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Case Finding For Pulmonary Tuberculosis Among People Who Inject Drugs In Dar Es Salaam, Tanzania

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CASE FINDING FOR PULMONARY TUBERCULOSIS AMONG PEOPLE WHO INJECT DRUGS IN DAR ES SALAAM, TANZANIA.

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Active case finding is a World Health Organization (WHO)-endorsed strategy for improving case detection of tuberculosis. Despite WHO recommendations for active case finding among people who inject drugs (PWID), there are few published studies. The historical focus of case finding has been in populations that are HIV-positive, incarcerated, or at higher occupational risk. We sought to examine the yield of active case finding among PWID newly started on methadone in Tanzania.

A questionnaire including tuberculosis symptoms and risk factors was administered to every consenting patient by a native Swahili-speaker. Additional chart review was performed for demographic information and HIV status. Two sputum samples were collected for every symptomatic patient, and samples were tested using smear microscopy as well as culture.

A total of 156 of 222 (70%) methadone clients met with study administrators; 150 of whom consented to the study. Median age was 34 years old, and 139 (93%) were male. Thirty-four (23%) were HIV-positive, and an additional 104 (69%) had an unknown HIV status. Of the 150 patients surveyed, 16 (11%) had one or more tuberculosis symptoms and were referred for laboratory testing. Six new cases of tuberculosis were identified, 5 of which were sputum smear-negative, and 1 of which was multi-drug resistant. The prevalence of tuberculosis was 4%

This study presents the first data on tuberculosis prevalence in a population of PWID in Tanzania. This prevalence is 23 times the general Tanzanian tuberculosis

prevalence of 0.2%. PWID in Tanzania should continue to be screened for tuberculosis with smear, culture and drug susceptibility testing. Screening should expand to PWID in the community.

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Introduction

History of Tuberculosis

Tuberculosis (TB) is a devastating infectious disease that has been infecting mankind for many millennia. The oldest skeletal remains of a TB patient come from Liguria, Italy around 5800 BCE.(1) The first written records come from ancient Egypt, where physicians first described the disease.(2) Investigators have found DNA evidence of the mycobacteria in Egyptian mummies buried between 2050 BC to 500 BC.(3) Hippocrates in Greece labeled the disease "phthisis"(2), and the disease appears often in Western literature as "consumption"(4). In 17th century London, the disease became so prevalent and had such high mortality that the English preacher John Bunyan dubbed TB, "The Captain among these men of death".(5) The industrial revolution brought increasingly crowded living conditions, drastically increasing TB transmission and incidence in Europe.(2) In London, 1 in 7 deaths were caused by TB at the beginning of the 18th century, 1 in 5.25 in the middle, and 1 in 4.2 by the end of the century.(6) TB caused 25% of deaths in Europe in the 19th century(5). Despite this large societal burden, the causative pathogen, *Mycobacterium tuberculosis*, was not discovered until 1882 by Robert Koch in Germany.(2)

In the 20th century, the developed world saw improvements in the TB death toll due to better living standards, including improved nutrition, income, and less crowded housing conditions.(5) Additionally, antimicrobial treatment was developed in the 1940s with the discovery of streptomycin, evolving into a multi-drug therapy regimen of several different antibiotics, greatly improving treatment outcomes from the era of sanatorium

and surgery-based care.(2) However, the advent of the HIV epidemic in the 1980s fueled a resurgence of TB, especially in Sub-Saharan Africa. TB control efforts now face the challenges of HIV/TB coinfection, drug-resistant organisms, inadequate diagnostic tests, and weak health systems in the countries most affected.(5)

Disease Characteristics

It is now known that the disease can be caused by a group of bacteria known as the *Mycobacterium tuberculosis* complex, including *Mycobacterium tuberculosis, Mycobacterium africanum, Mycobacterium bovis, Mycobacterium microti, and Mycobacterium canetti.* Before milk pasteurization became routine, *Mycobacterium bovis* caused up to 6% of TB cases.(5) After the *Mycobacteria* infect a human, most immunocompetent individuals either eliminate the bacteria or contain it in an inactive state called latent TB infection (LTBI).(5) Active TB disease is most commonly caused by reactivation of a latent infection, when the organism multiplies to cause pathology and active, symptomatic disease.(7) In an immunocompetent host the lifetime risk of reactivation is approximately 10%, with the greatest risk in the first few years after initial infection.(5) However, the reactivation risk is about 10% per year in HIV-infected persons.(8) in patients with impaired immunity, such as individuals with HIV. Recent research suggests that the binary division between latent and active disease states may be overly simplistic, and that many patients may exist on a spectrum between latent and active disease.(5)

Active TB manifests most commonly as pulmonary infection, resulting in cough with sputum production and/or hemoptysis. However, TB can cause disease in almost any body tissue, manifesting with organ-specific symptoms. Additionally, the disease often causes constitutional symptoms, including fevers, night sweats, and severe weight loss. Extrapulmonary and disseminated miliary TB is more common among HIV-infected individuals. (9)

Tuberculosis Diagnostics:

TB control efforts are significantly hampered by the lack of accurate and rapid diagnostics. For latent TB, the standard test for over a century has been Tuberculin Skin Testing (TST), which relies on delayed-type hypersensitivity immune response to mycobacteria placed intradermally.(10) However, the TST has several drawbacks. First, it requires patients to return in 48-72 to read the result, which can result in a loss-to-follow-up, especially in hard-to-reach populations such as homeless individuals and people who inject drugs and in resource-limited settings.(11) Secondly, TST can be affected by receipt of the BCG vaccine, which is currently given to more than 90% of children worldwide. Third, TST is not specific to TB and therefore can be positive in response to mycobacteria other than tuberculosis (MOTT).(10)

In more recent years, a second test for latent TB has been developed, called the Interferon-Gamma Release Assay (IGRA). This is a serum test that measures interferon-gamma release by T-cells in response to stimulation with the TB antigens ESAT-6 and CFP-10. IGRA has several advantages over TST testing: it is more specific, not affected

by prior administration of the BCG vaccine, and less affected by most environmental mycobacteria. Additionally, it does not require a follow-up visit, which is advantageous in hard-to-reach populations. The test is expensive, and requires access to a sophisticated laboratory – a serious liability in resource constrained areas.(11) Although there is evidence that it has high sensitivity in patients with active disease, it cannot distinguish between latent and active TB.(5) IGRA's cannot reliably distinguish between treated prior infection and reinfection, and cannot be used to reliably predict who is at risk of progressing to active disease.(12)

For active TB, culture of the organism is the most sensitive test, and is the current diagnostic gold standard. Although liquid culture systems are preferable due to faster turnaround time and higher yield, they are prohibitively expensive in many settings, and solid agar is still widely used. Conventional drug susceptibility testing (DST) requires culturing the organism. However, culture diagnosis takes a long time – even with the newer automated liquid culture systems, diagnosis still takes a minimum of 10-15 days.(13) This is due to the extremely slow doubling rate of *Mycobacterium tuberculosis*, which divides once every 15-20 hours.(5)

Most low and middle-income countries rely heavily on a combination of sputum smear microscopy and chest x-ray for diagnosis.(5) For sputum smear microscopy, the conventional Ziehl-Neelsen staining method was invented in the 1880s shortly after Koch first discovered the bacterium.(2) Although the results for sputum smear microscopy are relatively rapid, sensitivity ranges between 50 to 80%, and is subject to operator

performance.(13) Additionally, HIV can further decrease the likelihood of smear-positive TB.(14) The development of fluorescent microscopy with Auramine O increases the sensitivity, and can increase the efficiency of microscopy.(15)

More recently, Nucleic Acid Amplification Tests (NAATs) have been developed for active TB diagnosis. These tests are PCR-based, and offer many advantages to conventional microscopy and culture. Cepheid has recently developed the GeneXpert assay, which is a cartridge-based, automated test that can test for presence of *Mycobacterium tuberculosis* and simultaneously test for rifampicin resistance. The test can be performed with minimum laboratory expertise, and results can be available within 2 hours. In smear-positive patients, the assay has sensitivity of 98%. In smear-negative patients, the assay has sensitivities of 72.5%, 85.1%, and 90.2% on one, two, and three samples, respectively. Specificity is high at 99.2%.(16) In HIV-positive individuals, one study found an Xpert sensitivity of 66.4% when screening patients eligible for antiretroviral therapy in Ethiopia.(17) Among HIV-positive patients with a high clinical suspicion for TB in Peru, sensitivity was high as 97.8%, with a specificity of 97.7%.(18) The assay is also highly accurate for detection of rifampicin resistance, as long as the predominant strain of bacteria present in the sample is rifampicin-resistant. The threshold number of colony-forming units (CFUs) required for mycobacterial detection is much lower than smear microscopy, similar to solid culture, but less than liquid culture. As with any new technology, there are limitations. First, it cannot be used to monitor response to therapy, as it will detect killed organisms. Second, it is very expensive. Finally, although the turnaround time for diagnosis is significantly faster than for other

methods of diagnosis, it is still not quite point-of-care, which can make same-day clinical decisions difficult in crowded health facilities. Nevertheless, it represents a significant advance for TB diagnosis.(16)

Tuberculosis Treatment:

For patients with active TB, the World Health Organization (WHO) recommends as first-line therapy a combination of rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 months, followed by rifampin and isoniazid for another 4 months. Since the early 1990s, the WHO has endorsed Directly Observed Therapy (DOT) to improve medication adherence and successful treatment completion.(19)

Unfortunately, the world has seen the emergence of drug-resistant strains of TB, which are much more difficult to treat. Strains that are resistant to both rifampicin and isoniazid, which often co-occur, are called Multi-Drug Resistant Tuberculosis (MDR-TB). For MDR-TB, the WHO recommends using at least 4 drugs certain to be effective. The groups of drugs are separated into 5 groups: first-line oral agents, injectable agents, fluoroquinolones, oral bacteriostatic second-line agents, and 3rd line agents with unclear role in the treatment of drug-resistant TB. Choosing the correct drug regimen can be informed by DST testing for drugs that have good laboratory reliability, such as injectable agents and fluoroquinolones. Alternatively, it can be based on survey data showing rarity of resistance to the drug, or can be a drug that is not commonly used in the area. MDR-TB treatment regimens last for a minimum of 18 months from the last negative culture.(19)

Most worryingly, strains resistant to even more drugs have emerged. A strain is called "Extensively drug resistant" (XDR-TB) if it is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line agents. Therapy for this category is complex, and outcomes are highly variable.(20)

TB antimicrobial therapy went through a period of innovation in the 1940s-1960s. However, as TB became a less urgent threat in the developed world, drug development stalled. In the face of rising resistance, TB therapy has suffered from this lack of novel therapeutics. However, recently a drug called bedaquiline was approved by the FDA for TB treatment in 2012, the first new drug for TB in over forty years. Other agents are currently in the drug development pipeline.(21)

Global Epidemiology

An estimated 2 billion people worldwide are latently infected with *Mycobacterium tuberculosis*.(5) In the year 2013, there were an estimated 9.0 million new cases of active TB, for an incidence of 126 per 100,000 population. The South-East Asia and Western Pacific regions account for more than half (56%) of TB cases. About 1.1 million cases (13%) were co-infected with HIV. Globally in 2013, there were about 1.5 million deaths from TB, and 360,000 (24%) of these were co-infected with HIV.(22)

The African region is suffering the worst burden of disease. Although the region only accounts for about a quarter of total incidence cases in 2013, it has the highest prevalence

(300 per 100,000) incidence (280 cases per 100,000), and mortality (32 per 100,000 among HIV/TB coinfected people, and 42 per 100,000 excluding that group). The African region also has the highest proportion of TB cases (34%) that are co-infected with HIV.(22)

Globally, an estimated 5% of TB cases are estimated to be MDR-TB. Among new TB cases in 2013, the estimated proportion of MDR-TB cases was 3.5%. Trend analysis shows that the overall proportion of MDR-TB cases has not changed between 2008 to 2013, staying at about 3.5%. However, some countries have serious MDR-TB epidemics. These include many countries of Eastern Europe. In Belarus, for example, an estimated 35% of new TB cases are MDR-TB, and an estimated 55% of cases undergoing retreatment are MDR-TB. More than half the global burden of MDR-TB is in three countries: India, China, and the Russian Federation.(23)

XDR-TB was first described in 2006, after an alarming report by Gandhi and colleagues of an XDR-TB epidemic in the town of Tugela Ferry in the province of KwaZulu-Natal, South Africa, where 53 of 1539 (6%) patients were found to have XDR-TB over a 1-year period. Fifty-two of these patients died, 70% in the first 30 days after sputum collection.(24) Since this report, 100 countries have reported at least one XDR-TB case as of 2013.(23)

As discussed above, the largest risk factor for TB is HIV, which greatly increases susceptibility to infection, primary progressive disease, reactivation, and recurrence.

Other risk factors include diabetes, malnutrition, overcrowded living conditions, smoking, indoor air pollution, silicosis, alcohol, and immunosuppressive drugs, such as corticosteroids and TNF antagonists.(5)

Certain social groups have been historically associated with TB, especially in countries where the disease is not endemic. In the USA, for example, these include people with a history of homelessness(25), incarceration(26), or foreign-born from an endemic country(27). Another major high-risk population is people who use illicit drugs.(28)

Tuberculosis in People Who Use Illicit Drugs:

Drug use is associated with both a higher prevalence of latent TB infection and higher incidence of TB disease.(28-30) Drug users are more likely to be infectious, to take longer to achieve negative culture, and to be at increased risk of mortality from TB. In some studies, duration of injection drug use and older age were most commonly associated with latent TB. There is also evidence of increased rates of transmission among drug users, and there have been outbreaks among people who use drugs in many countries around the world. (28)

Drug use was described as a risk factor for TB even before the HIV era, in a study by Reichman and colleagues based in New York City in the 1970s.(31) One potential explanation for this association is from the immunosuppressive effects of certain illicit drugs. For example, opiates may directly impair the cell-mediated immune response. Additionally, drug use is associated with other behaviors and risk factors that overlap

with TB, including tobacco use, homelessness, alcohol abuse, and incarceration. Additionally, crowded venues for drug use with poor ventilation may serve as sites of transmission. TB outbreaks have also been associated with sharing drug equipment, and the practice of "shotgunning" (inhaling and exhaling smoke directly into another's mouth).(28)

Studies show mixed results on whether people who inject drugs (PWID) have an increased risk for latent TB over non-injectors. However, PWID are at increased risk of HIV from needle-sharing based transmission, and this confers a significantly increased risk of active TB disease. HIV-infected PWID may even be at increased risk of TB infection and disease compared with other HIV-infected individuals.(28)

In addition to this TB risk, PWID are at increased risk for many poor health outcomes, including viral hepatitis, bacterial soft tissue infections, infective endocarditis, and overdose.(32, 33) PWID worldwide are estimated to have a 14.7 times the mortality risk of the general population.(32)

For all of these reasons, PWID are an important target group for medical and public health services. However, due to many barriers including social stigma, unstable lifestyles, lack of health insurance, worries about narcotic withdrawal, poor knowledge of TB transmission, and provider perceptions, PWID have been a hard-to-reach population for most health systems.(28)

Tuberculosis Case Finding:

Surveillance for active TB relies largely on passive case finding, in which symptomatic patients present to healthcare sites for evaluation of disease.(34) The benefits of community-based population screening for active TB is debated, with studies showing mixed results on improvement in community TB prevalence.(35-37) However, passive case finding may be insufficient for certain high-risk groups, in whom TB burden is particularly high, or who do not regularly interface with the health system by their own volition. The WHO has strong recommendations to systematically screen households and other close contacts of TB cases, people living with HIV, and people with workplace exposure to silica. WHO also conditionally recommends screening prisoners, people living in high prevalence areas, and populations with poor access to healthcare, including homeless people, people living in urban slums or remote areas, and other vulnerable or marginalized groups.(34)

For the reasons specified above, people who use drugs are another group in whom active case finding can be beneficial. The WHO issued recommendations in 2008 for collaborative TB and HIV services for drug users. They recommend that all services dealing with drug users have a case-finding protocol for TB and HIV. At a minimum, the WHO recommends including a simple set of questions on the symptoms and signs of TB as a basis for active case finding at facilities providing services to drug users.(38)

Programmatically, different active case finding programs choose whether to start with a symptom screen or to screen all program participants with chest radiography or sputum collection. Symptom screens are simpler and cheaper to implement, but risk missing asymptomatic cases. Similarly, programs have to choose whether to limit to sputum smear analysis versus also culturing all collected sputum specimens. Sputum smear is cheaper and requires less trained personnel than culture, but using smear microscopy alone risks missing smear-negative TB. Culture is also required for drug susceptibility testing to detect drug-resistant TB. The best protocol for active case finding is debated, and often comes down to a decision based on local factors, such as available funding, laboratory capacity, and prevalence of HIV. (34, 39) For the purposes of determining isoniazid preventive therapy (IPT) eligibility among people living with HIV in resource-constrained settings, the WHO recommends symptom-based case finding at facilities, with the absence of four key symptoms enough to rule out active TB.(40) This conclusion was based on a study by Getahun and colleagues in 2010 that found the absence of current cough, fever, night sweats, and weight loss can identify a subset of people living with HIV who have a very low probability of having active TB.(41)

Tuberculosis in Tanzania:

Tanzania ranks 18th out of the 22 countries that have been labeled high-burden countries by the WHO. Together, these countries account for 80% of the world's TB cases. In 2013, the World Health Organization (WHO) estimated TB prevalence in Tanzania of 85,000 (172 per 100,000) and an incidence of 81,000 (164 per 100,000), with 1.1% of new cases being multi-drug resistant (MDR). Significantly, 37% of the tested TB patients are HIV-infected. As the first African country to implement Directly Observed Therapy (DOTS) under

the WHO, Tanzania has a relatively well-developed infrastructure for TB treatment, with treatment success rate of 90%. Despite this, there is an annual mortality of 6000 HIV-negative TB cases, with an additional mortality of 6100 in HIV/TB coinfected patients. (22)

Drug Injection in Tanzania and Study Rationale:

East Africa has been an important stop along international drug trafficking routes for three decades. The United Nations Office on Drugs and Crime (UNODC) predicts that 40-45 tons of Afghan heroin were trafficked to Africa in 2009, the majority entering East African ports from Pakistan, Iran, the United Arab Emirates, and India. The trade appears to be run by Nigerian traffickers, with heroin being transported through Nigeria before being shipped to Europe. However, users in Africa consume an estimated 34 tons of heroin, with only 7 tons being shipped onwards to Europe. UNODC estimated in 2011 that there are 1,736,000 heroin users in Africa, with approximately one-third residing in Eastern Africa.(42)

In Tanzania, there were an estimated 200,000 – 250,000 individuals using heroin in Tanzania, with approximately 40,000 injectors as of 2005.(43) The epidemics of TB and human immunodeficiency virus (HIV) are particularly intertwined with heroin addiction in Tanzania. While the 2012 estimate of HIV prevalence in the Tanzanian general population was 5.1%(44), an estimated 42% of people who inject drugs (PWID) in Dar es Salaam have HIV.(45)

The Tanzanian AIDS Prevention Programme introduced methadone-based Medication-Assisted Treatment (MAT) in 2011 at Muhimbili National Hospital in Dar es Salaam, Tanzania. The goal of the program was to address heroin addiction with the goal of reducing injection drug use, preventing HIV, and helping those with HIV to engage in care and treatment. This was the first public methadone clinic in sub-Saharan Africa, and all clients were heroin injectors. Patients were referred to the MAT clinic by Non-Governmental Organizations (NGOs) that worked with PWID in the community.

In the first 4 months the clinic operated prior to our project, three patients had already been diagnosed with pulmonary TB. One of these patients was hospitalized with severe symptoms and ultimately died. This prompted significant concern that other patients could have undiagnosed TB. The clinic staff was worried that these undiagnosed cases could be lethal without early treatment, and could pose an infection risk to fellow patients and healthcare workers.

Statement of Purpose

In response to concerns about undiagnosed TB in the patients of the MAT program at Muhimbili National Hospital, we implemented an active case finding project for pulmonary TB with the following goals:

1) To identify any undiagnosed pulmonary TB cases and link them to treatment

2) To assess the prevalence of active pulmonary TB in this population of PWID on methadone treatment

3) To determine the prevalence of HIV/TB coinfection in this population

4) To determine the proportion of cases with MDR-TB

5) To determine the proportion of cases that are smear-positive

6) To describe characteristics of TB cases

Methods:

Study Design:

This was a cross-sectional case finding study to determine the prevalence of active pulmonary TB cases within a population of Tanzanian PWID on methadone treatment. The primary outcome was to determine prevalence of active TB. Secondary outcomes included prevalence of HIV/TB coinfection, prevalence of MDR-TB, and prevalence of smear-positive TB.

Study Population and Recruitment:

The study was conducted at the Medically Assisted Treatment (MAT) program in the Psychiatry Department at Muhimbili National Hospital, Dar es Salaam. Our study population included all 222 registered patients who were regularly attending the MAT program as of August 22nd, 2011, when enrollment concluded.

An informational flyer was posted outside the methadone-dispensing window several days in advance of the study to inform patients of the upcoming screening. The pharmacist directed patients to meet with study administrators on-site after receiving methadone. Participants provided informed consent in Swahili prior to screening. Patients

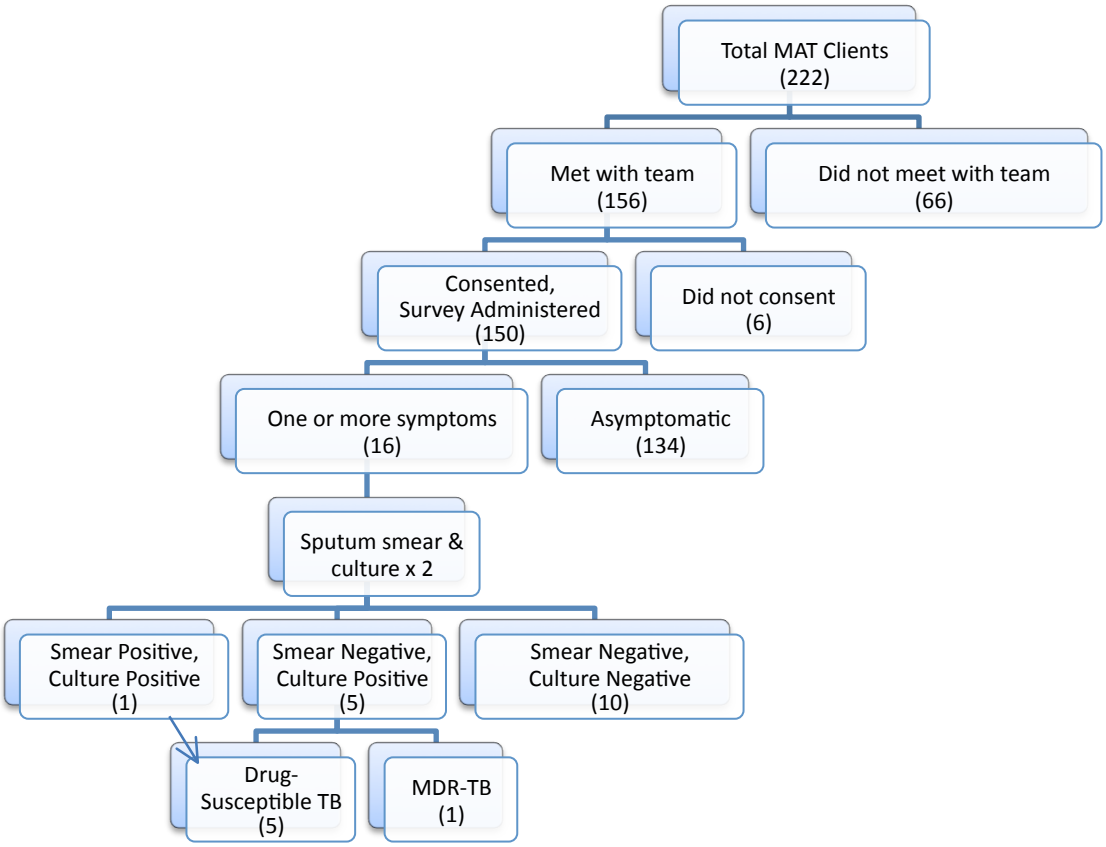
that were literate signed a consent form, and patients who could not write provided fingerprints on the consent form, consistent with standard practices.

TB Case Finding Protocol:

A symptom-based questionnaire was adapted from a previous TB survey in Ethiopia, and was administered to every consenting patient in Swahili by a native Swahili-speaker. Patients were asked about the following symptoms: cough greater than 2 weeks duration (with or without sputum, with or without hemoptysis), fever greater than 1 month duration, night sweats, weight loss, and change in appetite. If the patient reported a cough of less than 2 weeks duration, he or she was asked to return at 2 weeks duration to report if the cough had persisted. In addition, patients were asked about past TB history, housing and ventilation, and incarceration history (including pre-trial detention).

Any patient reporting one or more symptoms in the questionnaire was referred for sputum collection (see Figure 1). Patients were asked to produce two sputum samples: one was produced on-site after completion of the questionnaire and without exposure to direct sunlight, while one was produced the following morning and delivered to clinic staff when arriving for the patient's methadone. Samples were stored indoors in a cool environment out of direct sunlight for no longer than 12 hours. The study administrator delivered these samples, without exposure to sunlight, to the Central Tuberculosis Reference Laboratory located onsite at Muhimbili National Hospital.

Figure 1: Flow Chart of Survey and Laboratory Testing Protocol



MAT = Medication Assisted Treatment; TB = tuberculosis; MDR = multi-drug resistant.

Sputum smear analysis was performed by a trained technician using Auramine O staining. Each sample was cultured using Lowenstein-Jensen solid media (Modified Petroff Method). Culture-positive samples underwent Drug Susceptibility Testing (DST) against isoniazid, rifampin, streptomycin, and ethambutol. Samples with suspected Mycobacteria Other Than Tuberculosis (MOTT) were confirmed by rho-nitrobenzoic acid (PNB).

TB cases were defined as patients who had either smear or culture evidence of *Mycobacterium tuberculosis* in at least one sputum sample. MDR-TB was defined as resistance to isoniazid and rifampin.

Linking Cases to Treatment:

Clinicians at the MAT program were immediately informed of all patients with smear or culture results positive for TB. These patients were referred to the National Tuberculosis and Leprosy Programme (NTLP) at Muhimbili National Hospital, which prescribed their therapy regimen according to national guidelines. Treatment was delivered on-site along with methadone.

Chart Review:

As part of the MAT clinical program, patients have standardized assessments including the Addiction Severity Index (ASI)(46) throughout the course of their treatment. The ASI is a standardized instrument developed in 1980 by A. Thomas McLellan, used to establish the nature and severity of possible medical, employment, drug, alcohol, legal, family, social, and psychiatric problems. Each patient received a baseline ASI survey, and monthly follow-up ASI surveys up to 3-months, at which point they were performed as needed. A chart review of the ASI was used for demographic history, drug use history, legal history, and living situation. If multiple ASI were present, information was taken preferentially from the most recent follow-up ASI.

Chart review was also performed for laboratory documentation of HIV status. HIV-positive status was defined by any prior positive HIV test, whether at the MAT clinic or at another facility. HIV negative status was defined by a negative test at the MAT clinic within the prior 3 months. All other patients were classified as unknown HIV status. For patients not enrolled in our study, we collected basic demographic data from baseline registration information and HIV status from laboratory record review.

Data Analysis:

Data was entered into Microsoft Excel and basic proportions were calculated in Excel. To compare characteristics of enrolled vs. unenrolled patients, Stata was used to make comparisons using two-sample student's t-test for means and two-sample test for proportions. P values < 0.05 were considered significant.

Ethical Approval

This study was cleared by two Institutional Review Boards: the Yale University Human Investigations Committee granted an exemption, and the Muhimbili University of Health and Allied Sciences Senate Research & Publications Committee granted ethical approval.

Role of the Student Author:

The student author generated the idea for the study in an initial meeting with his thesis mentor, Dr. Bruce. He received an active case-finding questionnaire that had been recently implemented by a public health student in Ethiopia, and adjusted it to fit the Tanzanian setting. He then traveled to Dar es Salaam and worked with the Tanzanian

AIDS Prevention Programme to translate the questionnaire into Swahili. He met with clinicians, nurses, pharmacists, the Central Tuberculosis Reference Laboratory, and the National Tuberculosis and Leprosy Programme to design and refine the protocol and workflow. He was present for all patient interviews, and provided clarification and advice to the Swahili-speaking interviewer as needed. He supervised the collection of sputum specimens, and hand-delivered 90% of the samples to the laboratory. He performed all chart review for patients enrolled in the study. Chart review for patients who were not enrolled in the study was performed by a data manager at Pangaea Global AIDS Foundation. He also implemented a protocol whereby the clinic could continue to screen all of its future patients for TB upon registration. The student performed all data entry and analysis, and wrote the manuscript, which was published in the *International Journal of Tuberculosis and Lung Disease* in 2014.

Results

Recruitment:

From July 28 to August 22, 2011, 156 of 222 (70%) clients met with study administrators, of whom 150 consented to this study. Table 1 compares age, sex, HIV positivity rate, and prior history of arrest or charge between our sample and the 72 patients not enrolled in the study. Our sample was older than the unenrolled group (Mean 34.1 years vs. 31.5 years, p=0.002), and had a significantly higher percentage of known HIV-positives (23% vs. 11%, p=0.03). There were no significant differences between proportion of male patients and history of prior arrest or legal charge.

Table 1: Baseline characteristics for all patients on methadone treatment as of August 22nd, 2011 at Muhimbili Medication Assisted Treatment Program, Dar es Salaam, Tanzania

Characteristics	All registered patients (n=222)	Enrolled patients (n=150)	Un-enrolled patients (n=72)	p
Mean age in years (SD)	33.3 (5.7)	34.1 (5.9)	31.5 (5.1)	0.002
Male	204 (92%)	139 (93%)	65 (90%)	0.54
HIV-positive	42 (19%)	34 (23%)	8 (11%)	0.03
Prior arrest or charge	138 (62%)	88 (59%)	50 (69%)	0.12

Note: all information taken from chart review.
IQR = Interquartile Range

Background characteristics:

Demographics, risk factors, and TB history of our sample are summarized in Table 2. The median age was 34 years old, with an interquartile range (IQR) of 8. Men comprised the largest group with 139 of 150 (93%) participants. Most patients were single (61%), with a mean of 1.0 child. The majority of patients had been educated to a Primary (47%) or Low Secondary (41%) level. All patients had a prior history of heroin injection, as this was required for entry into the methadone program. In addition to heroin, marijuana (36%) and alcohol (11%) were the 2 most common substances used. A majority of patients (69%) reported staying with others, with a mean of 5 members per household. A history of incarceration (including prison, jail, or pre-trial detention) was reported by 107 (71%) patients.

Chart review demonstrated 34 (23%) HIV-infected patients, and 12 (8%) HIV un-infected within the previous 3 months. Despite the elevated HIV risk among PWID, 104 (69%) refused HIV testing, and their status was unknown. A prior history of TB was

reported by 26 patients (17%), and the median time since previous diagnosis was 5 years, with an IQR of 5.5 years. The majority reported a history of pulmonary TB (73%), but almost one-quarter (23%) had a history of extrapulmonary TB. In their previous diagnosis of TB, 14 (54%) patients reported diagnosis by laboratory methods, and an additional 3 (12%) of patients were diagnosed by both laboratory methods and x-ray. No laboratory or clinical data was available to confirm prior TB. Twenty-four (92%) patients reported completing a full course of treatment, with 10 (38%) completing an 8-month course and 14 (54%) completing a 6-month course. Only two patients (8%) reported a history of defaulting on TB treatment. Most (81%) patients said that they had tested negative after treatment, but 5 individuals (19%) said that they had never been tested after beginning treatment.

Table 2: Population demography, tuberculosis risk factors, HIV status, and tuberculosis history of patients on methadone treatment at Muhimbili Medication Assisted Treatment Program, Dar es Salaam, Tanzania

Characteristics	Total Sample (n = 150)	Non- tuberculosis Patients (n=144)	Tuberculosis Patients (n = 6)
Median Age, IQR	34, 8	34, 8	34.5, 6.25
Gender			
Male	93% (139/150)	92% (133/144)	100% (6/6)
Female	7% (11/150)	8% (11/144)	0%
Marital Status			
Single	61% (92/150)	62% (89/144)	50% (3/6)
Married	17% (25/150)	16% (23/144)	33% (2/6)
Divorced/Separated	20% (30/150)	20% (29/144)	17% (1/6)
Widowed	2% (3/150)	2% (3/144)	0%
Mean Number Children, SD	1.0, 0.9	1.0, 0.9	1.0, 0.9
Education			
No Education	0.7% (1/150)	0.7% (1/144)	0
Primary	47% (70/150)	46% (66/144)	67% (4/6)
Low Secondary	41% (62/150)	42% (60/144)	33% (2/6)
Upper Secondary	7% (11/150)	8% (11/144)	0%
University	4% (6/150)	4% (6/144)	0%
Additional Training*	9% (13/150)	9% (13/144)	0%
Primary (Non-Heroin) Substance of Abuse			
None	47% (70/150)	47% (68/144)	33% (2/6)
Alcohol	11% (17/150)	10% (15/144)	33% (2/6)
Sedatives, Hypnotics, Tranquilizers	4% (6/150)	4% (6/144)	0%
Cannabis	36% (54/150)	36% (52/144)	33% (2/6)
Polysubstance	2% (3/150)	2% (3/144)	0%
Housing			
Own	11% (16/150)	10% (15/144)	17% (1/6)
Rent	19% (29/150)	20% (29/144)	0%
Mean Rent TSH, SD	37600, 25,700	37600, 25,700	N/A
Staying with Others	69% (103/150)	68% (98/144)	83% (5/6)
Homeless	1% (2/150)	1% (2/144)	0%
Mean Years in Same House, SD	12.0, 14.1 (n=148)	12.0, 14.2 (n=141)	11.4, 13.1
Mean Number People, SD	4.9, 2.6 (n=145)	4.9, 2.6 (n=139)	4.6, 2.7 (n=7)
Mean Number Windows per Room	1.5, 0.6 (n=148)	1.6, 0.6 (n=142)	1.16, 0.4
Previously Incarcerated or in Jail**	71% (107/150)	71% (102/144)	83% (5/6)
Knowledge about tuberculosis (1-5), SD***	2.4, 1.0	2.4, 1.0	2.0, 0.6
Risk of tuberculosis (1-5), SD***	1.8, 1.0	1.8, 1.0 (n=143)	3.5, 0.5
Effort to Prevent tuberculosis (1-5), SD***	3.5, 1.2	3.5, 1.2	2.3, 0.5

HIV Status			
HIV Positive	23% (34/150)	22% (31/144)	50% (3/6)
HIV Negative	8% (12/150)	8% (11/144)	17% (1/6)
HIV Unknown	69% (104/150)	71% (102/144)	33% (2/6)
Previous History of tuberculosis	17% (26/150)	16% (23/144)	50% (3/6)
Years since Last Diagnosis (Median, IQR)	5.0, 5.5	5, 6.5	4.5, 2
Type of tuberculosis, Most Recently			
Pulmonary	73% (19/26)	74% (17/23)	67% (2/3)
Extrapulmonary	23% (6/26)	26% (6/23)	33% (1/3)
Not Sure	4% (1/26)	4% (1/23)	0%
How Diagnosed, Most Recently			
Laboratory Methods	54% (14/26)	52% (12/23)	67% (2/3)
X-ray	35% (9/26)	35% (8/23)	33% (1/3)
Laboratory and X-ray	12% (3/26)	13% (3/23)	0%
Amount of Treatment, Most Recently			
Complete, 8 months	38% (10/26)	43% (10/23)	33% (1/3)
Complete, 6 months	54% (14/26)	57% (13/23)	33% (1/3)
Incomplete, 5-6 months	4% (1/26)	0% (0/23)	33% (1/3)
Incomplete, <2 months	4% (1/26)	4% (1/23)	0%
Total Completing Treatment	92% (24/26)	96% (22/23)	67% (2/3)
Total Defaulting on Treatment	8% (2/26)	4% (1/23)	33% (1/3)
Most Recent Test after Treatment			
Positive	0%	0% (0/23)	0%
Negative	81% (21/26)	83% (19/23)	67% (2/3)
Not Tested after Beginning Treatment	19% (5/26)	17% (4/23)	33% (1/3)

*All of these recorded one of the categories above as well as additional training.

** This data comes from administered questionnaire, and is not equivalent to "Prior Arrest or Charge" from Table 1, which was taken from baseline Addiction Severity Index.

***Patients were asked to rate their knowledge of tuberculosis, risk of tuberculosis, and effort to prevent tuberculosis on a scale of 1-5.

Acronyms: IQR = Interquartile range; SD = Standard Deviation; TSH = Tanzanian Shillings

TB Active Case-Finding:

Of the 150 surveyed, 16 (11%) had one or more symptoms and were referred for laboratory testing (see Table 3). The sputum sample from 1 patient was AFB-positive on sputum smear, and subsequently culture-positive. Culture of sputum samples from the remaining 15 smear-negative patients revealed that 5 grew TB. Additionally, 1 patient was found to have a Mycobacterium Other Than Tuberculosis (MOTT). On Drug Susceptibility Testing (DST) of culture-positive cases, 1 patient was found to have MDR-

TB. Of note, this MDR patient's sputum was smear-negative. The sputum sample for 1 smear-negative, culture-positive patient was contaminated during DST. All patients identified with TB had a cough greater than two weeks, producing sputum. Of the 13 patients reporting cough, 6 (46%) had TB. All patients who reported hemoptysis were found to have TB.

Overall, 6 new cases of TB were identified in this active case finding program with a prevalence of 4%, or 4000 per 100,000 (see Table 3). The demographics of those with and without TB are presented in Table 2. Of importance, 5 patients with TB (83%) lived with, on average, 4.6 other individuals. Additionally 5 patients (83%) had a history of incarceration. Three patients were HIV-infected, while two were HIV-negative, with the remaining patient having an unknown HIV status. Three of the patients reported a prior history of TB; two of these (67%) reported completing the previous course of treatment, while one defaulted from treatment.

Table 3: Tuberculosis laboratory testing results of patients on methadone treatment at Muhimbili Medication Assisted Treatment Program, Dar es Salaam, Tanzania

Characteristic	**n**	**(%)**
Total Patients Surveyed	150	
Symptom Positive	16/150	(11%)
Smear-Positive, Culture-Positive	1/16	(6%)
Smear-Negative, Culture-Positive*	5/16	(31%)
Smear-Negative, Culture-Negative	10/16	(63%)
Total New Cases	6/150	(4%)
Multi-Drug Resistant**	1/6	(17%)

*On sputum culture, one patient with an unknown HIV status was found to have Mycobacterium Other Than Tuberculosis (MOTT). This patient was not considered a positive case, but may have an opportunistic infection.

**One sputum sample was contaminated during DST.

Discussion:

Our study met our goals by identifying undiagnosed pulmonary TB cases and link them to treatment; assessing the prevalence of active pulmonary TB in this population; determining the prevalence of HIV/TB coinfection; determining the proportion of cases with MDR-TB; determining the proportion of cases that are smear-positive; and describing characteristics of TB cases.

In our sample of 150 PWID on methadone maintenance, 4% (4000 per 100,000) had active pulmonary TB. This is roughly 23 times the national Tanzanian TB prevalence of 172 per 100,000.(22) Of these 6 cases, 5 cases were smear-negative, and one smear-negative case had MDR-TB. To our knowledge, this study represents the first data on TB in a population of PWID in Tanzania.

Our results have significant implications for TB control in this population. Tanzanian PWID are a subpopulation at high risk for TB, and should be actively screened. If passive case finding alone had continued, these individuals would have been undiagnosed for a longer period of time, with potentially lethal consequences. With the high frequency of cohabitation, these individuals were also at risk for infecting household contacts. As methadone patients are required to attend the clinic 7 days a week, these undiagnosed cases also presented a transmission risk to other MAT clients and their healthcare providers. The original layout of the clinic's waiting area lead to crowded conditions that allowed for ample opportunity for airborne transmission. The high proportion of patients with active pulmonary TB prompted the clinic staff to modify the structure of the waiting

room to increase ventilation. Thus the program was beneficial for both cases and their regular contacts, including patients and staff.

Comparison with other case finding and prevalence studies in Tanzania

Other Tanzanian studies on active TB have been performed in different populations with varying rates of TB.(47-53) For example, Munseri and colleagues examined a cohort of 1318 subjects in 2 voluntary counseling and testing (VCT) centers in Dar es Salaam in 2002-2003. One of these VCT centers was based at Muhimbili National Hospital, the same site where our study was implemented. Defining TB by both laboratory and clinical criteria, TB was present in 101 (7.7%) subjects, of whom 38 (38%) were already known TB cases and 63 (62%) were newly diagnosed. TB/HIV co-infection was detected in 70 (5.3%) of subjects. Limiting to laboratory-confirmed cases, 35 of 1280 (2.7%) of subjects with an unknown TB status were culture-positive, which is slightly lower than our microbiologically confirmed prevalence of 4%.(52)

Other studies have looked specifically at TB in HIV-positive populations in Tanzania. For example, Peck and colleagues followed a cohort of 2514 HIV-positive adults starting ART therapy at Bugando Medical Centre in Mwanza, Tanzania. Subjects did not have evidence of TB at the beginning of the study, and had monthly screenings for 6 months after starting ART. TB diagnosis was established by either microbiologic confirmation or by symptoms and chest radiographic findings consistent with TB, along with a positive response to anti-TB therapy. Although sputum smear microscopy was used, sputum culture was not available. Of the 2514 cases, 72 (3%) subjects were diagnosed with TB,

of which 66 (92%) subjects had pulmonary TB. Eleven (0.4% of cohort) subjects were smear-positive, and the rest of the cases were smear-negative but had clinical criteria consistent with TB.(48)

Comparison with other active TB studies in methadone clinics

Case finding studies for TB in methadone clinics have not been performed in Africa to date; however, they have been performed elsewhere.(54-58) In the pre-HIV era of the 1970s, Reichman and colleagues surveyed PWID enrolled in 20 citywide clinics in the New York City Methadone Maintenance Treatment Program. Subjects received TST for latent TB, and TST-positive subjects were referred to the health department for clinical evaluation and chest x-ray. Of 3818 subjects, 853 (22.5%) were TST-positive, and 52 (1.4%) had chest x-rays consistent with active TB.

After the advent of HIV in the late 1980s, Selwyn and colleagues prospectively studied 520 PWID enrolled in a methadone-maintenance program in the Bronx, New York. They screened all subjects on admission for HIV and for latent TB with Tuberculin Skin Testing (TST), and then followed them prospectively for development of latent TB or active TB for a mean of 22 months. At baseline, 217 (42%) were HIV-positive, and forty-nine of 217 (23%) HIV-positive subjects had a positive TST, compared to 62 of 303 (20%) HIV-negative subjects. Among those who had a negative PPD at the beginning of the study, a conversion to positive PPD at follow-up was seen in 15 of 131 (11%) HIV-positive subjects and 26 of 202 (13%) HIV-negative subjects. These rates did not significantly differ. However, the HIV-positive group was much more likely to develop

active TB: eight of the 215 (4%) HIV-positive subjects developed active TB within the follow-up period, and none of the HIV-negative group developed active TB. Among those HIV-positive subjects who had a positive PPD at enrollment, 7 of 49 (14%) developed active TB. Among our study's 6 cases, 1 was HIV-negative in the last 3 months, and the other 5 were either HIV-positive or had an unknown status. (55)

More recently, Ruutel and colleagues studied a cohort of 112 PWID at a methadone program in Estonia in 2007. They tested all eligible and consenting patients for HIV, and for latent TB with TST and interferon-gamma release assay (IGRA). Of all subjects, (86%) were HIV-positive, 17% were TST-positive, and 7.4% were IGRA positive. Of the 49 (43.8%) subjects who attended the TB clinic, none were diagnosed with active TB.(58)

Recently, two papers from Iran studied PWID in methadone programs. From 2008 to 2009, Mamani and colleagues surveyed 268 PWID in methadone maintenance programs in the city of Hamedan. About 30% of the subjects were HIV-positive. TST was performed on all patients. For patients with positive TST, chest x-ray and sputum smear microscopy was performed. TST was positive in 18.3% of subjects, and one case of active TB was diagnosed by chest x-ray and sputum smear.(59) From 2011-2012, Honarvar and colleagues surveyed 263 opiate users who attended university affiliated drop-in centers, methadone maintenance clinics, and harm-reduction facilities in southern Iran. About 75% were PWID, and the others were non-injectors. About 84% were on methadone, and about 56% were HIV-positive. All received a symptom screen, and all

symptomatic patients received sputum microscopy, sputum culture and chest x-ray. Three (1%) culture-positive cases were found, two of which were smear-positive, and 1 of which was in a PWID. The prevalence among PWID was 500 per 100,000, about one-eighth the prevalence in our study.(60)

Smear-Positivity:

In our study, 5 of 6 (83%) of the newly diagnosed cases were missed by sputum smear and identified only by sputum culture. One potential explanation for this finding is that HIV-infected individuals are more likely to have sputum-smear negative TB.(14) Two studies among HIV-infected patients within Tanzania have shown smear sensitivity of 40%(53) and 61.8%(50). Of our 5 smear-negative, culture-positive patients, 2 were known to be HIV-infected, and 2 had an unknown HIV status. Our results suggest that sputum culture be included in all active screening programs of PWID. Of critical importance, it took several weeks to reach a diagnosis for these smear-negative patients. These patients continued to pose an infection risk during this diagnostic delay, highlighting the need for rapid diagnostics in screening programs, such as the nucleic acid-based testing. Due to these results, the MAT clinic plans to invest in a GeneXpert array when resources are available.

Symptom Screen:

Our symptom analysis showed that cough greater than 2 weeks and sputum production were the most sensitive symptoms, with all new diagnoses having these symptoms. This is consistent with other studies, which have successfully used cough > 2-3 weeks as the

only symptom screen.(61) At Muhimbili National Hospital, the same site where our study was implemented, Mwita and colleagues surveyed 125 HIV-infected patients with cough in 2006. Screening was sputum smear with Ziehl-Neelsen stain, but no culture was performed. They found nine subjects (7.2%) with smear-positive TB.(47) This is similar to 1 of 13 (7.7%) patients with cough in our study, although 6 of 13 (46%) were culture-positive, suggesting that Mwita and colleagues may have found more patients if they had been able to culture sputum samples. Although cough greater than 2 weeks was 100% sensitive among the patients tested in our study, our protocol did not identify asymptomatic cases, so the sensitivity among the entire study population cannot be calculated.

Characteristics of Population and TB Cases:

Our study found several interesting characteristics of TB cases. First, five out of six patients with active TB in our sample lived with others, suggesting that household contacts were at increased risk for transmission. A 2009 study by Kifai and Bakari from Dar es Salaam found Mantoux skin test reactivity in more than 60% of household contacts of smear-positive cases.(62) Another study by Ntinginya and colleagues used the Cepheid Xpert MTB/RIF assay to conduct case finding among household contacts of TB cases in Mbeya, Tanzania. Among 219 patients surveyed, the prevalence of active TB was 2.3%.(63) The detection of at least one MDR-TB case in our sample makes the potential for transmission beyond the PWID community even more worrisome.

Additionally, there was a very high rate of past TB history in the population as a whole (17%), and even higher among patients currently infected with TB (38%). There is evidence of high rates of recurrent TB in Tanzania. For example, Lahey and colleagues examined a cohort of 979 HIV-infected, BCG-immunized adults with CD4 counts >= 200 cells/uL who received placebo in a TB vaccine trial in Tanzania. Among 80 subjects who reported prior active TB, 11 (13.8%) subsequently developed definite TB and 17 (21.3%) definite/probable TB during a median follow-up of 3.2 years.(49) This is similar to our rate of 11.5% (3 of 26).

In our study, a very high rate of patients had been previously incarcerated or held in pre-trial detention (71%), which may have served as a major transmission site for PWID. A study by Rutta and colleagues in the mid-1990s investigated prisoners at Bugando Medical Centre in Mwanza, Tanzania which receives referrals from all ill prisoners at nearby Butimba Prison. The investigators performed a chart review of all prisoners with TB. Of 625 prisoners diagnosed with TB over a 3-year period, 501 cases had complete patient records, of which 204 (40.7%) cases were smear-positive, suggesting a high proportion of TB cases were infectious. This suggests that Tanzanian prisons may be a high-yield site for case finding.

Limitations:

Our study has several limitations. First, our study used a small nonrandom sample, and was susceptible to selection bias. Our sample had a significantly higher known HIV-positivity rate than unenrolled patients. There are two potential explanations. First, chart

review was more thorough for patients in the sample, taking into account patient's self-report of positive status, while chart review for unenrolled patients was limited to registration data and laboratory testing. Second, patients who refused or avoided recruitment into our study may have also been more likely to refuse HIV testing, and may have had undiagnosed HIV infection.

Another limitation was laboratory testing only symptomatic patients (with an emphasis on pulmonary symptoms), missing asymptomatic cases and those with extra-pulmonary TB. Although the study by Getahun and colleagues(41) mentioned in the introduction showed that HIV-positive patients without the four key symptoms had a very low probability of having active TB disease, some small studies in Tanzania have discovered asymptomatic cases. For example, a prevalence study of 93 HIV patients in Dar es Salaam by Mtei and colleagues found 4 of 14 cases had no symptoms or chest x-ray findings consistent with TB.(51) In another study by Ngowi and colleagues of 233 patients in a rural Tanzanian HIV clinic, 75% of the 20 cases discovered had no symptoms or chest x-ray findings consistent with TB.(53) Without data on these potential asymptomatic cases, we could not calculate sensitivity and specificity of our screening questions for the entire study population.

Third, 69% of the sample had an unknown HIV status, which limited our ability to analyze rates of HIV-TB co-infection in this population. Fourth, the majority of our patients were male, and our data provides limited insight into TB among female injectors. This represents the gender distribution of the clinic as a whole, which had difficulty

recruiting female injectors. Next, we defined a TB case as smear or culture positive sputum – this may underestimate the TB prevalence in the MAT program in comparison with national prevalence rates that include cases that are clinically diagnosed and not microbiologically confirmed.

Finally, the scope of our study did not look at outcomes between patients identified by passive vs. active case finding to observe an impact on mortality, which would be the true sign of success of the screening program.

Future Steps:

This pilot study suggests high rates of active TB in PWID entering this methadone clinic, and all future clients should be screened at entry, at a minimum using a symptom screen with sputum smear and culture. If resources are found to conduct sputum testing on all patients at registration, it may provide information on asymptomatic cases. The MAT clinic has continued to screen patients with a symptom screen after the conclusion of this project, and has found a substantially increased prevalence. Over 50 patients have completed or are currently undergoing TB treatment along with daily methadone. Treatment outcomes should be evaluated and improved.

Additionally, as our data showed that many TB cases lived with several other people, future efforts should attempt contact tracing in the community. Household contact cases should be linked to directly-observed treatment to decrease community transmission.

Finally, the clients participating in the MAT program were selected based on their motivation and likelihood to succeed in methadone treatment; therefore, it is reasonable to believe that they represent a healthier subset of the larger PWID population, who may have a higher burden of HIV and TB. Future studies should attempt case finding in the community, potentially with the help of community-based NGOs and community outreach vans run by the Tanzanian AIDS Prevention Programme.

Finally, as TB and HIV treatment were delivered together with methadone, treatment outcomes should be studied to quantify benefits from this integrated approach to care for PWID.

Conclusion:

In conclusion, this pilot study actively screened 150 people who inject drugs who were started on methadone in Dar es Salaam, Tanzania and found that 6 patients had sputum cultures indicative of active TB. This TB prevalence of 4% is 23 times higher than the national prevalence of TB in Tanzania. Our study suggests sputum culture and DST should be obtained on all patients with a cough greater than 2 weeks, productive of sputum. Ongoing efforts to identify PWIDs with TB must be undertaken and effective treatment programs must be established to assist patients in completing treatment integrated with their methadone and antiretroviral therapy.

References

1. Bynum H. Spitting Blood: The History of Tuberculosis. OUP Oxford; 2012.
2. Madkour MM, Al-Otaibi KE, Swailem RA. Historical Aspects of Tuberculosis. In: Tuberculosis. Madkour, M. Monir ed. Berlin: Springer; 2004. p. 15-30.
3. Zink AR, Sola C, Reischl U, Grabner W, Rastogi N, Wolf H, et al. Characterization of Mycobacterium tuberculosis complex DNAs from Egyptian mummies by spoligotyping. J Clin Microbiol. 2003 Jan;41(1):359-67.
4. Lawlor C. Consumption and Literature: The Making of the Romantic Disease. Palgrave Macmillan; 2007.
5. Lawn SD, Zumla AI. Tuberculosis. Lancet. 2011 Jul 2;378(9785):57-72.
6. CHALKE HD. Some historical aspects of tuberculosis. Public Health. 1959 Dec;74:83-95.
7. Ernst JD. The immunological life cycle of tuberculosis. Nat Rev Immunol. 2012 Jul 13;12(8):581-91.
8. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011 Apr;24(2):351-76.
9. Friedland JS. Tuberculosis and other mycobacterial infections. In: Cohen J, Opal SM, Powderly WG, editors. Infectious Diseases. Third ed. Elsevier Limited; 2010. p. 309-27.
10. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep. 2000 Jun 9;49(RR-6):1-51.
11. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. MMWR Recomm Rep. 2010 Jun 25;59(RR-5):1-25.
12. Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. Clin Microbiol Rev. 2014 Jan;27(1):3-20.
13. Molicotti P, Bua A, Zanetti S. Cost-effectiveness in the diagnosis of tuberculosis: choices in developing countries. J Infect Dev Ctries. 2014 Jan 15;8(1):24-38.
14. Colebunders R, Bastian I. A review of the diagnosis and treatment of smear-negative pulmonary tuberculosis. Int J Tuberc Lung Dis. 2000 Feb;4(2):97-107.
15. Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis. 2006 Sep;6(9):570-81.

16. Lawn SD, Mwaba P, Bates M, Piatek A, Alexander H, Marais BJ, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. Lancet Infect Dis. 2013 Apr;13(4):349-61.
17. Balcha TT, Sturegard E, Winqvist N, Skogmar S, Reepalu A, Jemal ZH, et al. Intensified tuberculosis case-finding in HIV-positive adults managed at Ethiopian health centers: diagnostic yield of Xpert MTB/RIF compared with smear microscopy and liquid culture. PLoS One. 2014 Jan 22;9(1):e85478.
18. Carriquiry G, Otero L, Gonzalez-Lagos E, Zamudio C, Sanchez E, Nabeta P, et al. A diagnostic accuracy study of Xpert(R)MTB/RIF in HIV-positive patients with high clinical suspicion of pulmonary tuberculosis in Lima, Peru. PLoS One. 2012;7(9):e44626.
19. Treatment of Tuberculosis - Guidelines. Geneva: World Health Organization; 2010. Report No.: Fourth edition.
20. Gunther G. Multidrug-resistant and extensively drug-resistant tuberculosis: a review of current concepts and future challenges. Clin Med. 2014 Jun;14(3):279-85.
21. Zumla AI, Gillespie SH, Hoelscher M, Philips PP, Cole ST, Abubakar I, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. Lancet Infect Dis. 2014 Apr;14(4):327-40.
22. Global tuberculosis report 2014. Geneva: World Health Organization; 2014.
23. Drug-resistant TB: surveillance and response. Supplement to Global Tuberculosis Report 2014. Geneva: World Health Organization; 2014.
24. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, 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 Nov 4;368(9547):1575-80.
25. Prevention and control of tuberculosis among homeless persons. Recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR Recomm Rep. 1992 Apr 17;41(RR-5):13-23.
26. Centers for Disease Control and Prevention (CDC), National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Prevention and control of tuberculosis in correctional and detention facilities: recommendations from CDC. Endorsed by the Advisory Council for the Elimination of Tuberculosis, the National Commission on Correctional Health Care, and the American Correctional Association. MMWR Recomm Rep. 2006 Jul 7;55(RR-9):1-44.
27. Khan AD, Magee E, Grant G, Centers for Disease Control and Prevention (CDC). Tuberculosis - United States, 1993-2010. MMWR Surveill Summ. 2013 Nov 22;62 Suppl 3:149-54.

28. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. Clin Infect Dis. 2009 Jan 1;48(1):72-82.

29. Getahun H, Gunneberg C, Sculier D, Verster A, Raviglione M. Tuberculosis and HIV in people who inject drugs: evidence for action for tuberculosis, HIV, prison and harm reduction services. Curr Opin HIV AIDS. 2012 Jul;7(4):345-53.

30. Friedland G. Infectious disease comorbidities adversely affecting substance users with HIV: hepatitis C and tuberculosis. J Acquir Immune Defic Syndr. 2010 Dec;55 Suppl 1:S37-42.

31. Reichman LB, Felton CP, Edsall JR. Drug dependence, a possible new risk factor for tuberculosis disease. Arch Intern Med. 1979 Mar;139(3):337-9.

32. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull World Health Organ. 2013 Feb 1;91(2):102-23.

33. Cherubin CE, Sapira JD. The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. Ann Intern Med. 1993 Nov 15;119(10):1017-28.

34. Systematic screening for active tuberculosis - Principles and recommendations. Geneva: World Health Organization; 2013.

35. Kranzer K, Afnan-Holmes H, Tomlin K, Golub JE, Shapiro AE, Schaap A, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. Int J Tuberc Lung Dis. 2013 Apr;17(4):432-46.

36. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. Lancet. 2010 Oct 9;376(9748):1244-53.

37. Ayles H, Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwinga M, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. Lancet. 2013 Oct 5;382(9899):1183-94.

38. Policy guidelines for collaborative TB and HIV services for injecting and other drug users: an integrated approach. WHO; 2008.

39. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis. 2005 Nov;9(11):1183-203.

40. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011.

41. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. PLoS Med. 2011 Jan 18;8(1):e1000391.

42. The Global Afghan Opium Trade: A Threat Assessment. UNODC; .

43. McCurdy SA, Williams ML, Kilonzo GP, Ross MW, Leshabari MT. Heroin and HIV risk in Dar es Salaam, Tanzania: youth hangouts, mageto and injecting practices. AIDS Care. 2005 Jun;17 Suppl 1:S65-76.

44. Global Report - UNAIDS report on the global AIDS epidemic 2013. UNAIDS; 2013.

45. Williams ML, McCurdy SA, Bowen AM, Kilonzo GP, Atkinson JS, Ross MW, et al. HIV seroprevalence in a sample of Tanzanian intravenous drug users. AIDS Educ Prev. 2009 Oct;21(5):474-83.

46. McLellan AT, Cacciola JC, Alterman AI, Rikoon SH, Carise D. The Addiction Severity Index at 25: origins, contributions and transitions. Am J Addict. 2006 Mar-Apr;15(2):113-24.

47. Mwita J, Mugusi F, Pallangyo K. Pneumocyctis pneumonia and pulmonary tuberculosis among HIV-infected patients at Muhimbili National Hospital, Tanzania. East Afr J Public Health. 2012 Mar;9(1):10-2.

48. Peck RN, Luhanga A, Kalluvya S, Todd J, Lugoba S, Fitzgerald DW, et al. Predictors of tuberculosis in first 6 months after initiation of antiretroviral therapy: a case-control study. Int J Tuberc Lung Dis. 2012 Aug;16(8):1047-51.

49. Lahey T, Mackenzie T, Arbeit RD, Bakari M, Mtei L, Matee M, et al. Recurrent tuberculosis risk among HIV-infected adults in Tanzania with prior active tuberculosis. Clin Infect Dis. 2013 Jan;56(1):151-8.

50. Matee M, Mtei L, Lounasvaara T, Wieland-Alter W, Waddell R, Lyimo J, et al. Sputum microscopy for the diagnosis of HIV-associated pulmonary tuberculosis in Tanzania. BMC Public Health. 2008 Feb 21;8:68,2458-8-68.

51. Mtei L, Matee M, Herfort O, Bakari M, Horsburgh CR, Waddell R, et al. High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. Clin Infect Dis. 2005 May 15;40(10):1500-7.

52. Munseri PJ, Bakari M, Pallangyo K, Sandstrom E. Tuberculosis in HIV voluntary counselling and testing centres in Dar es Salaam, Tanzania. Scand J Infect Dis. 2010 Oct;42(10):767-74.

53. Ngowi BJ, Mfinanga SG, Bruun JN, Morkve O. Pulmonary tuberculosis among people living with HIV/AIDS attending care and treatment in rural northern Tanzania. BMC Public Health. 2008 Sep 30;8:341,2458-8-341.

54. Reichman LB, Felton CP, Edsall JR. Drug dependence, a possible new risk factor for tuberculosis disease. Arch Intern Med. 1979 Mar;139(3):337-9.

55. Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med. 1989 Mar 2;320(9):545-50.

56. Daley CL, Hahn JA, Moss AR, Hopewell PC, Schecter GF. Incidence of tuberculosis in injection drug users in San Francisco: impact of anergy. Am J Respir Crit Care Med. 1998 Jan;157(1):19-22.

57. Conover C, Ridzon R, Valway S, Schoenstadt L, McAuley J, Onorato I, et al. Outbreak of multidrug-resistant tuberculosis at a methadone treatment program. Int J Tuberc Lung Dis. 2001 Jan;5(1):59-64.

58. Ruutel K, Loit HM, Sepp T, Kliiman K, McNutt LA, Uuskula A. Enhanced tuberculosis case detection among substitution treatment patients: a randomized controlled trial. BMC Res Notes. 2011 Jun 15;4:192,0500-4-192.

59. Mamani M, Majzoobi MM, Torabian S, Mihan R, Alizadeh K. Latent and active tuberculosis: evaluation of injecting drug users. Iran Red Crescent Med J. 2013 Sep;15(9):775-9.

60. Honarvar B, Lankarani KB, Odoomi N, Roudgari A, Moghadami M, Kazerooni PA, et al. Pulmonary and latent tuberculosis screening in opiate drug users: an essential and neglected approach for harm-reduction facilities. J Addict Med. 2013 Jul-Aug;7(4):230-5.

61. Corbett EL, Charalambous S, Moloi VM, Fielding K, Grant AD, Dye C, et al. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. Am J Respir Crit Care Med. 2004 Sep 15;170(6):673-9.

62. Kifai EJ, Bakari M. Mantoux skin test reactivity among household contacts of HIV-infected and HIV un-infected patients with sputum smear positive TB in Dar es Salaam, Tanzania. East Afr J Public Health. 2009 Aug;6(2):211-8.

63. Ntinginya EN, Squire SB, Millington KA, Mtafya B, Saathoff E, Heinrich N, et al. Performance of the Xpert(R) MTB/RIF assay in an active case-finding strategy: a pilot study from Tanzania. Int J Tuberc Lung Dis. 2012 Nov;16(11):1468-70.