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Optimizing the Protection of Research Participants and Personnel in HIV-Related Research where TB is Prevalent: Practical Solutions for Improving Infection Control

Jason E. Farley, PhD, MPH, CRNP^{1,7}, Timothy F. Landers, PhD, CNP², Catherine Godfrey, MD, FRACP³, Virginia Lipke, RN, MHA, ACRN, CIC⁴, and Jeremy Sugarman, MD, MPH, MA^{5,6,7}

¹Johns Hopkins University School of Nursing

²The Ohio State University College of Nursing

³National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID)

⁴Centers for Disease Control and Prevention, Division of Global HIV/AIDS (GAP)

⁵Johns Hopkins Berman Institute of Bioethics

⁶Johns Hopkins University School of Medicine

⁷Johns Hopkins Center for AIDS Research (CFAR)

Abstract

Tuberculosis (TB) is a leading cause of death among persons with Human Immunodeficiency Virus (HIV) globally. HIV-related research in TB endemic areas raises some unique and important ethical issues in infection control related to protecting both research participants and personnel. In order to address such concerns, this paper provides practical guidance to help research teams develop strategies to prevent TB transmission in studies involving persons with HIV in TB endemic settings.

Keywords

infection control; TB; HIV; Clinical research; Human Subjects Protections; ethics

Mycobacterium tuberculosis (TB) is a leading cause of death among persons with Human Immunodeficiency Virus (HIV).¹ Molecular epidemiologic evaluations clearly demonstrate hospital-associated transmission of TB in settings with high HIV prevalence.^{2,3} Research participants and personnel conducting HIV-related research may be exposed to TB, including drug resistant TB strains through airborne exposure. Gathering participants for research purposes in some settings may therefore increase risk for transmission to research participants and personnel. Visit frequency, duration, the proximity to other participants, and many environmental factors affect this risk. Indeed, incident TB is often a primary outcome of clinical trials attempting to define the best strategies for preventing HIV-infection or treating those who are infected.^{4,5} Even in the best of circumstances with active case finding

Corresponding Author: Jason E. Farley, PhD, MPH, CRNP Assistant Professor, Johns Hopkins University School of Nursing Adult Nurse Practitioner, Johns Hopkins University School of Medicine Co-Director Clinical Core, Johns Hopkins University Center for AIDS Research (CFAR) Co-PI, Pennsylvania/MidAtlantic AIDS Education and Training Center (AETC) 525 N. Wolfe Street, Suite 525 Baltimore, MD 21205 Ph: 410-502-7563 FAX: 410-955-7733 jfarley1@jhu.edu.

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and policies which isolate individuals with cough,⁶ crowded waiting rooms, long study visits, and facilities with poor ventilation bring potentially infectious people in close contact with research personnel and research participants who are at high risk for developing TB. HIV-infected patients are more commonly sputum smear negative for TB than HIV uninfected patients, but they remain infectious and the diagnosis of TB may be delayed.⁷

In settings where TB is prevalent, trial design and conduct should account for factors that may pose additional risks to research participants and take measures to minimize them. Incorporating TB infection control (TBIC) into research may be challenging since evidence-based infection control practices have not been adopted in many clinical and community settings where HIV-related research may be conducted.⁸⁻¹³ The AIDS Clinical Trials Group has adopted a guideline for TB prevention at its clinical sites, but it is unclear whether similar approaches are being implemented in other research settings. Furthermore, there remains a paucity of literature on the implementation of TBIC measures¹⁴ and infection control measures¹⁵ specifically in HIV-related research settings.¹⁶⁻¹⁹ However, it is clear that biomedical interventions that may be included in HIV-related research, such as intensified case findings, rapid diagnostics, access to isoniazid preventative therapy to prevent activation of TB, and earlier antiretroviral therapy²⁰ confer TB prevention benefits both directly to the recipient of the intervention and to others as a result of decreased opportunities for exposure.^{21,22} Regardless, in order to minimize risk of TB transmission, it is essential that research teams implement comprehensive approaches to TB prevention that incorporate both biomedical interventions as well as system level IC interventions, including site level guidance to facilitate appropriate implementation.

In this paper, we outline practical strategies for clinical research teams in settings where TB is prevalent to follow established TB infection control (TBIC) practices and guidelines.²³⁻²⁵ In addition to antiretroviral therapy (ART) and appropriate biomedical management of HIV disease, these infection control strategies are critical to mitigate risk for research participants and personnel.

Proposed Steps in Protecting Research Participants and Personnel

Risk Assessment

A comprehensive TB risk assessment is an essential first step for TBIC. This begins with evaluating the settings where initial contact with participants will occur. Local TB epidemiology, administrative and environmental controls at the proposed sites and available personal protective equipment (PPE) should be reviewed. Baseline knowledge of TBIC principles among research personnel is a critical element in the initial assessment, and level of education regarding TBIC is a measurable outcome of TBIC initiatives.

The Centers for Disease Control and Prevention (CDC) has developed a brief TBIC monitoring and evaluation checklist for use in TB/HIV clinical settings. A modified version to facilitate the completion of a research site risk assessment is shown in Table 1.²⁶ This modified checklist for research includes: 1) integrating TBIC procedures into research protocols; 2) attending to managerial aspects of TBIC; 3) administrative controls; 4) environmental controls; and 5) promoting use of PPE among research participants and study personnel. As delineated in the Table, the comprehensive approach to TBIC that is developed should be incorporated into relevant parts of study protocols, procedure manuals and a managerial plan. Doing so helps to ensure transparency, accountability and implementation.

Administrative Controls

Administrative Controls (ACs) are system level changes designed to decrease exposure to infectious patient-participants.⁹ These standard TBIC activities include segregating coughing participants, fast-tracking smear-positive participants or requiring participants to wear a surgical mask. Cough hygiene and use of a simple surgical mask reduces airborne droplets²⁷ and has been shown to be highly acceptable to patients in clinical settings;²⁸ however, in a recent survey of research sites in resource limited settings only 40% of sites had cough hygiene information available to participants.²⁹

In clinical practice, these interventions are challenging because they require oversight, adequate resources for appropriate implementation, and may require sensitivity training to reduce stigma associated with mask use. Further, in many settings, there are no enforcement requirements for these interventions. Despite these challenges, efforts should be taken to implement ACs in research sites. For example, in designing recruitment plans consideration should be given to incorporating a risk reduction strategy to decrease the likelihood of persons with active TB being in contact with others. Sputum specimen collection should occur in a manner that minimizes risk to others at the site and follow-up visits should minimize transmission risk. Consideration should also be given toward adopting a robust TB diagnostic strategy, intensified case finding and the ability to offer isoniazid preventive therapy.

Environmental Controls

Environmental controls (ECs) include activities that decrease TB bacilli in the clinical environment. Practical ECs do not require costly renovations and small environmental changes can make a large difference. Adequate ventilation, measured in air exchanges per hour (ACH), is the most commonly applied EC and may have an important impact on infectivity. ACHs can be determined through simple calculations and standardized worksheets permit estimation in a variety of clinical settings.³⁰

Twelve ACH are recommended in conditions requiring airborne isolation and may be achievable with open windows and cross-ventilation under the right circumstances. In determining the appropriate placement and use of ECs, site staff should consider where study personnel meet with potential participants, particularly those who have not been screened or tested for TB or who are undergoing diagnostic procedures. Examples of low cost practical solutions include providing a covered space for outdoor sputum collection, covering a waiting area outdoors to prevent long waiting time indoors, and ensuring open window policies (including awnings that allow them to remain open in rainy weather). Wind driven roof turbines are a less costly alternative to mechanical ventilation and have been shown to meet minimum air exchange requirements.³¹ Where funding is available, consideration should be given to using upper room ultra violet germicidal irradiation (UVGI)³² with scheduled cleaning, working fans³³ and a routine maintenance plan to prevent dust and debris from collecting, which reduces their effectiveness.

Personal Protective Equipment

Use of a simple paper mask by patients has been shown to reduce TB transmission by over 50% in a guinea pig model in South Africa.²⁷ The use of N95 respirators in clinical personnel (also known as FFP2 respirators) with appropriate annual fit testing or seal checks prior to entering clinical areas is a proven intervention for the prevention of nosocomial spread of TB.³⁴ Although clinical settings in which drug resistant TB is common tend to have policies that require PPE use, adherence to these policies may be limited, and there are few regulatory controls regarding their enforcement.⁸ Research teams may be better positioned to enforce such policies. For example, study personnel may be required to attend

annual IC trainings and to use PPE; failure to do so could result in a poor performance appraisal or dismissal from duty. From the participants' perspective, implemented correctly (i.e., all persons attending the research site wear a mask while inside the research setting) then stigma or disclosure of status is not propagated because it is an expectation of everyone in the site.

Putting Infection Control Plans into Research Practice

Developing practical strategies for prevention of TB transmission in HIV-related research in areas where TB is prevalent can be accomplished with appropriate planning. Figure 1 provides a schematic overview of the critical elements of the necessary steps in this process. Education of personnel about TB transmission principles and personal risk is also critical. Periodic occupational health evaluation and training of staff can raise awareness of the importance of TBIC.³⁵ As described above, internationally recognized guidance for risk assessment and mitigation is available from the CDC and may be adapted for the specific research study plans²⁶ as well as trainings for the research team.¹⁴ Although mathematical modeling exercises³⁶ provide some perspective on the relative benefit of concomitant interventions, the key TBIC strategy is the careful analysis of the individual circumstances of each research study and the development of tailored SOPs to mitigate risk. While outside the scope of this paper, engaging local communities in TB and/or HIV research is an important step in developing TBIC plans that have buy-in within the targeted community.³⁷

Concluding Comments

Prevention of TB transmission in HIV-related clinical research is an important means of helping to minimize risks to research participants and personnel. Transmission of TB in hospitals and clinical sites where care of patients with HIV is given is well documented and usual practices in research settings may be inadequate to protect against TB transmission. In order to mitigate risk and protect research participants and personnel, investigators should examine each protocol carefully and the settings in which it will be implemented. Conducting risk assessments during protocol development should help to ensure that inadequacies in TBIC can be addressed. Further research is needed on TBIC implementation within research settings and data on the efficacy of these measures are required particularly given the additive costs incurred with implementation of both biomedical and other TBIC strategies. Regulatory measures, such as funder driven requirements, may strengthen implementation of TBIC. While there are emerging data on the cost-effectiveness of biomedical interventions for TB prevention,³⁸⁻⁴⁰ such data for programmatic TBIC strategies remain sparse within both clinical and research settings. Nonetheless, until such data are available, it seems reasonable to assume that having a keen understanding of biomedical as well as cultural, administrative, and environmental aspects of TBIC should help reduce the likelihood of TB transmission, thereby optimizing the protection of research participants and personnel.

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Reference

1. Tuberculosis Fact Sheet. World Health Organization; 2013. [serial online] [August 1, 2013]
2. Andrews JR, Gandhi NR, Moodley P, et al. Exogenous reinfection as a cause of multidrug-resistant and extensively drug-resistant tuberculosis in rural South Africa. *J Infect Dis.* 2008; 198:1582–1589. [PubMed: 18847372]
3. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet.* 2006; 368:1575–1580. [PubMed: 17084757]
4. Severe P, Juste MA, Ambroise A, et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *N Engl J Med.* 2010; 363:257–265. [PubMed: 20647201]
5. Cohen MS, Gay CL. Treatment to prevent transmission of HIV-1. *Clin Infect Dis.* 2010; 50(Suppl 3):S85–S95. [PubMed: 20397961]
6. Burgess AL, Fitzgerald DW, Severe P, et al. Integration of tuberculosis screening at an HIV voluntary counselling and testing centre in Haiti. *AIDS.* 2001; 15:1875–1879. [PubMed: 11579251]
7. Kanaya AM, Glidden DV, Chambers HF. Identifying pulmonary tuberculosis in patients with negative sputum smear results. *Chest.* 2001; 120:349–355. [PubMed: 11502628]
8. Farley JE, Tudor C, Mphahlele M, et al. A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa. *Int J Tuberc Lung Dis.* 2012; 16:82–89. [PubMed: 22236851]
9. Kompala T, Shenoi SV, Friedland G. Transmission of tuberculosis in resource-limited settings. *Curr HIV /AIDS Rep.* 2013; 10:264–272. [PubMed: 23824469]
10. Reid MJ, Saito S, Nash D, Scardigli A, Casalini C, Howard AA. Implementation of tuberculosis infection control measures at HIV care and treatment sites in sub-Saharan Africa. *Int J Tuberc Lung Dis.* 2012; 16:1605–1612. [PubMed: 23131257]
11. Woith W, Volchenkov G, Larson J. Barriers and motivators affecting tuberculosis infection control practices of Russian health care workers. *Int J Tuberc Lung Dis.* 2012; 16:1092–1096. [PubMed: 22687261]
12. Chai SJ, Mattingly DC, Varma JK. Protecting health care workers from tuberculosis in China: a review of policy and practice in China and the United States. *Health Policy Plan.* 2013; 28:100–109. [PubMed: 22427258]
13. Menon S. Preventing nosocomial MDR TB transmission in sub Saharan Africa: where are we at? *Glob J Health Sci.* 2013; 5:200–210. [PubMed: 2377736]
14. Cobelens F, van KS, Ochodo E, Atun R, Lienhardt C. Research on implementation of interventions in tuberculosis control in low- and middle-income countries: a systematic review. *PLoS Med.* 2012; 9:e1001358. [PubMed: 23271959]
15. Legido-Quigley H, Montgomery CM, Khan P, et al. Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. *Trop Med Int Health.* 2013; 18:199–211. [PubMed: 23217030]
16. Heilig CM, Chia D, El-Sadr W, et al. Unacceptable, Acceptable. “Justifying research risks in a clinical trial for treatment of multidrug-resistant tuberculosis.”. *IRB: EthIcs & human REsEaRch.* 2011; 1
17. Bayer R, Greco DB, Ramachandran R. The ethics of clinical and epidemiological research. *Int J Tuberc Lung Dis.* 2011; 15(Suppl 2):S25–S29. [PubMed: 21740656]
18. Davidow AL, Katz D, Reves R, Bethel J, Ngong L. The challenge of multisite epidemiologic studies in diverse populations: design and implementation of a 22-site study of tuberculosis in foreign-born people. *Public Health Rep.* 2009; 124:391–399. [PubMed: 19445415]
19. Chiang CY, Glaziou P, Enarson DA, Cobelens F, Lew WJ. Protecting patients' rights, ensuring safety and quality assurance in tuberculosis prevalence surveys. *Int J Tuberc Lung Dis.* 2009; 13:27–31. [PubMed: 19105875]
20. Wood R, Lawn SD. Antiretroviral treatment as prevention: impact of the ‘test and treat’ strategy on the tuberculosis epidemic. *Curr HIV Res.* 2011; 9:383–392. [PubMed: 21999773]
21. Kufa T, Mngomezulu V, Charalambous S, et al. Undiagnosed tuberculosis among HIV clinic attendees: association with antiretroviral therapy and implications for intensified case finding,

- isoniazid preventive therapy, and infection control. *J Acquir Immune Defic Syndr*. 2012; 60:e22–e28. [PubMed: 22627184]
22. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS*. 2009; 23:631–636. [PubMed: 19525621]
23. WHO Policy on TB Infection Control in Healthcare Facilities, Congregate Settings and Households. World Health Organization; 2009. [serial online] [August 1, 2013]
24. Plan to combat extensively drug-resistant tuberculosis: recommendations of the Federal Tuberculosis Task Force. *MMWR Recomm Rep*. 2009; 58:1–43.
25. Guidelines for Preventing Transmission of Mycobacterium tuberculosis in Health-Care Settings. Centers for Disease Control and Prevention; 2005. [serial online] [August 1, 2013]
26. TB Infection Control Monitoring and Evaluation Tool. Centers for Disease Control and Prevention; 2010. [serial online] [August 1, 2013]
27. Dharmadhikari AS, Mphahlele M, Stoltz A, et al. Surgical face masks worn by patients with multidrug-resistant tuberculosis: impact on infectivity of air on a hospital ward. *Am J Respir Crit Care Med*. 2012; 185:1104–1109. [PubMed: 22323300]
28. Gonzalez-Angulo Y, Geldenhuys H, Van AD, et al. Knowledge and acceptability of patient-specific infection control measures for pulmonary tuberculosis. *Am J Infect Control*. 2013; 41:717–722. [PubMed: 23375576]
29. Godfrey C, Villa CDL, et al. Controlling healthcare-associated infections in the international research setting. *JAIDS*. 2013; 62:e115–e118. [PubMed: 24135735]
30. Tuberculosis Infection Control. A Practical Manual for Preventing TB. Curry International Tuberculosis Center at University of California San Francisco; 2011. [serial online] [August 1, 2013]
31. Cox H, Escombe R, McDermid C, et al. Wind-driven roof turbines: a novel way to improve ventilation for TB infection control in health facilities. *PLoS One*. 2012; 7:e29589. [PubMed: 22253742]
32. Nardell E, Vincent R, Sliney DH. Upper-Room Ultraviolet Germicidal Irradiation (UVGI) for Air Disinfection: A Symposium in Print. *Photochem Photobiol*. 2013; 89:764–769. [PubMed: 23683092]
33. Zhu S, Srebric J, Rudnick SN, Vincent RL, Nardell EA. Numerical Investigation of Upper-Room UVGI Disinfection Efficacy in an Environmental Chamber with a Ceiling Fan. *Photochem Photobiol*. 2013; 89:782–791. [PubMed: 23311354]
34. Willeke K, Qian Y. Tuberculosis control through respirator wear: performance of National Institute for Occupational Safety and Health-regulated respirators. *Am J Infect Control*. 1998; 26:139–142. [PubMed: 9584808]
35. Torres CJ, Silva R, Sa R, Cardoso MJ, Nienhaus A. Results of five-year systematic screening for latent tuberculosis infection in healthcare workers in Portugal. *J Occup Med Toxicol*. 2010; 5:22. [PubMed: 20659314]
36. Basu S, Galvani AP. The transmission and control of XDR TB in South Africa: an operations research and mathematical modelling approach. *Epidemiol Infect*. 2008; 136:1585–1598. [PubMed: 18606028]
37. Boulanger RF, Seidel S, Lessem E, et al. Engaging communities in tuberculosis research. *Lancet Infect Dis*. 2013; 13:540–545. [PubMed: 23531390]
38. Hausler HP, Sinanovic E, Kumaranayake L, et al. Costs of measures to control tuberculosis/HIV in public primary care facilities in Cape Town, South Africa. *Bull World Health Organ*. 2006; 84:528–536. [PubMed: 16878226]
39. Shrestha RK, Mugisha B, Bunnell R, et al. Cost-effectiveness of including tuberculin skin testing in an IPT program for HIV-infected persons in Uganda. *Int J Tuberc Lung Dis*. 2006; 10:656–662. [PubMed: 16776453]
40. Yaesoubi R, Cohen T. Identifying dynamic tuberculosis case-finding policies for HIV/TB coepidemics. *Proc Natl Acad Sci U S A*. 2013; 110:9457–9462. [PubMed: 23690585]

Figure 1. Framework for risk assessment, protocol and SOP development in TB infection control (TBIC) activities in HIV related research. TB-Tuberculosis, HIV-Human Immunodeficiency Virus, SOP-Standard Operating Procedures, CAB-Community Advisory Board.

TB Infection Control Monitoring & Evaluation Tool Modified for Research Sites

	Research Protocol	Scoring
1	The research protocol is designed with integrated measures to prevent TB transmission.	Y or N
2	The SOP manual or study manual identifies procedures that may increase risk of TB transmission for each team member based on their specific duties within the study.	Y or N
3	The human subjects research section of the grant proposal and SOP, as appropriate, includes a plan to reduce transmission to participants and research personnel.	Y or N
4	TBIC training for all personnel and investigators is complete and updated annually. Records are maintained.	Y or N
	Managerial	
5	The principal investigator has identified the individual who will regularly monitor TBIC at the research site.	Y or N
6	A written IC plan or check list is available as part of the SOPs for this site.	Y or N
7	The facility design and participant flow have been assessed including best use of space and ventilation and documented in the IC plan in the SOPs.	Y or N
8	Monitoring and evaluation of TBIC data forms are reviewed routinely and reported to the appropriate infection control personnel members of the host facility.	Y or N
9	A tracking system for all TB suspects, referrals, and their sputum smear results is in place.	Y or N
10	A register is kept of all TB patients reported to the appropriate authority within the setting.	Y or N
11	All patients with TB are managed on DOT as per the national guidelines.	Y or N
12	Participant and visitor information on TBIC is available for all and offered by the personnel.	Y or N
13	Monitoring and evaluation to improve TBIC measures is conducted at this site.	Y or N
	Administrative	
14	Participants are routinely asked about cough upon entering site.	Y or N
15	Participants that are coughing are separated from others and “fast tracked” to the appropriate study team member.	Y or N
16	A “Cough Monitor” gives cough etiquette guidance and assists with triage.	Y or N
17	Signage for cough etiquette is present.	Y or N
18	Sputum samples are collected in a designated area and away from others.	Y or N
19	Health care workers and study personnel that assist with sputum collection take necessary precautions.	Y or N
20	A confidential log of diagnosis and referral of all personnel who develop TB is maintained	Y or N
21	Personnel receive a confidential evaluation for TB in an occupational health setting at least annually.	Y or N
22	Personnel are offered an HIV test annually and offered ART if positive through designated occupational health clinic or services.	Y or N
23	HIV-infected personnel are reassigned if requested by the worker.	Y or N
24	INH preventive treatment is offered to HIV-infected personnel through occupational health clinic	Y or N
	Environmental Controls	
25	Natural and/or mechanical airflow is monitored daily by personnel in all areas with infectious patients	Y or N
26	Regular maintenance for directional and extractor fans is conducted and documented in a log book.	Y or N
27	Signs are in place to keep doors and windows open when feasible.	Y or N
28	If UVGI is used, routine cleaning and maintenance is scheduled and documented.	Y or N
29	Participants are not crowded in hallways or waiting areas.	Y or N
30	Outdoor area waiting is utilized.	Y or N
	Personal Protective Equipment	
31	N-95 or FFP2 respirators are readily available for personnel and their use is required.	Y or N

	Research Protocol	Scoring
32	Personnel have been trained on proper fit of respirators and documentation of testing is kept in a log.	Y or N
33	Supplies are available to coughing participants (tissues, cloths, paper masks, trash bins, etc).	Y or N
34	Personnel are provided continuing education opportunities and annual exams on TBIC.	Y or N
35	Participants who are returning to the site for follow-up post treatment are provided a respirator if smear or culture positive patients will be present at any time in the same area during the visit.	Y or N

Legend: ART, anti-retroviral therapy; DOT, directly observed therapy; IC, infection control; SOP, standard operating procedures; TB, tuberculosis; TBIC, TB infection control; UVGI, ultra-violet germicidal irradiation,