome Activation by Mycobacterium tuberculosis in Infected Macrophages](#). Front Immunol. 2018 Jun 21;9:1427. PMID: 29977244, PMCID: PMC6021483
10. Moro RN, Scott NA, Vernon A, Tepper NK, Goldberg SV, Schwartzman K, Leung CC, Schluger NW, Belknap RW, Chaisson RE, Narita M, Machado ES, Lopez M, Sanchez J, Villarino ME, Sterling TR. [Exposure to Latent](#)

- [Tuberculosis Treatment during Pregnancy](#). The PREVENT TB and the iAdhere Trials. Ann Am Thorac Soc. 2018 May;15(5):570-580. PMID: 29393655
11. Huaman MA, Ticona E, Miranda G, Kryscio RJ, Mugruza R, Aranda E, Rondan P, Henson D, Ticona C, Sterling TR, Fichtenbaum C, Garvy BA. [The Relationship between Latent Tuberculosis Infection and Acute Myocardial Infarction](#). Clin Infect Dis. 2018 Mar 5;66(6):886-892. PMID: 29069328, PMCID:PMC5850031
  12. Ramírez S, Mejía F, Rojas M, Seas C, Van der Stuyft P, Gotuzzo E, Otero L. [HIV screening among newly diagnosed TB patients: a cross sectional study in Lima, Peru](#). BMC Infect Dis. 2018 Mar 20;18(1):136. PMID: 29558891, PMCID: PMC5861614
  13. Pettit AC, Giganti MJ, Ingle SM, May MT, Shepherd BE, Gill MJ, Fätkenheuer G, Abgrall S, Saag MS, Del Amo J, Justice AC, Miro JM, Cavasinni M, Dabis F, Monforte AD, Reiss P, Guest J, Moore D, Shepherd L, Obel N, Crane HM, Smith C, Teira R, Zangerle R, Sterne JA, Sterling TR; Antiretroviral Therapy Cohort Collaboration (ART-CC) investigators. [Increased non-AIDS mortality among persons with AIDS-defining events after antiretroviral therapy initiation](#). J Int AIDS Soc. 2018 Jan;21(1). PMID: 29334197, PMCID: PMC5810321
  14. Hussain S, Hasnain J, Hussain Z, Badshah M, Siddique H, Fiske C, Pettit A. [Type of Treatment Supporters in Successful Completion of Tuberculosis Treatment: A Retrospective Cohort Study in Pakistan](#). Open Infect Dis J. 2018;10:37-42. PMID: 30008966, PMCID: PMC6044441
  15. Bourgi K, Fiske C, Sterling TR. [Tuberculosis Meningitis](#). Curr Infect Dis Rep. 2017 Sep 11;19(11):30. PMID: 28895024.
  16. Belknap R, Holland D, Feng PJ, Millet JP, Caylà JA, Martinson NA, Wright A, Chen MP, Moro RN, Scott NA, Arevalo B, Miró JM, Villarino ME, Weiner M, Borisov AS; TB Trials Consortium iAdhere Study Team. [Self-administered Versus Directly Observed Once-Weekly Isoniazid and Rifapentine Treatment of Latent Tuberculosis Infection: A Randomized Trial](#). Ann Intern Med. 2017 Nov 7. [Epub ahead of print] PMID: 29114781
  17. Ashley RE, Blower TR, Berger JM, Osheroff N. [Recognition of DNA Supercoil Geometry by Mycobacterium tuberculosis Gyrase](#). Biochemistry. 2017 Oct 10;56(40):5440-5448. Epub 2017 Sep 25. PMCID: PMC5637011

## Updates on Continuing Projects

Updates are categorized by the VTC's four 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 has been working 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. TB Trials Consortium Study 33 evaluated self-administered vs. directly-observed once-weekly rifapentine + isoniazid for 3 months. The Metro Nashville/Vanderbilt site was among the highest enrolling sites in the TBTC. The results of this study were published in Annals of International Medicine in November 2017 (see publication list on pg. 8.) **Amy Kerrigan**, **Alicia Wright**, and **Diedra Freeman** were key contributors to this study.

**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 development and initiation of **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. This trial will also enroll through the **Tuberculosis Epidemiologic Studies Consortium (TBESC)** and the **British Medical Research**



**Council** (BMRC) and is expected to begin in early 2019. Sites are currently completing start-up activities. 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.

Work continued on the development of observational TB cohorts in Durban, South Africa, in collaboration with our partners at the **Africa Health Research Institute (AHRI)**. **Yuri van der Heijden, Fernanda Maruri, and Tim Sterling**, together with **Farina Karim, Khadija Khan, Yunus Moosa, and Alex Pym** have analyzed data from > 90,000 TB patients who received treatment at the Prince Cyril Zulu Communicable Diseases Clinic from 2000-2012. They published their findings that isoniazid-monoresistant tuberculosis was associated with poor treatment outcomes in the *International Journal of Tuberculosis and Lung Disease* in June 2017. In addition, enrollment in a prospective cohort in the Kwadabeka township near Durban has progressed, 100 patients have been enrolled as of December 2017. This work is supported by the U.S. National Institutes of Health and the South African Medical Research Council through **RePORT-South Arica**.

**Aaron Kipp** completed a study, “**Validation of TB stigma scales in Buffalo City Metropolitan, Nkangala and Tshwane Districts in South Africa**”. This was a new collaboration with **Andrew Medina-Marino** from Foundation for Professional Development in South Africa. This builds on Dr. Kipp’s early work on stigma and TB treatment outcomes. TB remains a stigmatized disease that adversely impacts testing, care, and treatment. Improving these outcomes requires being able to characterize these social factors in order to evaluate interventions that can reduce their impact.

## 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.*

**Neil Osheroff** continues 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. 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 and is planning future grant applications with his collaborators in South Africa.

Work continued 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) and **Rob Warren** from Stellenbosch University in South Africa.

The Vanderbilt TBTC partner site at the **Universidad Peruana Cayetano Heredia** in Lima, Peru completed enrollment into a levofloxacin dose-ranging study among patients with MDR-TB (TBTC Study 32). The results will

provide important information regarding the optimal dose of levofloxacin, a key component of MDR-TB treatment. This project is being led by **Eduardo Gotuzzo, Juanita Sedamano, Juan Santillan, Alvaro Schwalb, Rodrigo Cachay, and Bob Horsburgh.**

## 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.

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. Two abstracts from these data have been accepted for presentation at CROI 2019 in Seattle, WA.

**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 provision of antiretroviral therapy (ART). This 5-year grant allows VUMC/FGH to become the lead clinical partner within the province, expanding its work into 7 new districts within the province (in addition to taking over the provincial capital district of Quelimane a few years ago). The VUMC/FGH team is making great strides in numerous areas, as they now support 190 sites (as of September 30, 2018) that are providing potentially life-saving combination antiretroviral therapy (ART), a marked increase from 18 ART sites when the initiative began in late 2012. Within the last CDC grant year (October 1<sup>st</sup>, 2017 – September 30<sup>th</sup>, 2018), **~80,000 patients were screened for TB (including contacts of persons with TB) at their last clinical visit at VUMC/FGH supported sites; with 7,333 new TB patients being registered in the program and 94% 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 (October 1<sup>st</sup>, 2018 – September 30<sup>th</sup>, 2019), the VUMC/FGH team plans to specifically focus on improving the timeliness of TB diagnosis via the broad implementation of the Gene Xpert diagnostic test, improving the detection and management of persons with drug resistant TB, as well as improve TB infection control via site refurbishment to improve patient flow and air flow/ventilation.

**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**. Two studies of TB-HIV from the leDEA cohort have been published: one with **Kate Clouse** demonstrating low rates of use of the

GeneXpertTB diagnostic test in this population, and another led by Pediatric ID Fellow (now junior faculty member) **James Carlucci** on TB treatment outcomes in HIV/TB co-infected children in resource limited settings. Results of an ART-CC study examining mortality due to non-AIDS defining events in HIV patients on ART have also been published. 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 also conducting studies of social and behavioral determinants of HIV care with the support of NIH R01 funding.

Recent research suggests that HIV-positive women in southern Africa who initiate antiretroviral therapy during pregnancy may be at high risk of dropping out of HIV care after delivery. Through a four-year K01 award from the National Institute of Mental Health, **Kate Clouse** is exploring the impact of frequent mobility and travel around the time of delivery on postpartum retention in HIV care in South Africa. The work includes quantitative and qualitative components to explore “clinic shopping,” access to care, and to characterize patterns of mobility.

**Carolyn Audet** had a K01 career development award to assess feasibility of engaging traditional healers as HIV and TB treatment partners in Mozambique. HIV-positive people living in rural Mozambique often consult a traditional healer prior to seeking help from a clinic, delaying diagnosis and treatment. Healers are ideally positioned to improve HIV and TB health outcomes of this population by linking them to clinical care and treatment and improving medication adherence. Her study focuses on developing a sustainable, practical, and effective relationship between traditional healers and the health care system, the Mozambican Ministry of Health. This work led to successful funding of a new R01 grant focusing on partners-based HIV treatment for sero-concordant couples attending antenatal care.

### 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.*

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 will consist of at least 1200 TB cases and 2700 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. As of June 2018, 1,906 participants have been enrolled and > 50,000 specimens have been 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. The paper 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** serves as the study coordinator. As of December 2017, 100 participants have been enrolled into the cohort.

**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** are working 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.

**Christina Fiske** focuses on the human immune response to *M. tuberculosis*. Specifically, she is interested in the immune responses of persons with different manifestations of TB: latent *M. tuberculosis* infection, pulmonary TB and extrapulmonary TB. She is currently studying the expression and function of the Toll-like receptor 2 (TLR2) and vitamin D pathways in persons with previous TB disease and infection.

### [Next Steps and New Submissions](#)

There are currently several NIH grants in development or under review. Ms. Vansell 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.

The VTC will continue discussions with VUMC Office of Development to diversify its funding portfolio. This will be a long-term process that will require the cultivation of relationships with key groups/persons.

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 (IeDEA)—NIH
- The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA
- The Antiretroviral Therapy Cohort Collaboration
- The Caribbean, Central and South America Network (CCASAnet) for HIV Epidemiology-IeDEA
- 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 KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH), South Africa
- Stellenbosch University, South Africa
- University of Cape Town, South Africa
- University of Witwatersrand, South Africa