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Prevalence Of Tuberculosis Symptoms And Latent Tuberculosis Infection Among Prisoners In Northeastern Malaysia

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Prevalence of Tuberculosis Symptoms and Latent Tuberculosis Infection among Prisoners in Northeastern Malaysia

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Abstract:

Background: Tuberculosis (TB) is a known public health threat to prison systems due to poor hygiene, crowded living conditions, poor health of inmates, and poor prison healthcare systems. The large population of HIV-infected people living in prisons is especially susceptible to increased TB transmission and higher mortality. In Northeastern Malaysia, there is no screening for active or latent TB infection (LTBI) in the prison system.

Aims and Hypothesis: This study serves to measure the prevalence and correlates of LTBI and active TB symptoms in HIV-infected and non-HIV-infected prisoners in Northeastern Malaysia. Given the host of factors that contribute to TB transmission and burden in prisons, it is expected that the burden of LTBI is high. In studying a population of HIV-infected inmates who are not receiving antiretroviral therapy, it is expected that a significant number of inmates will display active TB symptoms.

Methods: This is a cross sectional study design that uses Tuberculin Skin Testing (TST) to measure LTBI, and the World Health Organization (WHO) TB symptom survey to measure active TB symptom prevalence. A total of 266 prisoners in Penjara Pengkalan Chepa, Kelantan, Malaysia, were enlisted in the study. After consent, participants underwent two-step TST and were surveyed for active TB symptoms. Standardized cutoffs of ≥5mm and ≥10mm were used to define reactive TST among prisoners with and without HIV, respectively. Clinical and behavioral data were assessed with a questionnaire and HIV-infected prisoners were stratified by CD4 status.

Results: LTBI prevalence in Penjara Pengkalan Chepa in July-August 2011 was 87.6%, with significantly lower TST-reactivity among HIV-infected compared to non-HIV-infected prisoners (83.6% vs. 91.5%; $p<0.05$); however, TB symptoms were similar (16.9% vs. 10.1%; $p=0.105$).

On multivariate analysis, previous incarceration (AOR=4.61: 95%CI=1.76-12.1) was the only significant correlate of LTBI. Increasing age (AOR=1.07: 95%CI=1.01-1.13), lower body mass index (AOR=0.82: 95%CI=0.70-0.96) and having a negative TST (AOR=3.46: 95%CI=1.20-9.97) were correlated with TB symptoms.

Conclusion: LTBI is highly prevalent, associated with previous incarceration, and suggests the need for routine TB screening at entry to Malaysian prisons as well as continued surveillance. The prevalence of LTBI symptoms among HIV-infected inmates is alarming and provides further justification for active screening measures. Treating LTBI in prisons is challenging, but new, shorter regimens hold promise for feasible treatment options in prisons.

Background:

1) Human immunodeficiency virus (HIV) and tuberculosis (TB) co-infection

a) Global epidemiology, pathophysiology, and treatment challenges of HIV/TB co-infection

Tuberculosis (TB) remains a global epidemic with 8.7 million incident cases and 1.4 million TB-related deaths reported in 2011.[1] TB-related mortality is disproportionately distributed among people living with HIV/AIDS (PLWHA), a population who accounted for 30% of TB related deaths, or 430,000 deaths, in 2011.[1] It is estimated that up to 1/3 of the world's population is latently infected with TB.[2] HIV infection is the single largest risk factor for developing active TB disease, and there are an estimated 14 million people co-infected with HIV and TB.[3] TB is the leading cause of death among PLWHA, and an increased number of these cases are multidrug resistant (MDR) or extensively drug resistant (XDR) compared to the non-HIV-infected population.[4] Infection with HIV increases a person's risk 20-fold of developing active TB.[5] The lifetime risk of TB activation among non-HIV-infected persons is reported between 5-10%, however he risk of TB activation among PLWHA increases to 5-10% *per year*.[6]

Over the past thirty years we have seen the resurgence of active TB closely parallel the geography of the HIV epidemic. In many regions of the world, prior to the HIV/AIDS epidemic, active TB infections actually decreased, especially in high-income countries. Eighty-two percent of the world's HIV/TB co-infection occurs in sub-Saharan Africa[7], with one fourth of co-infections occurring in South Africa alone in 2007.[4] Much of the rest of HIV/TB co-infection is concentrated in Eastern Europe and Southern and Southeast Asia, where injection drug use is the driving factor of HIV transmission.[8]

Co-infection with HIV and TB creates difficult diagnostic and therapeutic challenges as these two diseases augment each other's natural history and contribute to atypical presentations,

accelerated disease course, and specific treatment challenges. HIV infection depletes CD4 T lymphocytes, which play an important role in granuloma organization. Granuloma formation is essential for TB sequestration in the latent stage, and failure of this process contributes to the high risk of latent TB reactivation.[9] Unsurprisingly, the rate of progression to active TB increases with decreasing CD4 count since CD4 T cells control mycobacterial granuloma formation and structure.[10] TB also influences the pathophysiology of HIV infection. Elevated HIV plasma viral loads are detected in patients with active TB, and TB has been shown to increase HIV replication.[11] The presence of TB in PLWHA also increases susceptibility to other opportunistic infections, which are a common cause of death in HIV/TB co-infected people, especially at lower CD4 lymphocyte counts.[7] Recently it has been recognized that starting antiretroviral therapy (ART) is effective not only for reducing TB-related and non-TB related mortality among those with active disease, but also as a means of prevention against activation of latent TB.[12]

Several factors help explain why mortality is disproportionately higher among people with HIV/TB co-infection compared to those with either disease alone. Four main reasons include failure to diagnose TB in PLWHA, failure to diagnose HIV in people with TB, late diagnosis and treatment and ineffective eradication of latent TB infection (LTBI).[8] Autopsy studies in Africa confirm that many HIV-related deaths of unknown cause at time of death are due to disseminated TB.[8] The diagnostic challenges to diagnose TB in people with HIV are numerous. Early in HIV disease, TB is more likely to present similarly to that in a non-HIV-infected person, with pulmonary reactivation. In advanced HIV, TB has a more rapid clinical progression, is more likely to present with extrapulmonary disease, and has a higher chance of being asymptomatic or presenting with atypical symptoms such as hepatomegaly, splenomegaly, diarrhea or neurologic symptoms. In patients with CD4 counts <100, 70% of TB cases present

with extrapulmonary disease, often in multiple sites.[13] TB lymphadenitis is the most common extrapulmonary manifestation of TB in PLWHA. Disseminated TB is also more common in those with advanced HIV disease. It is the second most common extrapulmonary TB manifestation and is often misdiagnosed.[13]

Pulmonary TB reactivation also presents differently and is challenging to diagnose in PLWHA. Typical chest X-ray findings (upper lobe fibro-nodular and cavitary lesions) are less common. Atypical findings such as lower lobe involvement, pleural effusions, mediastinal lymphadenopathy, a miliary pattern, as well as a normal chest X-ray are commonly seen.[7] The gold standard for pulmonary TB diagnosis is sputum culture, which is not influenced by HIV infection. Due to the long time required to culture TB, however, this method of diagnosis is often solely confirmatory, and treatment can often not be delayed for culture results. In low-income settings a combination of clinical presentation, chest X-ray, and sputum smear microscopy are used to diagnose TB, all of which are influenced by the presence of HIV infection. Sputum smear microscopy is not highly sensitive in non-HIV-infected patients[14], but is even less so in PLWHA, detecting only one third to one half of culture positive cases.[15] Measures proven to increase sensitivity include early morning sampling, repeat sampling, and fluorescent microscopy. It is thought that smear positive sputum samples indicate a higher burden of infection and therefore higher risk of transmission, especially in people with advanced HIV disease. In short staffed health systems following public health guidelines for TB, a negative smear can imply no TB treatment, resulting in transmission among high risk communities.

At the cornerstone of efficient identification and treatment of HIV/TB co-infection is a way to rapidly and reliably diagnose active TB in all patients, especially those with HIV in whom the diagnosis is more challenging. There have been several promising advances in TB

diagnosis currently being studied in resource poor environments. The Gene Xpert MTB/RIF (Cepheid) is a nucleic acid amplification test that produces results in less than two hours and also tests for rifampicin resistance. When using two specimens, this test is reported to have very high sensitivity at 98.4%, but sensitivity is lower in patients with HIV at 93.9%.[16] A recent study using this technology with a single specimen, showed relatively low sensitivity, reducing its utility for screening in low-income settings.[17] Another recent advance in TB diagnosis is the urine test for TB antigen lipoaribinomannan. While it holds promise for a rapid urine dipstick diagnosis that is noninvasive and avoids creation of aerosol particles, it suffers in its low sensitivity among immunocompetent persons.[18]

b) HIV/TB co-infection in Southeast Asia

Southeast Asia accounts for 40% of the global burden of TB in terms of TB incidence.[19] The region ranks second under Africa for TB incidence, TB related mortality, and HIV/TB co-infection, and ranks first for TB prevalence.[20] TB deaths in Southeast Asia are predominantly concentrated in five countries: Bangladesh, India, Indonesia, Myanmar, and Thailand.[19] These five of the eleven members of the WHO Southeast Asian region are classified among the 22 high burden TB countries globally.[20] Southeast Asia houses an estimated 3.46 million PLWHA, 10% of the global HIV burden.[19] The estimated incidence of HIV/TB co-infection in Southeast Asia is 140,000 cases in 2011, or 7.7 per 100,000 people. This statistic varies widely between the countries of Southeast Asia, the highest in Myanmar at 38 per 100,000 and the lowest in the Maldives at 0.42 per 100,000. TB is the leading opportunistic infection among AIDS patients in Indonesia and Thailand.[21,22] Due to the success of TB control programs in the Southeast Asia region, there are relatively low percentages of MDR-TB among newly diagnosed cases (1.8-

2.5%.)[19] Yet given the large number of TB cases in Southeast Asia, it was estimated to house more than one fourth of the world's MDR-TB cases in 2011.

It has been well-established that the HIV epidemic in Southeast Asia is fueled by injection drug use and commercial sex work, and this population remains the most plagued with HIV/TB co-infection.[23] The result is increased HIV/TB co-infection among the young male age group. The WHO estimates HIV prevalence in Southeast Asia at 0.3%, and estimated the HIV prevalence among patients with TB at 5.7%.[24] Thailand, Myanmar, and nine states in India report generalized HIV epidemics, while Indonesia and Bangladesh report localized epidemics.[25] The death rate for HIV-infected TB patients in Southeast Asia during treatment is especially high from 20-50%, often due to late disease presentation (mean CD4 count at time of diagnosis of 54-57 cells/uL.)[26]

Diagnosis of TB in most areas of Southeast Asia is often challenging due to limited resources. Like many resource poor settings, diagnosis is often made by a combination of clinical symptoms, sputum smear, and chest X-ray, and sputum culture is often not included in the diagnostic algorithm. The WHO, in an effort to solve the dilemma of difficult TB diagnosis among HIV-infected patients who require immediate treatment, has implemented the Gene Xpert MTB/RIF assay in Southeast Asia. All eleven countries in Southeast Asia have ordered at least one Xpert MTB/RIF assay, but the large majority of settings in Southeast Asia continue to operate without a reliable means of rapid diagnosis due to the high cost of these machines.[24] There were no data revealed in a search for the use of the urine TB antigen lipoaribinomannan in Southeast Asia, but this test has the possibility for widespread usage in resource poor areas due to its low cost and simplicity.

c) HIV/TB co-infection in Malaysia

Malaysia, a middle-income country with intermediate TB prevalence reported 101 active TB cases per 100,000 people in 2011.[27] Overall, LTBI prevalence is 36% in Southeast Asia, yet LTBI prevalence is reported at 52.1% and 59.0% in two studies of Malaysian healthcare workers using tuberculin skin testing (TST).[28,29] Malaysia had seen a decline in TB incidence between 1970 and the early 1990's, but since the emergence of HIV and increased urban drug abuse, Malaysia has seen an increase in TB incidence from 58/100,000 in 1995 to 81/100,000 in 2011.[30] It is estimated that more than two in three of Malaysian HIV cases result from injection drug use in 2008, making drug use a vessel for HIV infection and subsequent TB disease.[31] Interestingly, in 2007 the Orang Asli (the ethnic group native to the Malaysian peninsula) were found to have higher rates of TB (up to 5.5 times higher) than the rest of the population for unknown reasons.[32] The most recent WHO TB country profile reports a total of 1629 cases of HIV/TB co-infection, and a total of 141 MDR-TB cases in 2011.[33] The prevalence of HIV among TB patients in Malaysia was 7.2% in 2010, which is low for Southeast Asia where the prevalence of HIV/TB co-infection ranges from 0.9-38.0%.[30] TB in Malaysia is the most common opportunistic infection among AIDS patients, and a study in Kuala Lumpur in 2002 showed that TB was responsible for 30.3% of all opportunistic infections among a group of AIDS patients (most common site was pulmonary, followed by lymph node.)[34]

There are few studies in Malaysia about survival or predictors of death in HIV/TB co-infected people. A study by Ismail in 2013 reported an 11.8% co-infection rate among a group of TB patients registered at three hospitals in Malaysia. The mean age of HIV/TB co-infected patients was 39.1, male to female ratio was 7:1, the highest proportion were ethnic Malays at 48.5%, followed by equal numbers of Chinese and Indians at 16.3%. Death rate among co-

infected patients being treated for TB was 23.3%, and predictors of death were Malay ethnicity, absence of ART, and low CD4 count.[30] As seen in the rest of Southeast Asia, treatment failure rates are high in Malaysia, and one study reported a TB treatment success rate of 53.5%, with lower rate of 42.7% among people who inject drugs (PWID).[35]

2) Tuberculosis burden in prisons

a) Overview and global epidemiology of tuberculosis in prisons

About 10 million people worldwide are incarcerated (with about 4-6 times this number when counting people incarcerated at some time in a given year).[36] HIV and TB are magnified within correctional settings where numerous risk factors contribute to the presence and transmission of both diseases.[37,38] TB prevalence in prisons has been reported by different studies from five to fifty times national averages.[39,40] A 2013 review of 24 studies reported a global median TB prevalence of 1913/100,000 in prisons, with North America and Western Europe having significantly lower prevalence. They report global median TB incidence in prisons of 7 cases per 1000 person years ranging from 0.25 to 40 cases per 1000 person years, and median prevalence of LTBI in prisoners at 17.9%.[41] HIV is also more prevalent in prisons, with rates of 10-20 times greater than in non-incarcerated populations.[36] Given these two coexisting epidemics in prison, it is not surprising that HIV/TB co-infection is also highly prevalent. The review previously cited documents global HIV/TB co-infection in prisons at 13.2%, and another reports 30-70% of prisoners with tuberculosis are also infected with HIV.[41,42] TB mortality in prisons is as high as 24% due to many factors that lead to late disease presentation and inadequate treatment.[43]Another reason for high TB mortality in prisons is the high prevalence of MDR-TB, specifically in Sub-Saharan Africa.[44] TB has been reported as the most common cause of death

in prisons in developing countries.[45]

The incarcerated population is not representative of the general population, and the differences form the foundation of increased TB risk in prisons. Prison populations are often drawn from people who are marginalized from society and who have poor access to healthcare before incarceration. Drug use and subsequent HIV infection are common, and predispose people infected with TB to developing active disease.[46] Many prisoners are repeat offenders, with multiple trips to prison, discontinuous health care, and a high chance of incomplete TB treatment if started during a previous imprisonment. Once in prison, a number of new risk factors become present. Substance misuse, low socioeconomic status, crowded housing units with poor ventilation, malnutrition, and proximity with active TB cases all increase TB risk in prisons,[46-48] as does previous incarceration as an independent risk factor.[49-52] Other risk factors include unhygienic drug use due to lack of clean supplies, unprotected sexual contact, delayed diagnosis and treatment due to absence of active screening, interrupted treatment due to prisoner movement resulting in drug resistant TB, and uncommon checks for treatment success.[36]

Prison social structures influence TB diagnosis and treatment due to the hospital setting as a commodity, TB medications themselves as currency, and the potential for TB treatment to delay prisoner release. Hierarchical prison systems result in uneven treatment among inmates, with more powerful and senior inmates receiving more attention and access to health care resources.[36] Inmates have been known to falsify sputum samples by trade with others to enter into TB treatment programs due to favorable conditions in the hospital setting. Also, TB medicines can be used as currency in a hierarchical social structure where select subpopulations do not have access to prison health services, another reason to falsify a sputum sample. In the instance of TB treatment potentially delaying an inmate's release, sputum could be falsified by

trading with an inmate without active TB to assure uninterrupted release. Some prisons have stopped using early morning sputum samples that usually have the highest yield to assure all samples are collected in the medical center to avoid falsification.

While prisons seem like "closed" systems to those living there, they are in fact very impactful to the rest of society via visitors, prison staff, prison transfers, and recidivists (Figure 3). TB transmission has been documented from prisoners to employees, visitors, volunteers, and other inmates.[53] In fact, the concepts of prison to population transmission and prisons as a TB reservoir are thought to contribute significantly to the overall TB incidence of the population.[54] Perhaps one of the most mobile components of the prison system are prisoners themselves. They often start off in remand blocks (also referred to as jails) while awaiting sentencing, which are places of high turnover. They are called with little notice for court dates and are often moved to a different facility or location with little congruity of their healthcare or current treatments, a setup for treatment failure and MDR-TB if undergoing TB treatment.[55] Generally, proving transmission between inmates is difficult and would require serial TSTs, which are not routinely performed for inmates, or genetic fingerprinting also not routinely performed due to cost. However, prison staff members are often tested regularly so their transmission is more clearly documented. What is clear is that TB identification and control in prisons is a general public health issue.[51]

Once active or latent TB is diagnosed in prison, multiple challenges remain to successful treatment and connection with community health services upon release. Healthcare in prisons worldwide rarely falls under jurisdiction of a country's Ministry of Health, and often is provided by the Ministry of Justice or Ministry of Interior, who place far less priority on providing the highest quality care. Subsequently, second line TB treatment is often not available in prisons in

lower resource settings, making MDR-TB a challenge to treat in prisons. Lack of adequate education in prisons results in inmates who are unaware of the dangers of not completing treatment regimens, further fueling MDR-TB.[45] Health statistics from agencies other than the Ministry of Health are often not reported, resulting in poor knowledge of HIV and TB burden in prisons in many countries. The structural, organizational, and situational circumstances that make prisons poor places to control TB are all hindrances to a disease that is relatively uncomplicated to diagnose and treat under ideal circumstances. Since the culmination of aforementioned risks results in significant morbidity and mortality in prisons which is readily preventable, access to adequate TB diagnosis and treatment has been thought by some to be a human rights issue, similar to the way HIV treatment is now considered a human right.[56]

b) Tuberculosis in prisons in Southeast Asia

There is a paucity of data regarding epidemiology of TB in prisons in Southeast Asia. Most of the work on TB in prisoners in Southeast Asia has taken place in Thailand, a country that implemented Directly Observed Therapy-short course (DOTS) in all its nation's prisons by the year 2002. In the majority of Southeast Asian countries, Thailand and Singapore specifically, TB surveillance in prisons is still passive, resulting in late disease presentation and poor treatment outcomes.[57,58] Active surveillance currently only occurs during research studies. In a study of 27 Thai prisons in which inmates were actively screened for TB symptoms, 30.9% were found to be TB suspects, and active TB prevalence was 363.3 per 100,000. This number is lower than that of the study mentioned below, but is likely due to the tendency to underestimate true prevalence when using symptom screening.[58] Another active case finding study reported smear positive TB prevalence at 1226 per 100,000, with 50.6% of cases resistant to at least one drug,

and 19.5% MDR-TB.[59] Despite Thailand's prison-wide DOTS program, treatment outcomes in Thai prisons are poor. Treatment success rate in a northern Thai prison was 47.4%, and 28.8% of inmates died during treatment.[60]

c) Tuberculosis in the Malaysian correctional facility system

There are currently minimal published data on active or latent TB epidemiology in Malaysian prisons. The Malaysian government does not collect this data. One study addressing TB in correctional facilities was conducted in a compulsory drug detention center (CDDC). These centers are structurally similar to prisons in that they contain a similar population, and often have substandard living conditions similar to prisons but do not operate under the Human Rights oversight for prisoners because individuals housed here do not go through the adjudication system and are therefore not under international oversight. CDDCs have flourished throughout Asia, especially in China, Vietnam, Cambodia and Malaysia. Little empirical data are known about these institutions, however, Fu et. al. reported 23% of participants in CDDCs in Malaysia screened positive for symptoms of active TB, but none were followed up with confirmatory testing due to resource limitations.[61] HIV-infected inmates in these facilities had no access to ART, where rates of HIV were noted at 2 times those in prison and 20 times that of general population.[61] Another study looking at the accuracy of the GeneXpert MTB/RIF assay in Malaysia's largest prison reported an active TB prevalence of 16.7% including those on current treatment among the HIV-infected population.[17][17]

Unpublished work by Al-Darraji et. al. comprises the most complete work on characterizing LTBI and active TB in the largest Malaysian prison. They report a positive TST rate of 84.7% among HIV-infected inmates and 92.5% among HIV-uninfected inmates, with a total prevalence

of 88.0%. Positive correlates of TST positivity included previous incarceration and negative HIV status. They also report an active TB rate of 13.8% among the entire sample. Like most Malaysian prisons, there was poor access to ART with only 6% of those meeting criteria (CD4 count below 350) being treated.[62] Data in Malaysia continue to support the well-established link between incarceration and TB infection, and show particularly high burden of latent and active TB.

3) Tuberculosis screening and treatment of latent tuberculosis infection (LTBI) in resource poor settings

a) WHO's three I's for HIV/TB

Global TB prevalence is dropping at 2% per year, but not fast enough to meet the goal of 1 case per million in 2050.[63] In response to the resurgence of TB with the onset of the HIV epidemic, and the failure to meet worldwide goals to reduce TB burden globally, the WHO created in 2008 a scaffold for reducing TB burden in PLWHA called the "Three I's".[64] The three I's stand for intensified case finding and treatment, infection control, and isoniazid (INH) preventive therapy (IPT). Cited by numerous publications, the three I's form a calling for accurate, rapid screening of latent tuberculosis to allow for safe and effective IPT. One of the most commonly cited reservations for widespread implementation of IPT, especially among an HIV-infected population with atypical TB presentations, is difficulty ruling out active TB, which is a contraindication to IPT.

b) Active and latent TB screening overview

In 1974, prior to the HIV/AIDS pandemic, the WHO withdrew its recommendation for mass TB screening.[65] However, TB screening is still recommended in specific groups such as PLWHA, household contacts of active TB cases, prison populations, refugees and diabetics. Currently the WHO recommends that all HIV-infected people be screened for both active and latent TB due to a clear benefit of early active TB treatment and eradication of latent TB in this population. The most efficacious ways to screen for either latent or active TB has not been established. What is clear is that screening high-risk populations does reduce the TB burden, evidenced by a median LTBI prevalence of 2,227/100,000 in prisons with no routine screening and 343.5/100,000 in prisons with routine screening.[41]

Screening measures are often required to fulfill a number of requirements to be successful and effective. General guidelines are that the disease has to be identifiable at an early stage with proven benefit to early treatment, screening has to be possible at a reasonable cost, and screening practices have to be able to alter disease outcome.[66] TB specific screening concerns in settings with limited resources include ability to provide quality diagnosis, adequate treatment, connection with healthcare management, expected public and/or individual health benefits, analysis of patient initiated screening, and ability to provide resources for screening without high burden on the healthcare system. Active TB screening and diagnosis is complicated by gaps in our understanding of TB transmissibility and its relation to TB symptoms and especially sputum smear status. While there are data proving that TB screening reduces overall TB burden, little data support a link between screening and reduced transmission rates. Ideally, screening would prevent late disease presentations and lead to treatment before long periods of high transmissibility.

TB screening is described by two methods, active and passive screening. Passive screening is patient initiated, and relies on symptomatic presentation for attention to be brought to cases, which is more unreliable in HIV-infected cases where atypical presentations are not uncommon. Active screening is healthcare provider driven, and in resource-limited settings generally consists of symptom questionnaire followed by sputum microscopy and/or chest X-ray. TB symptom screening currently focuses on four symptoms: cough, weight loss, fever, night sweats in past four weeks.[67] This selection has good negative predictive value when active TB prevalence is not very high. Up to 50% of PLWHA have a positive symptom screen for active TB and 10% of those with positive screen may be diagnosed with TB. Given the well-documented mortality advantage of early treatment in HIV associated TB, screening tools have been adapted that focus on high sensitivity with allowance of lower specificity. The WHO symptom survey previously consisted of asking about cough for at least two weeks, but it was shown that asking about cough of any duration identified more TB cases (93% sensitivity when asking about cough of any duration, night sweats or fever.)[68] Regardless, passive screening and even active screening with sputum microscopy have been shown to miss large numbers of smear negative culture positive cases as well as cases with atypical presentation. This has prompted a drive for rapid, accurate diagnostic tools to effectively diagnose active TB.

c) Diagnostic methods for LTBI

The TST was historically the sole method of determining LTBI for epidemiological studies as well as for informing treatment decisions. TST relies on delayed hypersensitivity to an intradermal injection of purified protein derivative (PPD) of mycobacterium bovis, an antigen found in both mycobacterium tuberculosis and other non-tuberculous mycobacteria (NTM).

Given that there is no gold standard for diagnosing LTBI, determining the sensitivity and specificity of the TST is very difficult. One review reports sensitivity and specificity of 89% and 85% for TST[69] when culture confirmed TB is used as the gold standard, although the TST has no role in diagnosing active TB.

There are several limitations and confounding factors of the TST with varying importance and clinical effect depending on the source of the study reviewed. First, TST quality is an operator dependent test, and requires trained and skilled healthcare professionals to correctly place and read the test. Even among trained healthcare workers, measurement of the TST induration is a qualitative measurement subjective to inter-observer measurement bias.[70] Second, the TST requires two visits, one for placement and one for reading, which among certain populations results in decreased adherence and unread tests. Third, there is a concern for false positive TST arising from three main sources: booster effect from frequent TST, cross reaction with Bacillus Calmette–Guérin (BCG) vaccine, and cross reactivity with NTM. The true effect of BCG vaccine on TST results remains elusive, as a wide body of literature exists with conflicting conclusions. If given in infancy only, it is believed that BCG does not markedly affect TST results in adults, and contributes to 1 false positive per 100 tests ten years after receiving the vaccine.[71] However, when BCG is given after 1 year of life, the number of false positives is higher, and the BCG effect lasts for longer, although it decreases with age. False positive TST results due to NTM are very uncommon, and are not thought to be clinically significant in high prevalence areas. If this is a concern in a specific population, there are intradermal tests that use tuberculosis specific antigens. Lastly, the TST is dependent on a functioning immune system, and its sensitivity declines with HIV infection due to inability to mount an immune response, termed anergy. There is no quantitative measure of CD4 count at which point an immune

response will no longer manifest, however it has been shown that more HIV-infected people have a positive TST with CD4>200 compared to those with CD4<200.[72]

As a response to the concerns with the TST, specifically the relatively low specificity and implications for starting IPT on people who would not draw benefit, newer tests were developed that rely on T-cell release of interferon gamma (IFNγ) in response to TB antigen exposure. These tests are named interferon gamma release assays (IGRA). Mycobacterium tuberculosis specific antigens are used to stimulate T-cell release of IFNγ, eliminating the possibility of cross-reaction with BCG vaccine or NTM. The IGRA has higher sensitivity and specificity in BCG vaccinated populations.[73] Additional benefits of the IGRA include quantitative result reporting and one step testing, improving adherence compared to the TST.[74] There are currently two IGRA tests, the QuantiFERON® TB Gold test and the T.SPOT.TB® test. IGRA testing is potentially more sensitive in detecting recent TB exposure compared with TST.[75] Multiple studies have evaluated the IGRA and TST and no reliable or reproducible data has supported use of one over the other. Specifically, when compared, neither test is superior in reducing risk of active TB when the tests are used to determine LTBI treatment with IPT.[64] Neither test has shown prognostic value for risk of progression to active TB.[69] Some evidence suggests that since IGRA's are not susceptible to the booster phenomenon, they should be preferred in populations who undergo repeat testing and exposure like healthcare workers. However, IGRA testing recently revealed increased false positive rates proven by repeat testing. IGRA limitations include its high cost and reliance on technology that is often not available in resource limited settings, accounting for its relatively low use in these settings. Additionally, IGRA sensitivity also decreases in HIV infected people due to its mechanism of measuring T cell immune response.[76]

d) Diagnostic methods for active TB

Sputum culture is the current gold standard for diagnosing active TB. Sputum culture needs as little as 100 bacilli per ml to detect active TB infection.[77] Drug resistance profiles and genetic profiling can be obtained from sputum culture, allowing the most informed treatment decisions and information about transmission for research purposes. Despite being the gold standard, in many places sputum culture is not obtained before treatment is started, and in most places it is not available at all. The major limitation of sputum culture is the time required for detection of AFB colonies, which ranges from a few weeks to as long as months. The delay in treatment that would result from waiting for culture results is often unacceptable, especially among the HIV-infected population in whom early treatment has been proven to decrease morbidity and mortality, especially where MDR-TB cases are prevalent.[78] New methods have been developed to decrease the amount of time it takes for culture results, thereby making the gold standard a more practically useful test. Automated liquid culture uses detection methods such as fluorescent, colorimetric, and pressure sensors to detect MTB growth as early as 1-2 weeks.[79] These technologies are currently expensive, rely on technologically advanced infrastructure, and are therefore not widely employed in resource-limited settings.

Stained sputum microscopy, or "smear," is the most widely used method of TB diagnosis, and requires greater than 10,000 bacilli per ml to detect active infection. Sputum is most often stained by the Ziehl-Neelson method, and sputum can be obtained in several ways including voluntary expectoration, induced expectoration, gastric aspiration, bronchoalveolar lavage, or a newly developed "string method" in which a string is swallowed and secretions adhere to the portion of the string in the pharynx.[80] The main drawback of sputum smear is its poor sensitivity, with numbers reported in the literature around 50% or less.[81] Sensitivity is highest in those with

cavitary lesions. Sputum smear is less sensitive in those with HIV due to the higher incidence of nonproductive cough or no cough at all, cited at 43-51%.[82] PLWHA are more likely to present with smear negative, culture positive TB. This diagnostic sequence often leads to undiagnosed TB and poor outcomes.[83] Historically, one way to increase the sensitivity of sputum smear was collecting three samples on three consecutive mornings. This places a significant administrative burden on the laboratories processing samples, and can be prohibitive in resource limited settings. Research shows that using two samples rather than three does not decrease sensitivity significantly, and therefore the WHO now recommends collection of two samples. Newer methods to increase sensitivity include detecting smaller amounts of MTB in a sample as well as modifying sputum to increase MTB concentration. Fluorescence microscopy, sample concentration, and bleach sedimentation have been shown to increase sensitivity of sputum smear without decreasing specificity.[14] Fluorescence microscopy can be prohibitively expensive for some low resource settings, and new methods involving ultra bright light emitting diodes and auramine-rhodamine fluorescence staining promise to bring this technology to these settings.[84] The second drawback of sputum smear is that it yields no information about drug sensitivity, so treatment options are generally uninformed and response to treatment is often the only way to detect drug resistance when further testing is unavailable.

In resource-rich countries, chest X-ray is commonly part of the diagnostic workup for active TB, and is also used for excluding active TB in those who have a positive TST. Typical presentations of TB include apical cavitary lesions with hilar lymphadenopathy, but TB can present with an array of chest X-ray findings, especially in PLWHA. Chest X-ray can appear normal in 7-14% of PLWHA[79], and other patterns such as miliary, and absence of cavitary lesions is commonly seen. Due to its cost and reliance on technology, chest X-ray is not

commonly part of the diagnostic algorithm in some resource poor settings. Lastly, chest X-ray is not specific for TB, and is not a confirmatory diagnostic test. Isolation of MTB from sputum culture or smear is still needed for diagnosis.

In the search for a rapid, noninvasive, sensitive, and specific test to diagnose TB disease, nucleic acid amplification tests (NAAT) are a promising option. These tests are cartridge based, have automatic sample processing, and detect specific MTB nucleotides using real-time PCR. As few as ten bacilli are needed in a sample for a positive result.[85] Sputum is most commonly used in the assays, but other biopsy fluids are being used to diagnose extrapulmonary TB. The most widely used assay, the GeneXpert MTB/RIF® provides results in under 2 hours and also provides information on rifampicin resistance. The GeneXpert MTB/RIF® has a specificity and sensitivity of 99% and 92.5% respectively for culture positive TB when two independent specimens are obtained.[86] Sensitivity among smear negative, culture positive samples was 72.5% and up to 90% with three samples. HIV infection does not alter the sensitivity of this test[87], though recent data suggest that a single Gene Xpert assay is only 53% sensitive in those with HIV. Limitations of this test are its requirement of ambient temperature lower than 30 degrees Celsius, and a stable electric power supply.[88] Given the promise of rapid and reliable diagnosis of active TB, the WHO has supported the use of the GeneXpert MTB/RIF® for diagnosis of TB, and is currently providing 21 countries with machines and cartridges to increase active TB diagnosis.

Another diagnostic tool for active TB is the detection of MTB antigens in the urine. Urine is easily collected, does not involve creating infectious particles as does sputum collection, and requires no preparation. Detection of urine lipoaribinomannan, a heat stable major glycolipid constituent of the MTB cell wall, is specific for MTB infection.[89] One study in

Tanzania reports sensitivity of 80% for culture confirmed TB and specificity of 99%. Interestingly, sensitivity with urine antigen testing is higher in PLWHA due to the likelihood of more disseminated or progressed disease resulting in clinically measurable antigen.[90] In fact, urine antigen detection was shown to be more sensitive than sputum microscopy in HIV patients.[91] This test is currently not widely used due to poorer sensitivity in non-HIV-infected people and HIV-infected people with higher CD4 counts. Future clinical use might be limited to the immunosuppressed population. An assay in dipstick format with high sensitivity and specificity for active infection would hold promise for use in resource-limited settings.

e) Treatment of LTBI overview

Identification of latent tuberculosis is performed for a number of causes in different settings. In low prevalence areas, high-risk populations are routinely tested for LTBI to eradicate carriers of latent infection. Tests for latent TB are also used in diagnostic work-ups when TB is suspected to test for distant exposure. Patients taking drugs with immunosuppressive properties, especially biologic agents, often require a TST before treatment to weigh the risks of TB reactivation due to a blunted immune response. In low-income countries where LTBI treatment is less available, LTBI testing can focus attention on a high TB burden population, and is used to rally for active TB screening or for access to LTBI treatment.

Treating LTBI is extremely important in PLWHA, as they are more likely to have TB reactivation, suffer worse outcomes, and be more infectious to others. In 1998 the WHO recommended early diagnosis and treatment of latent TB among PLWHA with 6 months INH.[92] Among all people, LTBI treatment has been shown to reduce the risk of future active TB from 75-90%.[63] However, a Cochrane review reports any and all treatment of LTBI among PLWHA

reduces the risk of active TB by just 32%.[93] The risk reduction in PLWHA is concentrated in those with a positive TST whose risk is reduced by 60% compared to 16% in those who are TST negative.[93] Due to poor availability of TST in many resource poor areas, this data prevented many PLWHA from accessing LTBI treatment. In 2011, the WHO recommended TST was no longer a requirement for starting IPT in PLWHA to promote increased access to treatment.[64] Adherence is a large issue in an often-marginalized community of PLWHA; one study in Spain reports LTBI completion rate of only 57.4% in this population.[94] The factor associated with treatment completion was acquisition of HIV through heterosexual sex.[94] On a population basis, LTBI treatment has not been proven to reduce all cause mortality for TB patients, however benefit is seen with INH monotherapy vs. placebo in TST positive PLWHA.[93]

Historically, LTBI treatment consisted of 6 months of INH therapy. Adherance to 6 month INH regimens varies widely in the literature, ranging from 34-98%.[64] After studies reported reduction in active TB of only 69% with 6 months INH[95], investigators looked into 9 and 12 month INH regimens and found 90% and 93% risk reduction, respectively.[95] However, adherence with longer regimens was poorer than 6-month regimens, limiting their use. Concerns with longer regimens of INH extend beyond adherence. Adverse effects of INH include nausea, vomiting, rash, fever, hepatitis, peripheral neuropathy and rare fatal hepatotoxicity. Risk factors for severe hepatotoxicity include increasing age, Asian race, female sex, alcohol use, baseline liver disease, and baseline elevated transaminases.[96] Fatal hepatotoxicity is rare enough that it is beneficial to give INH to potentially TST negative PLWHA given the benefits of LTBI treatment. Another concern with IPT is the risk of inducing INH resistance if someone with active TB misdiagnosed as latent TB receives IPT. A small number of INH resistant TB cases have been demonstrated after use of IPT, especially in those living with HIV, but benefits of IPT

have been shown to outweigh this small risk.[97]

In light of lengthy INH regimens with resultant poor adherence, newer regimens have been developed to allow equally efficacious, shorter LTBI treatment. The shortest of new regimens is two months of rifampicin/pyrazinamide, which is equally efficacious as 6 months INH. Unfortunately this regimen has increased risk of hepatotoxicity and death, and is currently only recommended for PLWHA who cannot tolerate longer therapies.[98] Four months of rifampicin is well tolerated, has high completion rates and is equally efficacious as 6 months INH. However, there is a paucity of data to support widely recommended use. The newest LTBI regimen is a 3 month course of weekly DOT INH and rifapentine, which has proven to be as efficacious as 9 months INH and has lower risks of hepatotoxicity and adverse events, but is currently not approved for the HIV-infected population.[99] Generally, among shorter non-INH or combined INH regimen, there is higher adherence but also higher adverse reactions. The risks of developing drug resistant TB on these newer regimens have not been studied sufficiently.

Once LTBI has been treated the risk of developing active TB does not regress completely, evidenced by the low risk reductions rates, especially with 6 months of INH. Subsequent active TB can arise secondary to short IPT duration, poor adherence, immunosuppression at time of treatment, poor treatment program performance, and/or reinfection. The duration of protection with IPT is lower in PLWHA, and ranges from 18 months to about 2.5 years in high prevalence settings.[92] Longer regimens of IPT (36 months) are proven to increase duration of protection in high prevalence areas with high transmission.[100] IPT could even be trending towards lifelong courses among PLWHA given the high morbidity and mortality of TB in this population. However, this prospect raises more concern about the removed TST requirement for LTBI treatment given the potential harms of long term IPT in

those who are TST negative.[72]

f) Treatment of LTBI in correctional facilities

Treatment of LTBI in correctional facilities poses specific challenges due to mobility of inmates, poor healthcare delivery systems, poor transfer of care to the community setting, and inadequate patient education. Correctional facilities hold potential for consistent and reliable treatment given easy access to their inmates and a centralized healthcare system. Given a centralized location, DOT is more feasible and is often already in place for inmates prescribed methadone for opiate addiction. Despite ease of patient mobility and communication, completion rates for LTBI treatment in prisons are low. LTBI treatment completion rates with DOT in a Spanish prison were 76.6% for short course therapies and 67.8% for 9 months INH. Reasons for withdrawal included voluntary withdrawal, release, and adverse reactions.[101] Adherence was poorer among HIV-infected inmates. Rates of IPT completion in correctional facilities is generally low and broadly reported between 3% and 87%.[96] Jails present an especially difficult setting for LTBI treatment adherence due to high turnover and short periods of incarceration. Treatment adherence was 48% in a trial of 2 months rifampicin/pyrazinamide administered by DOT.[102] Despite mostly low adherence, IPT in correctional facilities has shown to be cost effective due to the large burden of disease in this setting. The CDC recommends testing all US prisoners for LTBI, targets to start IPT in at least 80% of those eligible, and strives for complete treatment in 75% of those who start.[103]

One of the most difficult challenges in completing LTBI treatment for inmates is continuation of therapy after release. Upon release from a Washington jail, 30% of those on self-administered IPT completed treatment, and only 60% of those on DOT IPT completed

treatment.[104] Numerous other studies show similar completion rates in US jails. Reasons for poor adherence post-release are multifactorial, but high prevalence of comorbid substance abuse disorders may play a large role in chaotic lifestyle and inability to maintain treatment. It is postulated that addressing substance abuse disorders can help increase adherence with infectious disease treatment.[96] Thus far, intensive inmate education and even financial incentives have not yielded impressive completion rates. Another concern with LTBI treatment in correctional facilities is the high rate of INH hepatotoxicity, up to 10 times higher than the general population. Reasons for this include correct dosing with DOT rather than lower than prescribed dosing, increased prevalence of viral hepatitis and previous alcohol consumption.[57] LTBI treatment in correctional facilities is of extreme importance given the population at risk and its effect on the outside community, and requires novel implementation methods to increase rates of successful treatment while assuring safety.

AIMS AND HYPOTHESIS:

Like many prisons globally, rural Malaysian prisons do not utilize routine screening for active TB, nor do they screen for or treat LTBI. Given the high prevalence of HIV in Malaysian prisons fueled by injection drug use, prisoners are at high risk for active TB and are in a setting where rapid transmission could lead to a TB epidemic. Congregated HIV-infected housing units, standard in Malaysia, assure that immunocompromised inmates surround highly infectious inmates. Routine active TB screening and LTBI treatment is a large endeavor in Malaysian prisons, where infrastructure is poor and administrators have little support for health improvement programs. Data is needed to drive lobbying to prove that the burden of TB is high, and risk is significant to inmates, correctional officers, and the outside community.

We therefore screened HIV-infected and non-HIV-infected prisoners in a Northeastern Malaysian prison for LTBI and active TB symptoms using standardized recommended two-step TST and a standardized World Health Organization (WHO) symptom screening survey.[105] We administered a brief questionnaire to gather demographic data, and investigate the correlates of LTBI and active TB symptoms. We also obtained CD4 counts for inmates with HIV to assess their disease progression, characterize the need for ARVs in prison, potentially explain anergic TST responses, and correlate HIV progression with likelihood of experiencing TB symptoms.

Given Malaysia's status as a middle prevalence country for TB, and its national policy of BCG vaccination at birth and at age 12, we would expect a high rate of TST positive individuals. This would mostly be indicative of a high rate of LTBI, with some potential confounding by late BCG vaccination, especially in younger inmates. We hypothesize that prevalence of TB symptoms will be high in the HIV-infected population, since the caseload of TB should be disproportionately represented in these prisoners who are not on ARV and who are in close contact with other potential active TB cases. Those with the lowest CD4 count will likely be the most at risk for TB reactivation or transmission, and should display the most TB symptoms.

STUDY POPULATION AND METHODS:

1) Setting

Malaysia, a country of the WHO Western Pacific Region, is a middle-income country with a population of 29.2 million people in 2012. Malaysian people consist of four major ethnic groups. Malays are native to Southeast Asia, comprise about 50% of the population, and are Muslim by constitutional definition. The next largest ethnicity is the Chinese who comprise about 25% of the population. They mainly dominate trade and business, and are largely

Buddhist. Indians, a majority Tamil, make up the third largest ethnic group at about 7% of the population, and are mostly Hindu. Malaysia's official language is Bahasa Malaysia, the language spoken by the Malay people, but English is also widely spoken.

Kelantan is Malaysia's most northeastern state, and houses about 1.5 million people. It is largely agrarian and is historically isolated from the rest of the country, resulting in a unique set of customs and a dialect that is almost unintelligible to some native Bahasa Malaysia speakers. 95% of Kelantan's population is Malay, which means Islam is the overwhelmingly dominant religious influence in the area. Kelantan's capital is Kota Bharu with a population just under 0.5 million. Kota Bharu, translation "New City," is an "Islamic city" and Islamic laws are more conservative and strictly enforced than elsewhere in Malaysia.

Kelantan has one prison, Penjara Pengkalan Chepa, located in Kota Bharu that houses around 1400 inmates at any one time. This facility is a combined jail and prison, and houses both sentenced and unsentenced (i.e remand) prisoners. All inmates undergo mandatory HIV testing upon entry to prison, and HIV-infected inmates are housed in congregated housing blocks. Housing blocks hold 40 to 50 inmates each, and are designed with open-air architecture. Units are about 50x20 foot single rooms and consist of two solid walls, one wall consisting mostly of chain link fence, and one wall with a small chain link fence window that spans the top of the wall. Inmates sleep on floor mats that are rolled onto the concrete floor at night, and spend the majority of their day together in their respective housing units. Sentenced and remand prisoners are kept in separate areas of Pengkalan Chepa prison. Unsentenced prisoners are more likely to be first time offenders without history of previous incarceration. Currently there are no screening programs for active or latent TB at Pengkalan Chepa prison, and identification of TB cases is by passive reporting of symptoms to correctional officers. Pengkalan Chepa prison does have a

methadone maintenance program and opiate dependent inmates are administered methadone under daily DOT.

2) Recruitment and sample

Penjara Pengkalan Chepa administrators provided a list of all HIV-infected inmates, both sentenced and those in remand housing. Correctional officers transported inmates from HIV-infected housing blocks one block at a time to a large meeting area for information sessions. Information sessions consisted of a study description, elaboration of risks and benefits, and explanation of the voluntary nature of participation. At the completion of the information session, a sign up sheet was distributed and inmates voluntarily signed up for participation by listing their name, prison ID number, and housing block. Inmates were then called for study participation in groups of 10-12 to the prison medical clinic. Due to time restriction, and the desire to completely sample the sentenced HIV-infected prisoners, we first completed data collection on all sentenced HIV-infected prisoners before moving to HIV-infected prisoners in remand housing. After all HIV-infected inmates finished study procedures we turned to recruitment of an equally sized non-HIV-infected population.

Non-HIV-infected inmates largely outnumbered HIV-infected inmates. Correctional officers brought randomly chosen HIV negative housing blocks for information sessions until we reached an equivalent number to the HIV-infected sample. Information sessions for non-HIV-infected inmates were identical to those in the HIV-infected group, with the exception of no discussion about CD4 count. After an equivalent number of HIV-infected and non-HIV-infected participants was obtained, we simultaneously sampled from HIV-infected and non-HIV-infected

remand prisoners for the remainder of the study duration, keeping the sample populations as equal as possible.

A G*Power power analysis determined the necessary sample size to detect a difference in LTBI prevalence between groups. A minimum sample of 134 was required with a moderate effect size of 0.3 with an alpha of 0.05 and a power of 0.95. This sample size was exceeded in our actual procedure. After inmates who had signed up for the study were brought to the medical clinic, they were again explained the nature of informed consent by research staff not affiliated with the prison administration, signed consent forms, and were then interviewed, and underwent TST in a private room. HIV-infected individuals underwent CD4 testing with phlebotomy performed by the prison medical director. Reasons for not completing the study protocol included transfer or prison-release. Inmates were not rewarded or punished based on their decision to participate.

3) Survey administration

A structured questionnaire, administered by a trained research assistant in Bahasa Malaysia, included information on demographics, HIV risk behavior, TB history, active TB contacts, incarceration history, and presence of active TB symptoms. Active TB symptoms were assessed using the standardized WHO TB symptom screening assessment[105], and we defined "high risk" for active TB as a cough lasting greater than two weeks plus the presence of another symptom on the survey (e.g., night sweats, weight loss, fever, or hemoptysis). Chronic cough is the most sensitive symptom, and inclusion of another symptom increases specificity.[105] The English-version instrument was translated to Bahasa Malaysia and validated using back translation. Patients with symptoms suggesting TB were referred to medical staff for further

evaluation. Research personnel did not have jurisdiction over the quality or the content of the prison-based assessment after referral, and were therefore not allowed further access to the assessment information. After the survey, height and weight was measured and body mass index (BMI) was calculated. The same scale was used throughout the study for accuracy. Interviews were conducted in private counseling rooms with no correctional officer present to assure privacy and reduce perceived coercion.

4) Tuberculin skin testing

All participants underwent TST unless one of three conditions was met: 1) self-reported previous positive TST; 2) documented current receipt of TB treatment (confirmed by prison medical records); or 3) self-reported previous TB diagnosis and treatment. A single trained investigator (BM), to avoid variation in implantation and reading, intradermally injected two units of purified protein derivative (PPD-RT23) using the Mantoux method and induration was measured in the transverse direction 48-72 hours later. Cutoff values of 5 mm and 10 mm were used for HIV-infected and non-HIV-infected prisoners, respectively. CDC-recommended two-step TST testing was performed to identify participants with remote TB exposures, immunosuppression or who were malnourished who may falsely test negative. False negative cases can exhibit a "booster phenomenon" and mount an immune response to a second TST placed 1-3 weeks after an initial negative TST. Initially negative TST participants underwent repeat TST after 1-3 weeks. The TST result is reported as positive only if the repeat test was positive. Participants who reported a previous positive TST or reported previous active TB diagnosis and uncompleted treatment were considered TST positive for analysis. When calculating induration size for repeat testers, the larger of the induration diameters was recorded.

5) Analysis of CD4 lymphocyte count

All HIV-infected inmates were offered CD4 count testing. Twenty-seven (19.7%) HIV-infected participants refused testing because they were recently tested or anticipated release too soon to receive results. Blood was drawn in the mornings by the prison's medical assistant and brought by car during lunchtime to Hospital Kota Bharu where CD4 testing was performed. Test reports were communicated to patients directly when possible, and other results were provided to both the medical clinic and to an outside community outreach program called "Sahabat." Sahabat is a local organization that links PWUD/PWID to community resources and medical care.

6) Data analysis

Analyses were conducted using IBM SPSS v.19 (IBM Corporation, NY). Chi square testing was used to determine significant differences between the HIV-infected and non-HIV-infected participants. After bivariate logistic regression was used to estimate odds ratios for each independent variable, those with $p<0.20$ were included in the final multivariate logistic regression model. Akaike Information Criterion (AIC) was used to assess model goodness-of-fit.

7) Ethical oversight

The IRBs at Yale University and the University of Malaya approved this study. Participants were advised that they could refuse participation in any part of the study, or withdraw at any time. After data collection, all data were de-identified and personal identifiers were destroyed.

RESULTS:

1) Population characteristics

Figure 1 describes the participant disposition and Table 1 compares HIV-infected and non-infected subjects. Nearly all (N=266, 92%) of the 288 initially recruited participants completed the study survey and LTBI was identified for 227 (87.6%) participants of the 259 with complete TST results. The surveyed population had a mean age of 33.4 (SD=7.2) years, 96.2% were male, and 97.0% were of Malay ethnicity.

Compared to non-HIV-infected participants, HIV-infected subjects were significantly older (35.5 vs. 31.3 years), more likely to have been previously incarcerated (82.5% vs. 51.2%), and were more likely to report pre-incarceration alcohol use (92.0% vs. 82.2%) and needle sharing (95.6% versus 13.2%). HIV-infected participants were also significantly more likely to report previous active TB (17.5% vs. 3.1%) and contact with active TB cases (69.3% vs. 43.4%) than non-HIV-infected participants. Nearly all TB contacts were cellmates with active TB. None of the HIV-infected participants in our survey were receiving ART.

2) Prevalence of latent TB Infection

The LTBI prevalence in the entire sample was 87.6% (Table 1) and was higher among non-HIV-infected prisoners (91.5% vs. 83.6%, $p<0.05$). High overall TST reactivity resulted in only 41 participants undergoing booster testing; 6 of 24 HIV-infected and 7 of 17 non-HIV-infected participants transitioned to TST-positive results. On bivariate analysis, HIV-infected subjects, particularly those at the lowest CD4 strata (<200 cells/mL) had the lowest likelihood of being TST positive compared to non-HIV-infected participants (OR=0.24, 95%CI 0.08-0.076, $p<0.05$). Low CD4 strata did not, however, remain significant in the multivariate model. After

controlling for other potentially confounding variables in the final model, inmates with previous incarceration history were nearly five times more likely (AOR=4.61, 95%CI 1.76–12.1, p<0.05) to be TST-positive (Table 2). TST reactivity between sentenced and un-sentenced prisoners (p=0.65) did not differ (data not shown).

Mean TST induration size was 13.8mm (SD 6.1) for the entire population, and was significantly larger for the non-HIV-infected population (14.9mm vs 12.4mm, p<0.05). Induration size and CD4 count as continuous variables showed no significant correlation, however when CD4 was stratified (CD4 <200, CD4 ≥200 and <500, CD4 ≥500), results showed significant positive association between higher CD4 and larger induration with β= 1.80 and P=0.022.

3) Prevalence of active TB symptoms and stratification by CD4 count

Symptoms suggestive of active TB occurred in 13.6% of the sample and trended toward significantly higher prevalence among HIV-infected prisoners (16.9% vs. 10.1%; p=0.105). Those who screened positive for active TB symptoms were significantly older (AOR=1.07, 95%CI 1.01-1.13, p<0.05) and had a lower BMI (AOR=0.82, 95%CI 0.70-0.96, p<0.05). TST-negative participants, a minority of the sample (12.4%), were 3.5 fold more likely to have positive TB screening symptoms (AOR=3.5, 95%CI 1.20-9.97, p<0.05). Screening symptoms consistent with active TB among HIV-infected participants trended towards being significantly higher (Figure 2) among those with CD4<200 compared to those with CD4>350 (33.3% vs. 17.2%, p=0.066) and significantly higher than non-HIV-infected participants (10.1%, p=0.005).

DISCUSSION:

The prevalence of LTBI among prisoners in Northeastern Malaysia is remarkably high (87.6%) and to our knowledge, the highest reported among prisoners globally. Although much debate remains about the utility of TST in BCG-vaccinated populations, the immunogenic effects of BCG wane after 8-10 years.[106] While numerous studies have shown that the majority of TST-positive, IGRA-negative discordances occur in BCG-vaccinated populations,[107,108] these are relatively infrequent. The WHO therefore supports the use of TST to detect LTBI in settings where BCG is used.[109] However, there is a paucity of data regarding the effect of late BCG vaccination (in this case at age 12) on TST positivity, and it is unclear whether the conclusions about the waning of BCG effect on TST is applicable with later vaccination.

LTBI among Malaysian prisoners remains markedly higher than the 36% reported overall in SE Asia and higher than the 52.1% and 59.0% prevalence reported among at-risk healthcare workers from two other Malaysian studies using similar methods.[28,29] The higher prevalence in our sample, when viewed alongside other high-risk Malaysians who were also BCG-vaccinated at age 12, suggests that false positives are not responsible for the high LTBI prevalence among prisoners. LTBI prevalence in prison settings elsewhere in Spain (40.3%)[110] and Nigeria (54.2%)[111] is lower than our observed prevalence. These comparisons to Malaysian prisoners and among prisoners elsewhere suggest that uncharacterized factors are driving the exceedingly high LTBI prevalence among Malaysian prisoners. The previously cited Malaysian studies were all conducted in Kuala Lumpur, and it is possible that regional differences in TST positivity could account for our prevalence rate. A further study of TST positivity among residents of Kelantan, or more specifically Kota Bharu, would be helpful in determining if the population sampled in this study had a concentrated burden of LTBI compared to a representative population.

Kelantan's prison is constructed with "open air" architecture and makes use of extensive natural ventilation. While this measure hypothetically reduces TB transmission[112], the LTBI burden in this prison is very high, and is comparatively similar (84%) to those reported among HIV-infected inmates in a prison with poor ventilation in the Selangor state of Malaysia, suggesting that adequate ventilation alone is insufficient to control TB in these high prevalent settings.[113] These results highlight the urgent need for routine and proactive measures to screen for, initiative preventive therapy and ultimately control TB transmission upon prison-entry. Additional public health incentives derive from the knowledge that TB negatively impacts both prison staff and communities to which prisoners return.[114,115] Proactive and routine TB surveillance and preventive measures include isoniazid preventative therapy (IPT) for TST-reactive individuals, symptom-based TB screening followed by sputum culture, isolation for symptomatic inmates, as well as increasing ART among HIV-infected prisoners.[116]

IPT is now recommended for all HIV-infected persons.[64] It is inexpensive, but requires treatment for a minimum of six months, which could be problematic in detention settings where transition to the community is particularly challenging as noted in two recent systematic reviews.[96,117] New trials document efficacy of shorter IPT regimens, including a three-month course of weekly rifapentine plus isoniazid, which is equivalent to 9-month IPT in non-HIV-infected populations.[118] IPT options with shorter courses are likely to have a greater impact on TB prevention strategies where prison sentences are short. In addition to the logistical benefit of shorter treatment plans, there may also be therapeutic benefit especially in Malaysia's prison population. Many HIV-infected inmates are PWID, and carry a significant burden of co-infection with HCV. This increases the risk of hepatotoxicity with prolonged INH treatment and can serve as another benefit of shorter treatment, as 12 weeks of INH and rifapentine has less hepatotoxity

than other regimens. Data do not currently confirm efficacy of 12 week INH and rifapentine for the HIV-infected population. However, benefits of this shorter treatment that potentially makes LTBI treatment in prison possible should not be overlooked.

It has been shown that HIV treatment is in itself a method of preventing active TB among PLWHA. The most significant effect is seen in those with advanced HIV disease.[8] Starting ART in PLWHA results in an 80% risk reduction for active TB[7], but risk never returns to the lifetime risk of someone without HIV. Widespread ART in PLWHA has even been shown to reduce TB rates at the population level in Malawi by decreasing the pool of infectious carriers.[119] While the risk reduction is most prominent for those with advanced disease, it is important to start ART early, preferably at HIV diagnosis. Early ART initiation improves the chance that patients will not already have active TB, and confers the most benefit. WHO guidelines currently recommend ART initiation in those with CD4<500, while other organizations like the International AIDS Society recommend ART for all HIV-infected people. In the prison setting and elsewhere in resource-limited settings, the costs of a public health approach to national HIV programs limit ART eligibility based on CD4 count; obtaining the CD4 count measurement is also another barrier to ART initiation. In our setting, although HIV testing is done for the purpose of segregated housing, no further diagnostic workup or treatment plan is made. Cost, administrative barriers, and practical considerations of time spent in prison are all potential barriers to initiation of ART based on CD4 count in prisons. In Kuala Lumpur's Kajang prison, active surveillance for TB and HIV, including CD4 count measurements has recently been implemented. Despite these measures, access to ART remains limited due to poor supply, short prison stay, and poor availability of many inmates due to prison-instituted restrictions. In Kajang prison, PWID who are not on methadone do not receive ART by local physicians, since they are perceived likely to

struggle with adherence in the setting of untreated substance abuse.

Though our data do not justify use of negative TST results in identifying active TB cases, our findings of a negative TST in this particularly high TST prevalent setting among HIV-positive inmates may have important implications. For example in this setting where TST reactivity among non-HIV-infected inmates was 91.5%, a negative TST in the HIV-infected might potentially be an indication of advanced HIV disease and be a marker of cutaneous anergy. This observation coupled with the high prevalence of TB-related symptoms among those with CD4<200 is compelling. HIV-infected prisoners with a negative TST in our sample were over three-fold more likely to have TB-related symptoms, underscoring the importance of not only relying on TST to indicate TB exposure, but to incorporate other measures to detect active TB, including symptom surveys, chest radiographs and sputum testing for smear and culture.

The cross-sectional nature of this study makes it impossible to confirm that the prison environment is responsible for increased LTBI or if previous incarceration portends a higher LTBI risk for unmeasured reasons. Regardless, proactive measures to reduce the numbers of PLWHA who become imprisoned will likely improve the health of this population, and our data support the vast body of literature that show prison conditions are correlated with high TB prevalence and promote poor health outcomes. Many HIV-infected prisoners were imprisoned solely for drug use, suggesting that expanding community-based opioid substitution treatment could reduce incarceration of this vulnerable population.[120] Alternatively, introducing prison-based methadone maintenance before prison release and continuing in the community could serve as an important conduit to continuity of care,[120,121] including treatment for active TB or LTBI.

Our study has a number of limitations. The use of the TST in a population with BCG vaccination raises concern for false positives. However, the age of our sample suggests that BCG contributes little to positive TSTs since the effects of BCG wane within 8-10 years and we were unable to demonstrate an association between TST reactivity and lower age. Correlation of TST positive cases with an IGRA result would be ideal, but this assay was not available in this setting. Using the TST in an untreated HIV-infected population also raises concerns, since the TST relies on a functional immune response; however, TST result in this study was not associated with CD4 strata. Also, our sampling strategy for non-HIV-infected inmates was a convenience sample not guaranteed to represent the demographic of all HIV-infected prisoners. The majority of HIV-infected prisoners were PWID who likely had unmeasured risk factors that distinguish them from the non-HIV-infected inmates who were not primarily PWIDs. Lastly, though it would have been useful to examine the relationship between TB symptoms and diagnostically confirmed active TB, IRB concerns and logistical constraints restricted access to this information, but further investigations are warranted.

CONCLUSIONS:

We found that the prevalence of LTBI among prisoners in Kota Bharu's only prison is remarkably high, and rivals the upper limit of globally reported data. In addition, Penjara Pengkalan Chepa houses a significant HIV-infected population who carry many risk factors for TB. Regardless of the source of LTBI transmission, whether in the community, in prison, or from childhood exposure, the fact remains that a large number of HIV/TB co-infected inmates are congregated with poor living conditions. This environment is conducive to further TB transmission, and the pathophysiology of HIV/TB co-infection exacerbates both disease

processes. Penjara Pengkalan Chepa's lack of TB screening results in advanced disease presentation, and the potential for active TB cases to propagate through the prison community.

Prisoners with LTBI in Penjara Pengkalan Chepa were more likely to have a history of previous incarceration, confirming the well-established correlation between imprisonment and TB transmission and burden. The HIV-infected population was untreated, displayed a wide range of immunosuppression evidenced by CD4 count, and as expected produced less robust TST reactions than non-HIV-infected inmates. Determining the significance of the lower LTBI prevalence by TST in the HIV-infected population is difficult, since it cannot be known if the HIV-infected and non-HIV-infected populations carry different LTBI prevalence using TST, due to HIV's modification of TST result. Given the high prevalence in both populations and a relatively small difference, it is likely that both populations carry a similar burden of LTBI.

TB symptom prevalence was also high, and was concentrated among those with HIV, decreased BMI, decreased CD4 count, and those who were TST negative. Symptom screening is a key tool in identifying those who should undergo further diagnostic evaluation for active TB, and has the potential to help reduce TB burden if treatment is made accessible. Given a large population of inmates with LTBI, and a subpopulation co-infected with HIV, active TB screening and treatment should be employed in Penjara Pengkalan Chepa with access to hospital referral and in-prison DOT for active TB treatment. Furthermore, to improve the health of prisoners and decrease the risk of TB transmission to prison staff, LTBI treatment should be offered in accordance with WHO guidelines to all HIV-infected inmates. Reducing TB burden, both active and latent, is of grave importance in a system at high risk for an active TB epidemic.

Logistical barriers to TB screening and treatment are impressive in Penjara Pengkalan Chepa, reflecting a larger difficulty of correctional facilities to implement health screening and

treatment services. Cultural beliefs about the imprisoned population, administrative barriers given the ministry of justice's poor prioritization of healthcare, and unpredictable shifts in the prison population all contribute to difficulty treating TB in prisons. New shorter regimens of TB treatment hold promise for bringing TB treatment into the realm of shorter prison sentences, but their efficacy has not yet been proven in HIV-infected populations.

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Table 1: Study population characteristics

	Total population N=266	Non-HIV-infected N=129 (48.4%)	HIV-infected N=137 (51.5%)	P-value
DEMOGRAPHIC				
Mean age (years)	33.4, SD 7.2	31.3, SD 7.8	35.5, SD 6.0	**<0.001**
Sex				0.923
Male	256 (96.2%)	124 (96.1%)	132 (96.4%)	
Female	10 (3.8%)	5 (3.9%)	5 (3.6%)	
Ethnicity				0.216
Malay	258 (97.0%)	122 (94.6%)	136 (99.3%)	
Chinese	4 (1.5%)	3 (2.3%)	1 (0.7%)	
Indian	2 (0.8%)	2 (1.6%)	0	
Asli (native)	1 (0.4%)	1 (0.8%)	0	
Other	1 (0.4%)	1 (0.8%)	0	
INCARCERATION HISTORY				
Previously incarcerated	179 (67.3%)	66 (51.2%)	113 (82.5%)	**<0.001**
Cumulative time incarcerated				**<0.001**
None	87 (32.7%)	63 (48.8%)	24 (17.5%)	
1-6 months	29 (10.9%)	17 (13.2%)	12 (8.8%)	
>6 months	150 (56.4%)	49 (38.0%)	101 (73.7%)	
HEALTH HISTORY				
History of smoking	261 (98.1%)	124 (96.1%)	137 (100%)	**0.020**
History of alcohol use	232 (87.2%)	106 (82.2%)	126 (92.0%)	**0.017**
History of BCG vaccination	260 (97.7%)	127 (98.4%)	133 (97.1%)	0.452
History of needle sharing	148 (55.6%)	17 (13.2%)	131 (95.6%)	**<0.001**
TB HISTORY AND WORKUP				
History of previous active TB	28 (10.5%)	4 (3.1%)	24 (17.5%)	**<0.001**
Contact with active TB cases[1]	151 (56.8%)	56 (43.4%)	95 (69.3%)	**<0.001**
Family contact	26 (9.8%)	16 (12.4%)	10 (7.3%)	0.161
Cellmate contact	132 (49.6%)	44 (34.1%)	88 (64.2%)	**<0.001**
Friend contact	9 (3.4%)	5 (3.9%)	4 (2.9%)	0.532
TST result, N=259				**0.040**
Positive	227 (87.6%)	115 (91.5%)	112 (83.6%)	
Negative	32 (12.4%)	10 (8.0%)	22 (16.4%)	
Mean induration size (mm)	13.8 SD 6.1	14.9, SD 5.2	12.4, SD 8.5	**0.007**
Mean body mass index	22.4, SD 3.4	23.2, SD 3.7	21.6, SD 2.8	**<0.001**
TB SYMPTOM SCREEN				
Positive screen	36 (13.6%)	13 (10.1%)	23 (16.9%)	0.105

BCG= Bacillus Calmette-Guérin; TB=tuberculosis; TST= tuberculin skin test; SD= standard deviation; P values from Chi-square analyses

[1] Includes anyone with reported contact with active TB cases. Some people reported multiple exposures and totals do not equal 100%.

Table 2: Bivariate and multivariate correlates of positive tuberculin skin testing results (N=259)

	Total N=259	TST (-) N=32 (12.4%)	TST (+) N=227 (87.6%)	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
DEMOGRAPHIC							
Age (years)	33.4, SD 7.2	31.5, SD 6.2	33.7, SD 7.3	1.05 (0.99-1.11)	0.120		
Sex							
Female	10 (3.9%)	3 (9.4%)	7 (3.1%)	0.31 (0.08-1.26)	0.100	0.32 (0.07-1.41)	0.131
Male	249 (96.1%)	29 (90.6%)	220 (96.9%)	Referent	-	Referent	-
Body mass index	22.4, SD 3.4	22.3, SD 3.0	22.5, SD 3.4	1.02 (0.91-1.15)	0.712	.	
Malnutrition							
BMI≤18.5	22 (8.5%)	3 (9.4%)	19 (8.4%)	0.88	0.849		
BMI>18.5	237 (91.5%)	29 (90.6%)	208 (91.6%)	Referent	-		
INCARCERATION HISTORY							
Previously incarcerated	175 (67.6%)	15 (46.9%)	160 (70.5%)	2.71 (1.28-5.73)	**0.009**	4.61 (1.76-12.1)	**0.002**
HEALTH HISTORY							
History of needle sharing	144 (55.6%)	22 (68.8%)	122 (53.7%)	0.53 (0.24-1.17)	0.114	0.61 (0.10-3.61)	0.584
HIV Status X CD4 (N=235)[1]							
HIV-infected CD4 ≥ 200	86 (36.6%)	13 (44.8%)	73 (35.4%)	0.48 (0.20-1.16)	0.104	0.37 (0.06-2.09)	0.259
HIV-infected CD4 < 200	23 (9.8%)	6 (20.7%)	17 (8.3%)	0.24 (0.08-0.76)	**0.015**	0.25 (0.04-1.61)	0.143
Non-HIV-infected	126 (53.6%)	10 (34.5%)	116 (56.3%)	Referent	-	-	-
HIV Status[2]							
Non-infected	125 (48.3%)	10 (20.8%)	115 (54.5%)	2.26 (1.02-4.99)	**0.044**		
Infected	134 (51.7%)	22 (68.8%)	112 (49.5%)	Referent	-		
							AIC=41.4

TB= tuberculosis; OR= odds ratio; CI= confidence interval; TST= tuberculin skin test; BMI=body mass index; SD= standard deviation; AIC=Akaike Information Criterion

[1] This sample of 235 excludes HIV-infected participants who did not complete CD4 testing, but did complete TST testing

[2] Not included in multivariate model because HIV status stratified by CD4

Table 3: Correlates of a positive TB symptom screen

	Total N=265[1]	Negative Screen N= 229 (86.4%)	Positive Screen N= 36 (13.6%)	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
DEMOGRAPHIC							
Age (continuous)	33.4, SD 7.2	32.9, SD 6.7	36.2, SD 9.5	1.06 (1.01-1.11)	**0.014**	1.07 (1.01-1.13)	**0.013**
Mean body mass index	22.4, SD 3.4	22.6, SD 3.4	21.0, SD 2.6	0.82 (0.72-0.94)	**0.005**	0.82 (0.70-0.96)	**0.014**
BMI≤18.5	24 (9.1%)	18 (7.9%)	6 (16.7)	2.34 (0.86-6.37)	0.095		
BMI>18.5	241 (90.9%)	211 (92.1%)	30 (83.3%)	Referent	-		
HEALTH HISTORY							
History of alcohol use	231 (87.2%)	204 (89.1%)	27 (75.0%)	0.37 (0.16-0.87)	**0.023**	0.38 (0.14-1.06)	0.064
HIV status[2]							
Infected	136 (51.3%)	113 (49.3%)	23 (63.9%)	1.82 (0.88-3.76)	0.108		
Non-infected	129 (48.7%)	116 (50.7%)	13 (36.1%)	Referent			
HIV STATUS X CD4 (N=238)[3]							
HIV-infected CD4 ≥ 200	85 (35.7%)	71 (35.0%)	14 (40.0%)	1.78 (0.79-3.99)	0.165	1.47 (0.41-5.27)	0.552
HIV-infected CD4 < 200	24 (10.1%)	16 (7.9%)	8 (22.9%)	4.80 (1.71-13.47)	**0.003**	1.13 (0.45-2.85)	0.803
Non-HIV-infected	129 (54.2%)	116 (57.1%)	13 (37.1%)	Referent	-	Referent	-
TB Evaluation							
History of active TB	27 (10.2%)	19 (8.3%)	8 (22.2%)	3.16 (1.26-7.89)	**0.014**	1.84 (0.58-5.88)	0.303
TST Result							
Positive	32 (12.4%)	23 (10.4%)	9 (25.0%)	Referent	-	Referent	-
Negative	227 (87.6%)	199 (89.6%)	27 (75.0%)	2.88 (1.21-6.88)	**0.017**	**3.46 (1.20-9.97)**	**.021**
						AIC = 183.2	

TB= tuberculosis; OR= odds ratio; CI= confidence interval; TST= tuberculin skin test; SD= standard deviation; AIC=Akaike Information Criterion

[1] One participant did not complete the TB symptom screening

[2] Not included in final model because HIV status stratified by CD4

[3] This sample of 238 excludes HIV-infected participants who did not complete CD4 testing, but did complete TB symptom screening

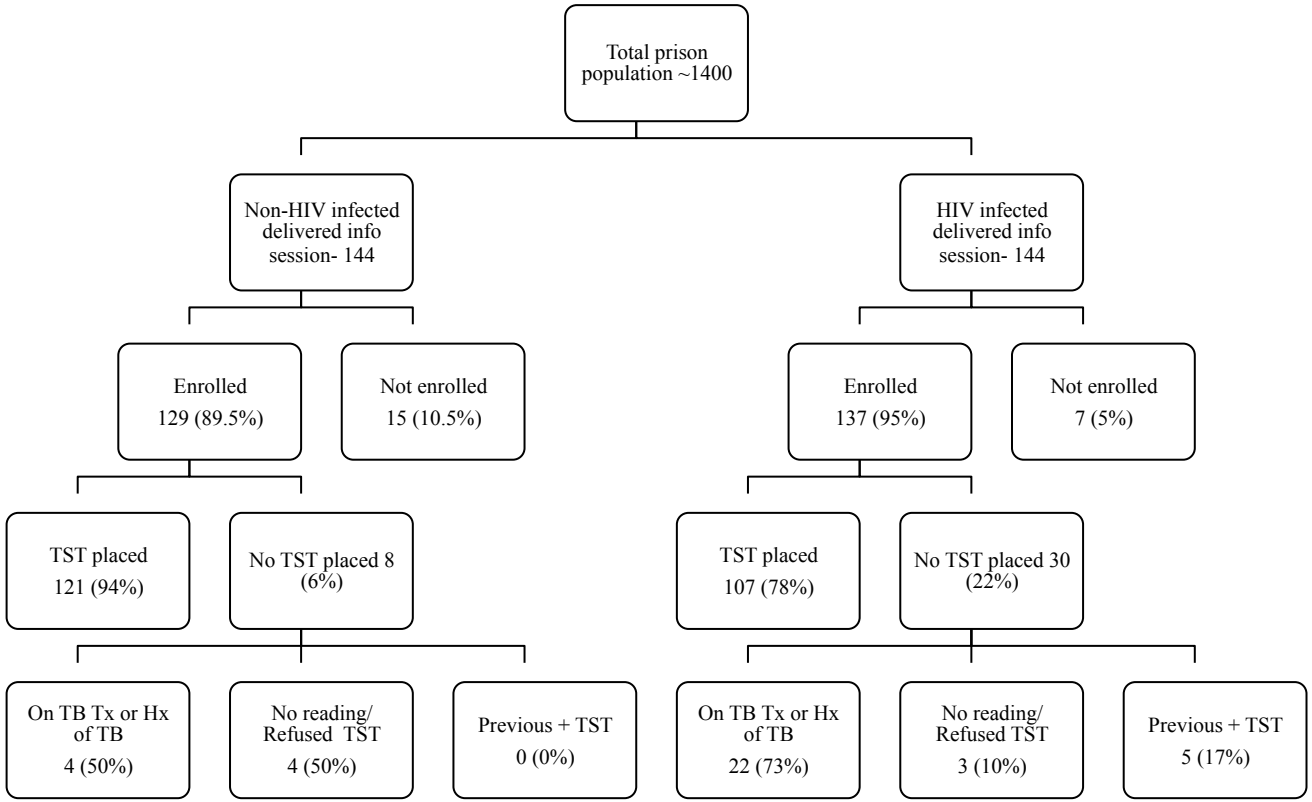

Figure 1: Study Sampling and Participant Disposition
TST= tuberculin skin test, TB= tuberculosis, Tx= treatment, Hx = history

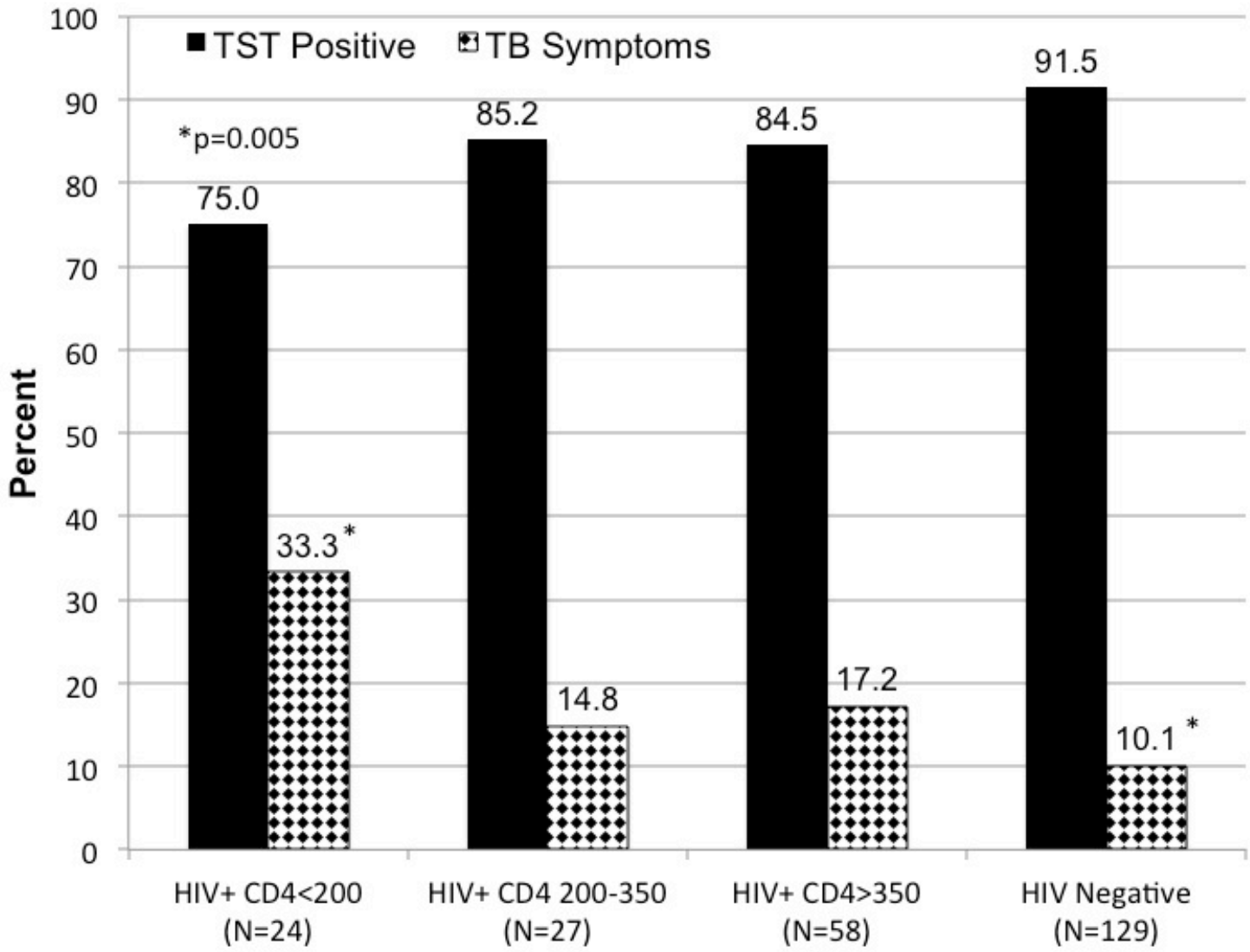

Figure 2: Prevalence of tuberculosis symptoms and latent tuberculosis infection among inmates of Pengkalan Chepa prison

HIV= human immunodeficiency virus; TST= tuberculin skin test, TB= tuberculosis

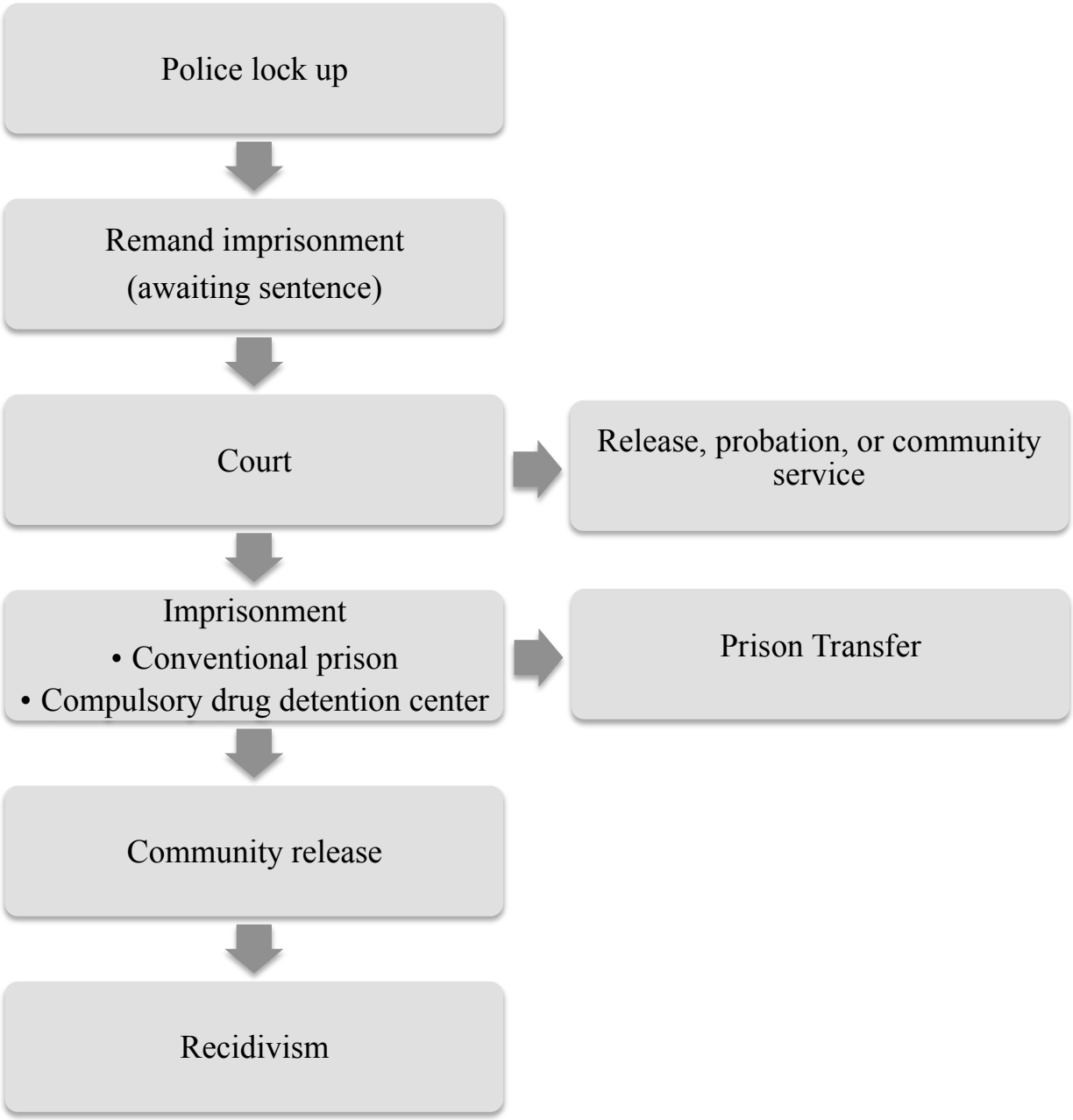

Figure 3: Organization of correctional system in Malaysia highlighting various points of inmate contact with the community

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