FEDERAL UNIVERSITY OF MATO GROSSO DO SUL
DOCTORATE PROGRAM IN INFECTIOUS AND PARASITIC DISEASES

PROPHYLAXIS FOR PRIMARY PREVENTION OF TUBERCULOSIS IN PRISONERS

CAMPO GRANDE-MS, BRAZIL

JUNE/2018

ADMINISTRATIVE INFORMATIONS

Public title: Prophylaxis for Primary Prevention of Tuberculosis in Prisoners

Public acronym: PCL 06/2017

Evaluation Record: ClinicalTrials.gov, Identifier: NCT03028129

Protocol Version: 6 of 06/12/2018

Financing: National Council for Scientific and Technological Development (Process 420672/2017-6 and Process 401824/2016-0)

Sponsor Name and Contact Information: Clinical Research Platform, Vice Presidency of Research and Biological Collections of the Oswaldo Cruz Foundation. Phone: + 55 21 3882-9238 / +55 21 3882-9239. Email: pesquisaclinica@fiocruz.br

LIST OF ABBREVIATIONS

ALT	Alanate Aminotransferase
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorder Identification Test
BCG	*Bacillus Calmette-Guérin*
CEP	Research ethics committee
DNA	Deoxyribonucleic Acid
AE	Adverse Event
SAE	Serious advers event
HIV	Human Imunodeficiency Virus
INH	Isoniazid
IGRA	Interferon gamma realease assay
LPCS/UFGD	Research Laboratory in Health Sciences/Federal university of Grande Dourados
MDR	Multidrug-resistant
MS	Ministry of Health
Mtb	*Mycobacterium tuberculosis*
WHO	World Health Organization
PED	State Penitentiary of Dourados
SOP	Standard Operational Procedure
PPD	Purified Protein Derivative
TB	Tuberculosis
TCLE	Informed consent form
DOT	Directly Observed Treatment
UEMS	State University of Mato Grosso do Sul
XDR	Extensively Drug-resistant

LIST OF FIGURES

SUMMARY

1 INTRODUCTION

Despite being a disease known to humanity for more than 9,000 years ago, tuberculosis (TB) still represents a serious public health problem in developing countries.

TB is an infectious, airborne disease that can present in both active and latent forms. Despite the biological aspect of transmission, unhealthy environmental conditions (eg, environment without direct sunlight, poor ventilation, overcrowding, etc.) and individual factors (malnutrition, immunosuppression, use of alcohol, other drugs, etc.) have a significant influence on the transmissibility and infectivity of the disease.

With the discovery of active drugs against *Mycobacterium tuberculosis*, a reduction in the incidence of the disease was seen worldwide. Despite this decreasing incidence, the World Health Organization (WHO) classified TB as a global public health problem, due to the appearance of multidrug resistant or extensively resistant tuberculosis disease, resistant to treatment. In addition reactivation of latent TB was consistently observed with the advent of HIV.

Several studies have shown a direct relationship between the incidence of TB and the prison environment. The presence of prison units in a locality raises the incidence of the disease, suggesting tuberculosis transmission between the prison and the community.

To date, TB control in prisons is based on screening individuals with active and/or latent TB and their treatment. To identify individuals with active disease, diagnostic algorithms using respiratory symptoms (mainly cough), sputum culture, and chest radiography are used. Regarding the search of individuals with latent tuberculosis, the skin test with the PPD can be performed.

Prisoners in Brazil have short incarceration terms, usually leaving prison within one to two years. Therefore, an intervention that protects prisoners from acquiring recent infection during prison stay may be adequate for long-term tuberculosis control in these prisons. Although there is a large body of empirical evidence demonstrating that isoniazid prevents progression to active tuberculosis, whether isoniazid prevents primary infection is unknown.

The aim of this study was to determine the efficacy of primary prophylaxis in the prison population in order to gather new scientific evidence that would bring accessible methods for the control of TB in prisons.

2 BACKGROUND

2.1 *Mycobacterium tuberculosis*

M. tuberculosis was discovered by Robert Koch in 1882. It is an immobile, aerobic bacterium of the *Mycobacterium tuberculosis* complex. This complex is formed by several species of mycobacteria, causal agents of TB in different hosts: *M. tuberculosis, M. africanum, M. canetti* (affect humans); *M. microti* (infect mice); *M. bovis* (affect cattle); *M. pinnipedi* (found in seals and sea lions); *M. caprae* (infect sheep and goats) and BCG vaccine strain(1). Different bacterial strains of the *M. tuberculosis* complex are closely related, with 99.9% genetic similarity and strong host specificity(2,3).

M. tuberculosis is primarily responsible for most TB cases in humans. The main characteristics of *M. tuberculosis* aree the high content of guanine-cytosine in its DNA; the long generation time (cell division between 12 to 24 hours under favorable conditions) and the special cell wall, shared by all species of the Mtb complex. The structure of this wall is its composition: highly cross-linked peptideoglycans and mycolic acid, making the bacterium highly hydrophobic and acid-resistant, a characteristic that is used to diagnose the disease(4,5). The lipid-rich cell wall forms the basis for the intrinsic resistance of Mtb to most antibiotics(6).

TB is transmitted primarily through aerosols. Aerosols are tiny droplets containing bacteria, formed when a patient with active TB coughs or sneezes. If these droplets are inhaled by another susceptible person (or animal), the bacteria enter the lung where they are phagocytosed by the macrophages. In other words, Mtb must be active to be transmitted. A person with active TB can infect an average of 10 to 15 people within a year(7). However, the amount of bacilli present, its virulence, health status (co-infections, immunosuppression), the individual's age, and adequate environmental factors such as ventilation and exposure to sunlight (ultraviolet light) have a great influence on infectivity. Yet, theoretically, TB is infectious for a long time while bacteria are viable in the sputum. If a patient is under treatment, it takes about 4 to 8 weeks until no more bacteria are detected in his sputum(4). As the first organ affected is the lung, most cases of TB are called pulmonary TB. Even so, TB can affect other parts of the body, in this case called extrapulmonary TB. In these occasions, the individual is usually not infectious, since the bacterium is not expelled through the aerosols, however, may present clinical of the disease.

Once the bacteria entered the lung they are phagocytosed by alveolar macrophages. Mtb can grow within macrophages by inhibiting the fusion of phagosomes with lysosomes, thus avoiding their digestion. Granulomas are formed - aggregation of infected phagocytes (macrophages, neutrophils, monocytes and dendritic cells) and surrounded by B and T lymphocytes(8). At first three scenarios are possible: first, the immune system overcomes bacteria, which are killed and eliminated completely; Second, bacteria outgrow the immune system and multiply in the lung, causing disease; Third, there is a balance between the bacteria and the immune system, which are in a dormant state called latent TB. When the individual has latent TB, the infection remains clinically silent and the bacteria do not spread. In 90-95% of cases the bacteria remain dormant and never reactivate. In the remaining 5-10% reactivation of bacteria occurs after a few years, leading to clinical disease, called secondary TB(9).

The hypotheses described above must be seen as a result of a dynamic transmission system, in which the course depends on both host and bacterial factors(10). One reason for the reactivation of latent TB is HIV co-infection. CD4 lymphocytes play a key role in the formation of granulomas, as they produce cytokines (eg, IL-12 and IFN-γ) that activate macrophages. CD4 lymphocyte count is generally low with the advancement of HIV infection, patients living with HIV are at high risk (over 40 times) of becoming infected with TB and progressing to TB(11,12).

The most common symptom of TB is productive and persistent cough for several weeks, thus serving as an indicator for TB screening in endemic countries. It is often accompanied by other nonspecific symptoms such as fatigue, fever, night sweats and later weight loss, chest pain and difficulty breathing(7).

2.2 Epidemiology

TB and humans have coexisted for a long time. Estimates suggest that this relationship occurs at least 70,000 years(13). Physical evidence of bacteria in humans has been found in two 9,000-year-old bodies from Haifa, Israel, and from Egyptian mummies dating from 1550 to 1080 BC(14,15). However, TB only appeared epidemic in Europe and North America in the 18th and 19th centuries, declining with the introduction of isolation and chemoprophylaxis and reemerging again in the 1980s and early 1990s as a result of the HIV pandemic and increased resistance to drugs used in treatment(16,17).

In 1993, WHO declared TB a global emergency, given the rise in multi-drug resistant cases and the HIV epidemic(18). As a consequence, the DOT strategy was developed and, after a few years, the STOP TB Strategy was formed, a network of public and private organizations from several countries, with the participation of governments and collaborators, whose purpose is to reduce drastically the burden of disease worldwide(19,20).

TB remains the leading global health problem today. One third of the global population is infected and 8.6 million people developed the disease, resulting in 1.3 million deaths in 2012(7). Most TB cases are found in Southeast Asia (29%), Africa (27%) and Western Pacific Region (19%). The 22 countries with the highest burden of disease represent 82% of the reported cases in the world, with India and China alone representing 39% of this. TB affects more men than women and yet causes one in three deaths in this population, especially those living with HIV. All age groups are affected by the disease, but most cases occur in the economically active population. TB in children has been neglected for a long time, since they do not represent the most infectious cases. However, children are an indicator for active transmission and in 2012 accounted for 6% of the total cases detected(7).

To reduce the global burden of TB, the STOP TB Strategy formulated several targets to be achieved by 2015, in line with the Millennium Development Goals(21). Although the overall mortality rate has dropped by 45 per cent and the prevalence by 37 per cent since 1990, several of the targets proposed, for example the goal of reducing the prevalence of active TB by 50 per cent, have probably not been met by 2015, especially in Africa and European region formed by the countries of the Soviet Union, where mortality and prevalence remain high(22). Large numbers of people with latent infection, HIV pandemic and increased bacterial resistance challenge the achievement of targets to eliminate TB as a public health problem by 2050. Every year about 450,000 new cases of MDR are detected, with the estimated global rate of 9.6% in new cases and 92 countries have reported at least one case of XDR TB so far (7,23). Less than 25% of estimated MDR TB cases worldwide are detected and only 50% of cases initiating therapy are successfully treated.

2.3 The relation prison and tuberculosis

The world prison population is currently estimated at 10.2 million people(24). Brazil has the third largest population in the world, with 688,759 individuals in 1,449 establishments, and the incidence of TB in this population has increased in the last seven years(25). Although prisoners represent only 0.3% of the country's population, an increase in the prison population over this period has resulted in almost double the proportion of all TB cases among prisoners (4.1% in 2007, 8% 1% in 2013).

The prison environment contributes greatly to the transmission of TB. Prisons are an ideal environment for the transmission of the disease, since they bring together individuals who use tobacco and alcohol in high doses, in addition to drug abuse, in overcrowded cells, with little ventilation and with limited access to care. health and diagnosis of TB. Urrego et al.(26) collected architectural and ventilation data in a southern prison in Mato Grosso do Sul and, using a modified Wells-Riley model for indoor TB transmission, projected TB transmission rates within each cell , provided that an infectious case was present. They estimated that 53-70% of cell mates would be infected after four months of exposure.

In a case-control study associated with molecular methods, Sacchi and cols.(27) examined the role of prison in TB burden in the population of Dourados. Among 240 cases of TB reported over a 46-month period, 180 (75%) occurred in the general population and 60 (25%) in the prison population, showing a 40-fold increased risk (incidence) among prisoners of TB. Among the TB cases of the general population, 23% occurred among residents who were previously incarcerated. Previous incarceration was the strongest risk factor for TB in the community (adjusted OR, 28.5). Among 97 isolates for which restriction fragment polymorphism (IS6110) genotyping was performed, 79 could be classified into 17 groups. Ten of these 17 sets, comprising 82% of the clustered isolates, involved two prisoners and community members, including the former detainees. These results demonstrate a high degree of linkage between lineages in prisons and in the community; and indicate that the approach to TB transmission in prisons will be critical to disease control among the general population.

Carbone et al.(28) carried out a cross-sectional study to estimate the prevalence of active and latent TB and associated risk factors among 3,380 prisoners (2,861 men, 519 women) from the 12 penitentiaries in Mato Grosso do Sul. The prevalence of active TB was calculated as 917 cases per 100,000 inmates and the latent one, at 21%. Comparing the prevalence and annual reports of TB, the mean infection time was estimated at 4.8 months.

2.4 Prophylactic use of isoniazid

The discovery of INH was based on the activity of nicotinamide against TB bacilli in an animal model, observed by Chorine in 1945, and the rearrangement of chemical groups in thiosemicarbazone. INH represents an important milestone in TB chemotherapy because it is highly active against bacilli, low cost and without significant side effects.

In 1952 it was proved that the drug had tuberculostatic activity, however, the target of action was unknown(29,30). Subsequently, it has been found that INH inhibits the synthesis of mycolic acids, α-alkyl β-hydroxy and higher chain fatty acids that cover the surface of the mycobacteria. The main molecular target of action of INH is the inhA gene, which encodes the enzyme inhA. This enzyme catalyzes the transfer of a hydrogen atom to the substrate at its catalytic site using NADH, which is a reducing agent found in numerous biochemical processes in living beings as a source of hydrogen(31).

Due to the bacterial resistance to streptomycin (discovered in the previous decade) the use of INH in the treatment of TB started successfully. Although it was generally well tolerated by patients, cases progressing with pruritus and hepatitis were recorded(32). Salpeter(33), in a review covering 20,212 individuals who started chemoprophylaxis with INH, estimated the incidence of hepatitis at 1%, with 8,700 individuals being 35 years of age or older.

In 1963 Hanson, Comstock, and Haley(34) conducted a community-based clinical trial in Alaska using chemoprophylaxis with INH in half a population (about 9,000 subjects) who received a daily dose of the drug (5mg / kg) for 12 months. The intervention was performed based on the epidemiological picture of the region, whose TB incidence was 20 times higher than the North

American population, in addition to conditions considered propitious for transmission (small, overcrowded, poorly ventilated and malnourished individuals). The results showed the occurrence of 32 cases of TB in the control group, compared to 1 case in the treatment.

The conditions described by Hanson, Comstock and Haley in the Alaskan population are similar to those currently found in the prison system in developing countries. However, in this review, no studies were found on the prophylactic use of INH in prisons, and its use was restricted to cases of latent TB.

2.5 Isoniazid in the treatment of latent TB

In 1999, Smieja et al(35), in a review to identify the efficacy of INH in non-HIV subjects, found that the relative risk of acquiring TB after 6 months of prophylaxis with 300mg of the drug was 0.40 (95% CI 0.31 -0.52), with an absolute risk reduction of 0.01, ie, it would take 100 treatments to avoid 1 case of active TB. The most frequent adverse reactions were mild and transient headache, nausea, dizziness. The occurrence of hepatitis was 0.12% in the controls and 0.52% in the treatments, having as risk factors age greater than 45 years and alcohol use.

Sharma et al.(36) in a review comparing regimens with rifamycin (and its derivatives, including rifapentine) and INH, conclude that regimens using rifamycin alone are longer, have a lower completion rate, and do not present advantages over the INH regimen alone.

Epidemiological conditions conducive to high TB transmission are currently found in the prison system (26). Macintyre et al.(37) conducted a cohort study in 16 of the 23 prisons in Maryland and concluded that the use of INH prophylaxis reduced the risk of progression to active TB in individuals reacting to the skin test by 50%. Al-Darraji; Kamarulzaman and Altice(38) have shown, through a systematic review covering 18 publications (between cohort and transverse studies) that the efficacy in cases of latent TB is about 60% in non-HIV individuals and 36% in individuals with HIV, using INH for 6 months. The hepatotoxicity rate was on average 6%. Approximately two-thirds of these studies were conducted in countries with low endemicity for the disease. In view of this, the authors recommend that further studies should be conducted, but in countries highly endemic for the disease, to explore the efficacy and safety of INH in closed prisoners.

Two randomized clinical trials showed an 83.8% and 69% adherence rate with an isolated INH regimen and a hepatotoxicity of 2.4% and 2.7%(39,40). It is noteworthy that in the aforementioned studies all the individuals allocated in the treatment group had latent TB diagnosed through the skin test with PPD.

3 RATIONALE

Despite advances in TB diagnosis and treatment, it is the third leading cause of death from infectious diseases in the world(41). In 2015, WHO estimated that 9.6 million new TB cases worldwide occur, with about 1.1 million deaths. For Brazil, the incidence of 44 cases per 100,000 inhabitants(42) was estimated. The incidence of TB has decreased by around 2% per year.

Brazil occupies the 22nd place in the WHO ranking with an annual rate estimated in 83,310 cases of the disease (42). Over the past seven years, it has been estimated that the incidence declined only 0.7% (per year). A key factor in this slow progress in TB control in Brazil and in other emerging countries is the existence of high-risk subpopulations, including favelas and prisons, which serve as reservoirs and amplifiers for the transmission of the disease(43,44). A recent systematic review has shown that the average incidence of TB in the prison population may be up to 23 times that recorded in the general population(45).

With the third largest population of prisoners in the world, the increase in the incidence of TB among prisoners in the last seven years is observed in Brazil. Although prisoners represent only 0.3% of the country's population, an increase in the prison population over this period has resulted in almost double the proportion of all TB cases among prisoners (4.1% in 2007, 8% 1% in 2013).

Prisons are an ideal environment for TB transmission, since they bring together high-dose tobacco and alcohol users, as well as drug abuse, in overcrowded, poorly ventilated, and limited access health and diagnosis of TB. Currently, the Ministry of Health recommends the active search for TB at the entrance to the prison and once a year, through the chest X-ray. Due to cost and logistics, most prisons do not adhere to this recommendation. There is also a clear recommendation not to use the tuberculin test or to perform treatment for latent TB. Whether procedures for active case detection and / or prophylactic treatment would impact on the high transmission of the disease in prisons is an issue that remains open(38).

The concentration of TB cases in prisons may represent both an obstacle and an opportunity for disease control, depending on the effectiveness of the interventions performed in these settings.

Preliminary studies show a high annual rate of TB infection (26%) among the prison population of 12 penitentiaries in Mato Grosso do Sul. In addition to the large burden of disease in this population, the dispersion of TB from prisons to the community is significant(27). Cross-sectional studies show a high yield of annual screening for TB, however, the effectiveness of this measure associated with other interventions has not yet been clarified(46–52). Because of the combination of the high force of infection in prisons and the short period of incarceration, primary prophylaxis can be an effective intervention.

This approach has not yet been evaluated in the context of prisons in middle- and low-income countries. Thus, in order to assess the impact of program strategies for TB control and primary prophylaxis, longitudinal data will be essential. Given the infrastructure that has been created for prospective long-term studies in Brazil, there is an excellent opportunity to close the fundamental knowledge gaps that have been barriers to effective implementation of TB control in high-transmission prisons.

4 AIMS

4.1 General

To determine the efficacy of primary prophylaxis with INH 900mg twice weekly in innmates in a closed regimen.

4.2 Especifics

- Determine the impact of INH use on the incidence of active and latent TB in the prison population;
- To quantify the occurrence of adverse events, including hepatotoxicity, due to the use of INH;
- Evaluate residual protective effect until the 12th month after intervention;

5 OUTCOMES

5.1 Primary outcome

Reduction of 50% in latent TB in the treatment group after 12 months of intervention, estimated by IGRA QuantiFERON TB Gold Plus – Qiagen.

5.2 Secondary outcome

Reduction of 50% in active TB in the treatment group after 12 months of intervention, estimated by sputum positive culture.

6 METHODOLOGY

6.1 Study designer

Phase IV, randomized, double-blind, placebo-controlled clinical trial with innmates serving time in a closed regimen.

6.1.1 Sample and population of the study

This research will be carried out at one prison unit, located in the city of Dourados, in the state of Mato Grosso do Sul. Currently, this prison unit has approximately 2,300 inmates, with a mean age of 31.5 ± 9.4 years; an average of 9.7 (± 4.2) individuals per cell, who remain in a closed regimen, about 20.8 (± 24.1) months. The TB indicators show a tuberculin test serocoversion rate of 26% (23-26) and incidence, 2.45 / 100,000(28).

The sample was calculated for a significance level of 5%, detection power of 90%, considering a percentage of occurrence of latent TB of 20% in the control group after one year of follow-up and 10% in the experimental group. For these parameters, 560 individuals will be needed for the study, however, 30% will be added for possible losses, ending the sample in 728 participants. Memory calculation available at https://www.sealedenvelope.com/power/binary-superiority/.

6.1.2 Randomization and masking

Two groups, called intervention (INH) and control (placebo), respectively, each composed of 364 participants, will be formed from a simple randomization process using the True Random Number Service developed by the School of Computer Science and Statistics in Dublin, Ireland and available at <www.random.org>. The sequence generator mode used by the principal investigator will produce 728 random alpha-numerical codes, composed of three digits each, that will be delivered to the pharmacist for individual randomization (intervention vs control) containing only the identifying code.

The study pharmacist will be responsible for randomization of the participants and organization of INH-containing bottles or placebo for dispensing during DOT visits. As this is a double-blind study, the other team members are blind and do not have access to the randomization list. The study participants will also not know in which group they are allocated. The description of the pharmacist's activities in the clinical trial are detailed in specific SOP.

The use of placebo was a strategy because there is no clinical trial of primary prophylaxis for TB.

6.1.3 Blinding Break

In the event of any significant AE, the sigil will be broken to identify in which group the participant was allocated. The request for blinding should be made by the study coordinator or lead investigator to the study pharmacist.

In case of breach of blinding, the sponsor must be notified within 48 hours, and the justification for the early breakdown is informed in detail. The reason for the rupture of the blinding should be described in the participant's chart.

At the end of the study randomization will be opened, thus allowing for statistical analysis.

6.2 Inclusion criteria

- Age above 18 and under 45 at the time of inclusion;
- Sign the informed consent form.

6.3 Exclusion criteria

- Be indigenous;
- Active TB or previous use of INH;
- Sscore AUDIT ≥15.
- Reactive serology for HIV, hepatitis B and C;
- Reactive result for IGRA, considering as positive the result of TB1 Tube and / or TB2 Tube above 0.2 IU/mL(53);
- Liver enzymes (AST and ALT) three times the upper limit;
- History or treatment for epilepsy;

6.4 Indications for premature exclusion

The participant may be withdrawn from the clinical trial at any time for the reasons listed below:

• at the request of the participant (withdrawal or withdrawal of consent);

• non-compliance with the protocol;

• interruption of treatment or sum of temporary interruptions of intervention ≥90 days, either by decision of the participant or at medical discretion;

• transfer to another prison unit or early release;

• Clinical or laboratory AE requiring permanent discontinuation of medication (according to study-specific SOP);

• any exclusion criterion according to item 5.3 that, incidentally, arises during the follow-up (both recently diagnosed and not previously recognized);

• use of acetaminophen, valproic acid, carbamazepine, cycloserine, ethionamide, corticosteroids, diazepam, triazolam, disulfiram, phenytoin, aluminum hydroxide and rifampicin which, at the discretion of the investigator, are used in a dose that may interfere with the efficacy of INH as medication;

• another reason, at the discretion of the principal investigator or study coordinator.

At the time of the participant's withdrawal, a premature exclusion visit with clinical evaluation, evaluation of AE and blood and / or sputum collection should be performed according to the clinical judgment, according to the study schedule (figure 1).

In addition, for cases in which treatment has been interrupted by decision of the participant or at medical discretion, as of 6 months from the start of the DOT, the participant will have two options: to remain in the study without the intervention (DOT), but with the accomplishment of all the visits anticipated in the protocol or to leave completely of the study without the realization of

additional collections and other accompaniments. For the latter case, follow-ups will be carried out only if the participant presents some AE at the time of their withdrawal.

6.5 Conducting the study

Participants will be invited to participate in the clinical trial through the consent process and will agree to participate in the study by signing the ICF.

In the recruitment interval, prior to any intervention, participants will respond to the AUDIT questionnaire - which assesses various levels of alcohol use, from safe use to likely dependence - and eligibility criteria will be checked. In the recruitment interval, participants will have a 9mL sample of peripheral blood collected for testing of IGRA (QuantiFERON® TB GOLD PLUS kit - Qiagen, HIV, hepatitis B (HBsAg) and C (Anti-HCV) and serum levels of liver enzymes (AST and ALT).

After the results of these initial tests (HIV, hepatitis B and C, IGRA, AST and ALT), if eligible, the participant will answer questionnaires containing socioeconomic, medical and criminal history and have a sample of sputum collected for culture.

The participant will be included in the study without the result of the culture and, in case of a positive result for Mtb, the intervention will be suspended, the same will be excluded from the study and treated according to the MS protocol. If the sputum culture is contaminated, a new sample should be collected within 30 days after the result.

The recruitment interval will last 20 to 45 days.

On the day of initiation of DOT (D0), each participant will receive a supervised dose (three oral tablets) of INH (900mg) or placebo. The same will happen twice a week for 12 months. During the DOT the participant will be asked about AE.

Blood samples will be collected every three months after D0 to measure hepatic enzyme levels (AST and ALT), as well as clinical evaluation and verification of AE, as shown in figure 1.

At six months and at the end of the intervention (12th month), all participants will have a sample of sputum collected for culture and a blood sample for detection / quantification of interferon gamma. The same evaluation will be repeated in the 24th month counted from D0, that is, one year after the end of the intervention.

At follow-up visits of 6, 12 and 24 months, if the interferon gamma result is indeterminate, the participant remains in the clinical trial and a new sample is collected within 30 days. If the IGRA result is positive (result standardized according to the package insert of the Qiagen®), the participant will suspend the medication (in the case of the 6-month visit), will be excluded from the study and treatment for latent TB.

If the sputum culture is positive for Mtb, the participant will be excluded from the study and treatment for active TB according to MS will be offered. If the sputum culture is contaminated, a new sample should be collected within 30 days after the result.

In the occurrence of hepatotoxicity, diagnosed through hepatic enzyme levels (elevation greater than five times the upper limit of the test if the individual is asymptomatic) and / or clinical examination (presence of jaundice, right upper quadrant pain, dark urine, fever, asthenia, myalgia), the intervention will be interrupted and the participant will be led to clinical care by the project team, according to the project's SOP. In this study, the following values will be used as laboratory parameter: AST: 8-40 IU / mL and ALT: 5-30 IU / mL(54,55). Other laboratory tests may be

requested from the research participants, according to the clinical judgment of the physician responsible for the care of the AE and according to the specific SOP of the project.

IGRA, smear culture, and serology for HIV, hepatitis B and C are performed LPCS / UFGD. The AST/ALT exams and other laboratory tests, when necessary, are performed in an external laboratory.

During the course of the study, the Notification of Injury Information System will be used to identify the occurrence of active TB cases in both groups.

The box below summarizes the activities to be developed at each stage of the protocol.

	Enrollment	DOT start (D0)	1st visit (3 mo± 15 d)	2nd visit (6 mo± 15 d)	3rd visit (9 mo± 15 d)	4th visit (12 mo± 30 d)	5th visit (24 mo± 30 d)	Early exclusion visit
Consent process	X							
Verification of inclusion and exclusion criteria	X							
AUDIT	X							
Medical history	X							
Criminal history	X							
Randomization		X						
DOT star		X						
DOT end						X		
IGRA	X			X		X	X	(X)
ALT, AST	X		X	X	X	X		(X)
Another laboratory exams	(X)		(X)	(X)	(X)	(X)		(X)
Anti-HIV, HBsAg e Anti-HCV	X							(X)
Sputum coleccion	X			X		X	X	(X)
Clínical evaluation	X	X	X	X	X	X	X	X
Adverses events evaluation			X	X	X	X	X	X

DOT = Directly Observed Treatment, mo = months, d = days

Figura 1 - Schedule, second quarters, of research activities. The parentheses indicate that the procedures are optional.

6.6 Estatistical analysis

Data on demographic, socioeconomic, medical and criminal history, as well as on pre, intra and post-intervention laboratory tests will be stored online at REDCap, available at <http://www.matogrossodosul.fiocruz.br/redcap/>, where each researcher is identified by single user and password, guaranteeing restricted and confidential access. Statistical analysis will be done with IBM® SPPS Statistics software.

The incidence will be calculated on the basis of the new cases detected during the follow-up period, per 100 person-years. It will be considered a new case of TB individuals, regardless of the group, who present bacilloscopy or positive culture. For latent TB, a seroconversion will be considered for individuals who exhibit interferon gamma levels above the upper limit considered by the manufacturer of the QuantiFERON® TB Gold Plus commercial test in the 12th or 24th month.

The effect of the intervention will be calculated through Relative Risk (RR), considering a Confidence Interval of 95% (95% CI). To determine the effectiveness of the intervention will be used Relative Risk Reduction (RRR) and Absolute Risk Reduction (RAR). In addition, to measure the impact of the intervention, the Number Needed to Treat (NNT) will be calculated.

Two protocols will be performed for statistical analysis: 1) intention-to-treat analysis and 2) per protocol. The sample calculation for the primary outcomes is based on intention-to-treat analysis.

The intent-to-treat analysis will be performed for all subjects who complete at least 6 months of treatment. The participant may decide to withdraw the consent in whole or in part. In the case of withdrawal of partial consent IGRA will be withdrawn at the 12th or 24th month and the participant will remain in the study according to the initial randomization.

Analysis by protocol will be performed only using the group of individuals who completed at least 80% of the predicted doses of the study.

6.7 Interim analysis

After a 6-month visit of at least 100 participants, in addition to the follow-up clinic-laboratorial evaluation (which includes blood collection for hepatic enzyme dosage and directed clinical examination), an evaluation of the effectiveness of the intervention will be carried out, through sputum culture and interferon-gamma dosing / quantification. It is estimated that there is a linear relationship between follow-up time and the risk of acquisition of latent TB.

This evaluation intends to verify the feasibility of continuity of the study and adequacy of the sample calculation. The study will be discontinued if the primary endpoint is less than 2.5% as compared to the control group, or if the difference between the intervention group and the control group is greater than 12.5% according to the box below:

	Intervention (isoniazid) (N=162)	Control (placebo) (N=162)	Finale total number (N final+30%)
Reference	5.0%	10%	726
Insufficient sample	7.5%	10%	3357
Insufficient sample	10.0%	12.5%	3910
Insufficient sample	12.5%	15.0%	4555
Insufficient sample	15.0%	17.5%	5114
Insufficient sample	17.5%	20.0%	5361
Sufficient sample	5.0%	17.5%	172
Sufficient sample	7.5%	20.0%	187
Sufficient sample	10.0%	22.5%	213
Sufficient sample	12.5%	25.0%	218
Sufficient sample	15.0%	27.5%	229

Figura 2 - Sample table of the sample values in both groups (intervention and control), based on the primary outcome.

6.8 Study interruption

The study may be terminated early according to the outcome of the interim analysis or at the discretion of the research team, which shall prepare written notices to the IRB and to the sponsor, detailing the reasons interruption of the study.

Participants should be informed about early termination of the study, treatment discontinued, and premature exclusion visit according to figure 1.

6.9 Ethical aspects

Following the provisions of Resolution 466/12 of the National Health Council, the present study was sent to the IRB of the UEMS, having its first approval in the Opinion no. 1,677,965, CAAE no. 57333716.8.0000.8030.

This study will use REDCap to capture data and it will be used as a source document of the information contained in it. A copy of the completed document will be printed and archived in the participant's folder.

It is registered and approved in the Brazilian Registry of Clinical Trials, available at <http://www.ensaiosclinicos.gov.br/rg/RBR-4n67h3/> and in the Clinical Trials, available at <https://clinicaltrials.gov/ct2/home>, identifier NCT03028129.

All individuals approached by the researcher and team should read and sign the TCLE to participate in the research.

During the course of the experiment, participants will be monitored clinically and laboratorially for the occurrence of adverse effects, particularly hepatotoxicity, a more frequent event (1%) according to the literature(33).

If the intervention results in greater than expected benefit, the team will discontinue the experiment and provide all participants with INH treatment.

6.10 Quality control

Sponsor will provide monitoring visits that will include reviewing forms, batch counting of drugs, checking laboratory data, monitoring adverse events, and documenting any violations or deviations from the protocol.

This study may be subject to audit procedures in cases where the sponsor or the Brazilian regulatory agency (ANVISA) deems relevant.

6.11 Potential risks

1) The protocol will identify active and latent cases of TB among inmates. Although the diagnosis of TB provides the prisoner with situations that can be understood as benefits, such as admission to less busy wards and access to better services, the disease in Brazil, as in many countries, is potentially stigmatizing.

2) During recruitment, cases of HIV and viral hepatitis (B and C) may be identified, which, although treatable, as well as TB, are potentially stigmatizing.

3) Participants allocated to the experimental group will receive INH. Mild and serious adverses events including hepatotoxicity may occur. All participants will be monitored every three months through clinical consultation and blood tests when necessary.

4) The study team will extract information about demographics, behaviors, and past medical history during interviews, so there is the potential risk of discomfort in answering questions and breach of confidentiality regarding personal information.

5) Blood samples will be collected by venipuncture during the study, which, despite having minimal risks, may be associated with discomfort and bruising.

6) Innmates are inherently vulnerable populations who may feel compelled to participate in the study and may perceive that their involvement in the proposed study provides benefits or risks in relation to the conduct of officials and other prisoners.

7) The study team is exposed to the risk of infections and work-related illnesses due to the high rate of TB transmission in the study sites (prison).

6.12 Expected benefits

1) Reduce the risk of becoming infected with TB or developing the disease during incarceration.

2) Quantification of the risk / benefit of primary prophylaxis in subjects without tTB (active or latent), but strongly exposed to the risk of becoming infected with TB or developing the disease.

3) Produce scientific evidence to modify the recommendations of the competent organs regarding primary prophylaxis in the prison system.

REFERENCES

1. Smith NH, Kremer K, Inwald J, Dale J, Driscoll JR, Gordon SV, et al. Ecotypes of the Mycobacterium tuberculosis complex. J Theor Biol. março de 2006;239(2):220–5.

2. Brosch R, Gordon SV, Marmiesse M, Brodin P, Buchrieser C, Eiglmeier K, et al. A new evolutionary scenario for the *Mycobacterium tuberculosis* complex. Proc Natl Acad Sci. 19 de março de 2002;99(6):3684–9.

3. Sreevatsan S, Pan X, Stockbauer KE, Connell ND, Kreiswirth BN, Whittam TS, et al. Restricted structural gene polymorphism in the Mycobacterium tuberculosis complex indicates evolutionarily recent global dissemination. Proc Natl Acad Sci. 2 de setembro de 1997;94(18):9869–74.

4. Juan Carlos Palomino, Sylvia Cardoso Leão, Viviana Ritacco. Tuberculosis 2007: From basic science to patient care. 1º ed. s.l.: s.n.; 2007. 687 p.

5. Steingart KR, Ng V, Henry M, Hopewell PC, Ramsay A, Cunningham J, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis. outubro de 2006;6(10):664–74.

6. Nguyen L, Pieters J. Mycobacterial Subversion of Chemotherapeutic Reagents and Host Defense Tactics: Challenges in Tuberculosis Drug Development. Annu Rev Pharmacol Toxicol. fevereiro de 2009;49(1):427–53.

7. TB Fact sheet 104.pdf. Saude Med J. novembro de 2013;34(11):1205–7.

8. Ernst JD. The immunological life cycle of tuberculosis. Nat Rev Immunol. agosto de 2012;12(8):581–91.

9. Schluger NW, Rom WN. The Host Immune Response to Tuberculosis. Am J Respir Crit Care Med. março de 1998;157(3):679–91.

10. Barry CE, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol. dezembro de 2009;7(12):845–55.

11. Brites D, Gagneux S. Old and new selective pressures on Mycobacterium tuberculosis. Infect Genet Evol. junho de 2012;12(4):678–85.

12. Nunn P, Williams B, Floyd K, Dye C, Elzinga G, Raviglione M. Tuberculosis control in the era of HIV. Nat Rev Immunol. outubro de 2005;5(10):819–26.

13. Comas I, Coscolla M, Luo T, Borrell S, Holt KE, Kato-Maeda M, et al. Out-of-Africa migration and Neolithic coexpansion of Mycobacterium tuberculosis with modern humans. Nat Genet. outubro de 2013;45(10):1176–82.

14. Hershkovitz I, Donoghue HD, Minnikin DE, Besra GS, Lee OY-C, Gernaey AM, et al. Detection and Molecular Characterization of 9000-Year-Old Mycobacterium tuberculosis from a Neolithic Settlement in the Eastern Mediterranean. Ahmed N, organizador. PLoS ONE. 15 de outubro de 2008;3(10):e3426.

15. Nerlich AG, Haas CJ, Zink A, Szeimies U, Hagedorn HG. Molecular evidence for tuberculosis in an ancient Egyptian mummy. The Lancet. novembro de 1997;350(9088):1404.

16. Daniel TM. The history of tuberculosis. Respir Med. novembro de 2006;100(11):1862–70.

17. Porter JD, McAdam KP. The re-emergence of tuberculosis. Annu Rev Public Health. 1994;15:303–23.

18. Nakajima H. Tuberculosis: a global emergency. World Health. 1993;46(4):3.

19. Organization WH. WHO Tuberculosis Programme framework for effective tuberculosis control. World Health Organ WHOTB94. 1994;1:1–7.

20. The Stop TB Strategy: Building on and enhancing DOTS to meet the TB-related Millennium Development Goals. 2006.

21. Stop TB Partnership (World Health Organization). The global plan to stob TB 2011-2015: transforming the fight towards elimination of tuberculosis. Geneva: World Health Organization; 2011.

22. Organization WH. Global tuberculosis report 2013. World Health Organization; 2013.

23. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response [Internet]. Geneva, Switzerland: World Health Organization; 2010 [citado 30 de julho de 2018]. Disponível em: http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf

24. Walmsley R. World Prison Population List. p. 6.

25. BRASIL. Levantamento nacional de informações penitenciárias: INFOPEN atualização junho/2016. [Internet]. Brasília/DF: Ministério da Justiça e Segurança Pública; 2017 [citado 22 de setembro de 2018]. 65 p. Disponível em: http://depen.gov.br/DEPEN/depen/sisdepen/infopen/relatorio_2016_22-11.pdf

26. Urrego J, Ko AI, da Silva Santos Carbone A, Paião DSG, Sgarbi RVE, Yeckel CW, et al. The Impact of Ventilation and Early Diagnosis on Tuberculosis Transmission in Brazilian Prisons. Am J Trop Med Hyg. 7 de outubro de 2015;93(4):739–46.

27. Sacchi FPC, Praça RM, Tatara MB, Simonsen V, Ferrazoli L, Croda MG, et al. Prisons as Reservoir for Community Transmission of Tuberculosis, Brazil. Emerg Infect Dis. março de 2015;21(3):452–5.

28. Carbone A da SS, Paião DSG, Sgarbi RVE, Lemos EF, Cazanti RF, Ota MM, et al. Active and latent tuberculosis in Brazilian correctional facilities: a cross-sectional study. BMC Infect Dis [Internet]. dezembro de 2015 [citado 1º de julho de 2018];15(1). Disponível em: http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-015-0764-8

29. Yale HL, Losee K, Martins J, Holsing M, Perry FM, Bernstein J. Chemotherapy of Experimental Tuberculosis. VIII. The Synthesis of Acid Hydrazides, their Derivatives and Related Compounds [1,2]. J Am Chem Soc. abril de 1953;75(8):1933–42.

30. Fox HH. The chemical approach to the control of tuberculosis. Science. 8 de agosto de 1952;116(3006):129–34.

31. Banerjee A, Dubnau E, Quemard A, Balasubramanian V, Um K, Wilson T, et al. inhA, a gene encoding a target for isoniazid and ethionamide in Mycobacterium tuberculosis. Science. 14 de janeiro de 1994;263(5144):227–30.

32. Thoren M, Hinshaw HC. Therapy of pulmonary tuberculosis with isoniazid alone and in combination with streptomycin and with para-amino-salicylic acid. Stanf Med Bull. novembro de 1952;10(4):316–8.

33. Salpeter SR. Fatal isoniazid-induced hepatitis. Its risk during chemoprophylaxis. West J Med. novembro de 1993;159(5):560–4.

34. Mary L. HANSON, G. W. COMSTOCK, C. E. HALEY. Community Isoniazid Prophylaxis Program in an Underdeveloped Area of Alaska.pdf. Public Health Rep. dezembro de 1967;82(12):1045–56.

35. Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Infectious Diseases Group, organizador. Cochrane Database Syst Rev [Internet]. 25 de janeiro de 1999 [citado 30 de julho de 2018]; Disponível em: http://doi.wiley.com/10.1002/14651858.CD001363

36. Sharma SK, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Infectious Diseases Group, organizador. Cochrane Database Syst Rev [Internet]. 5 de julho de 2013 [citado 30 de julho de 2018]; Disponível em: http://doi.wiley.com/10.1002/14651858.CD007545.pub2

37. MacIntyre CR, Kendig N, Kummer L, Birago S, Graham NM. Impact of tuberculosis control measures and crowding on the incidence of tuberculous infection in Maryland prisons. Clin Infect Dis Off Publ Infect Dis Soc Am. junho de 1997;24(6):1060–7.

38. Al-Darraji H a. A, Kamarulzaman A, Altice FL. Isoniazid preventive therapy in correctional facilities: a systematic review. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. julho de 2012;16(7):871–9.

39. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New Regimens to Prevent Tuberculosis in Adults with HIV Infection. N Engl J Med. 7 de julho de 2011;365(1):11–20.

40. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. N Engl J Med. 8 de dezembro de 2011;365(23):2155–66.

41. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. janeiro de 2015;385(9963):117–71.

42. Zumla A, George A, Sharma V, Herbert RHN, Oxley A, Oliver M. The WHO 2014 Global tuberculosis report—further to go. Lancet Glob Health. janeiro de 2015;3(1):e10–2.

43. Basu S, Stuckler D, McKee M. Addressing Institutional Amplifiers in the Dynamics and Control of Tuberculosis Epidemics. Am J Trop Med Hyg. 5 de janeiro de 2011;84(1):30–7.

44. Dowdy DW, Golub JE, Chaisson RE, Saraceni V. Heterogeneity in tuberculosis transmission and the role of geographic hotspots in propagating epidemics. Proc Natl Acad Sci. 12 de junho de 2012;109(24):9557–62.

45. Baussano I, Williams BG, Nunn P, Beggiato M, Fedeli U, Scano F. Tuberculosis Incidence in Prisons: A Systematic Review. Menzies D, organizador. PLoS Med. 21 de dezembro de 2010;7(12):e1000381.

46. Ferreira MMC, Ferrazoli L, Palaci M, Salles PS, Medeiros LA, Novoa P, et al. Tuberculosis and HIV Infection Among Female Inmates in São Paulo, Brazil: A Prospective Cohort Study: J Acquir Immune Defic Syndr Hum Retrovirol. outubro de 1996;13(2):177–83.

47. Fournet N, Sanchez A, Massari V, Penna L, Natal S, Biondi E, et al. Development and evaluation of tuberculosis screening scores in Brazilian prisons. Public Health. outubro de 2006;120(10):976–83.

48. Lemos EF, Alves AM da S, Oliveira G de C, Rodrigues MP, Martins NDG, Croda J. Health-service performance of TB treatment for indigenous and non-indigenous populations in Brazil: a cross-sectional study. BMC Health Serv Res [Internet]. dezembro de 2014 [citado 6 de julho de 2018];14(1). Disponível em: http://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6963-14-237

49. Vieira AA, Ribeiro SA, Siqueira AM de, Galesi VMN, Santos LAR dos, Golub JE. Prevalence of patients with respiratory symptoms through active case finding and diagnosis of pulmonary tuberculosis among prisoners and related predictors in a jail in the city of Carapicuíba, Brazil. Rev Bras Epidemiol. dezembro de 2010;13(4):641–50.

50. Sanchez A, Massari V, Gerhardt G, Espinola AB, Siriwardana M, Camacho LAB, et al. X ray screening at entry and systematic screening for the control of tuberculosis in a highly endemic prison. BMC Public Health [Internet]. dezembro de 2013 [citado 3 de agosto de 2018];13(1). Disponível em: http://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-13-983

51. Nogueira PA, Abrahão RMC de M, Galesi VMN. Tuberculosis and latent tuberculosis in prison inmates. Rev Saúde Pública. fevereiro de 2012;46(1):119–27.

52. Estevan AO, Oliveira SM do VL de, Croda J. Active and latent tuberculosis in prisoners in the Central-West Region of Brazil. Rev Soc Bras Med Trop. 12 de julho de 2013;46(4):515–8.

53. Nemes E, Rozot V, Geldenhuys H, Bilek N, Mabwe S, Abrahams D, et al. Optimization and Interpretation of Serial QuantiFERON Testing to Measure Acquisition of *Mycobacterium tuberculosis* Infection. Am J Respir Crit Care Med. setembro de 2017;196(5):638–48.

54. Reitman S, Frankel S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. Am J Clin Pathol. julho de 1957;28(1):56–63.

55. Billing BH. A chromatographic method for the determination of the three bile pigments in serum. J Clin Pathol. maio de 1955;8(2):126–9.