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Keywords:	Anti-tuberculosis treatment, adverse drug reactions, prospective observational study

The Home-based Anti-Tuberculosis Treatment Adverse Reactions (HATTAR) study: a protocol for a prospective observational study

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ABSTRACT

Introduction Tuberculosis (TB) continues to be an important public health problem throughout much of the world. Drug treatment is the only effective treatment method, but adverse drug events (ADEs) and adverse drug reactions (ADRs) can affect medication compliance. As the number of drug-resistant TB patients and the number of anti-TB drugs have increased, it is necessary to explore the risk factors for ADEs/ADRs in order to reduce their occurrence. This study aims to build a home-based anti-TB treatment cohort and to recognize the incidences, prognosis and risk factors of anti-TB drug-induced ADEs/ADR in real-world experiences.

Methods and analysis This study is a multicenter, prospective observational cohort study. The study population will consist of 3200 newly diagnosed TB patients between January 2019 and December 2020. After initiating the anti-TB treatment, all patients will be followed up until finishing treatment unless they withdraw, and we will record personal drug use and signs and/or symptoms of discomfort. Patients will receive scheduled laboratory tests in designated hospitals every two weeks during the first two months, and the residual blood sample after conducting the laboratory tests will be preserved. The ADEs/ADRs will be placed into 8 categories: liver dysfunction, gastrointestinal reactions, drug allergy, arthralgia or muscle pain, nervous system disorders, hematologic system disorders, renal impairment and others.

Ethics and dissemination This study protocol has been approved by the ethics committees of Nanjing Medical University. All patients will give written informed consent before enrollment. The findings of the study will be published in peer-reviewed journals and will be presented at national and international conferences.

Keywords

Anti-tuberculosis treatment, adverse drug reactions, prospective observational study

Strengths and limitations of this study

- This is a prospective study design with a home-based, large-scale consecutive anti-TB treatment cohort under real-world experiences in China.
- A method combining active self-recorded diaries and passive scheduled laboratory tests will be used to enhance the identification of adverse reactions.
- The residual blood sample after the laboratory tests will be preserved for future research.
- A limitation is that it will recruit all eligible patients, including a floating population, who will add uncertainty to the follow up.

Introduction

Tuberculosis (TB) is one of the top 10 causes of death and the leading cause from a single infectious agent. In 2017, approximately 10.0 million people developed TB disease, and TB caused an estimated 1.3 million deaths[1]. Drug treatment is the only effective treatment method for TB, and the World Health Organization (WHO) has implemented a standardized directly observed treatment, the short-course (DOTS)/Stop TB Strategy, to improve TB prevention and control. Although the WHO set the global target rate for a successful treatment outcome at 85%[2], the treatment success rate remains low, at 82% for all TB patients and 55% for drug-resistant TB (DR-TB) patients[1]. Many factors have influenced the treatment success rate, such as sociodemographic and socioeconomic factors, nutrition, HIV, drug resistance, and strategies for TB management including DOTS[3]. Additionally, effective chemotherapy is largely based on patients' willingness to comply with the prescribed regimen, and adverse drug events (ADEs) and adverse drug reactions (ADRs) are significant factors affecting the compliance of patients to medications[4]. Long-term anti-TB combination regimens could lead to various types and levels of ADEs/ADRs, which could subsequently lead to treatment discontinuation or interruption, treatment time extension and an increased risk for developing drug resistance, treatment failure and relapse[5]. All of these negative consequences have posed a challenge to TB treatment and have implications for TB control.

Among the various ADEs/ADRs, the most common ones induced by first-line anti-TB drugs are hepatotoxicity, gastrointestinal disorders, allergic reactions, arthralgia, neurological disorders and so on[6], while in multidrug-resistant TB (MDR-TB) patients, common types are arthralgia, gastrointestinal disorders, hypothyroidism, dermatologic disorders, hematologic disorders, hepatotoxicity, ototoxicity, and nervous system or psychiatric disorders[7]. TB patients treated by second-line anti-TB drugs in the context of high HIV coinfection had more severe ADEs/ADRs, and the most common severe type reported was hearing loss or ototoxicity[8]. Women, patients of an advanced age and recurrent TB patients were found to be at a higher risk of leukopenia[9]. As problems such as DR-TB, MDR-TB, extensively drug-resistant TB (XDR-TB), and a recently emerging threat by a totally drug-resistant TB (TDR-TB) are increasing in prevalence, several novel drugs will cause a significant shift in the landscape of TB treatment but can cause some other ADEs/ADRs. For example, bedaquiline and delamanid can prolong cardiac QTc[10, 11]. The majority of TB patients receive community-based or home-based treatment; however, most studies of ADRs are hospital-based[7-9]. Treatment interruption due to ADEs/ADRs could decrease the chance of a cure[12] and lead to patient loss to follow-up, further increasing the development of drug resistance[13]. Additionally, community-based care for MDR-TB patients is more effective than care in a central specialized hospital[14]. Home-based care could increase MDR-TB treatment success[14] and has potential in improving treatment outcomes[15]. Therefore, it is necessary to strengthen research on ADEs/ADRs in home-based anti-TB treatment.

Between October 2007 and June 2008, a cohort of Anti-tuberculosis Drugs induced Adverse Reactions in China National Tuberculosis Prevention and Control Scheme Study (ADACS) was established by us in China[16]. Based on this cohort, ADRs and genetic susceptibility in anti-TB treatment patients were widely studied[6, 17-21], which made a great contribution to the pharmacoepidemiology of Chinese TB patients. However, two limitations cannot be ignored. First, blood samples were collected with FTA cards, which could not be used in subsequent high-throughput genomics studies and led to the inability to conduct serum marker studies. The combination of chemical, biological, and large-scale observational health data is critical to predict ADRs in both individual patients and global populations[22]. In addition, serum or plasma samples obtained both before and during treatment of all subjects are also needed to enable future studies of new proteomic, metabonomic and other soluble biomarkers or predictors of drug induced hepatotoxicity[23]. Second, only sputum smear-positive pulmonary TB patients treated with the DOTS strategy were included, and the percentage of bacteriologically confirmed cases among total new and relapsed pulmonary TB cases was only 32% in 2017[1]. Thus, it is necessary to study ADRs in other types of patients. In addition to first-line drugs, the number of second-line drugs and new drugs for treating different types of DR-TB patients are also gradually increasing[10], and ADRs induced by those drugs still need further study. Thus far, there are no other similar new cohorts in China that can satisfy the need for a study of ADEs/ADRs.

For these reasons, we plan to establish a new prospective observational cohort, the Home-based Anti-Tuberculosis Treatment Adverse Reactions (HATTAR) study, based on newly diagnosed TB patients receiving home-based anti-TB treatment in China, and to recognize the incidences, prognosis and risk factors of anti-TB drug-induced ADRs in real-world experiences. The goals are as follows:

(1) To complete an epidemiological survey of anti-TB treatment patients, including baseline characteristics, diagnosis and treatment, clinical outcomes, ADEs/ADRs, risk factors, and to evaluate the incidence of various ADEs/ADRs in this population.

(2) To build a biological specimen bank for future research, including plasma and blood cells at different treatment times and incorporating existing routine biochemical test results.

(3) To explore demographic factors, genetic variants and environmental risk factors relevant to anti-TB induced ADEs/ADRs, and their interactions.

Methods and analysis

Study design

This is a multicenter, prospective observational cohort study of Chinese patients being treated for TB, sponsored by Nanjing Medical University. The participating hospitals are two infectious disease hospitals and two local designated TB diagnosis and treatment centers in general hospitals located in Jiangsu Province of China.

Study population

Recruitment of a baseline cohort of 3200 newly diagnosed TB patients will be conducted between January 2019 and December 2020. The patients will be followed up until finishing anti-TB treatment.

Newly diagnosed TB patients who are ready to receive anti-TB treatment, are willing to join the study and sign the informed consent form or have a surrogate do so will be included in this study.

Exclusion criteria: (1) having a psychiatric disease that requires the incorporation of a questionnaire investigation and (2) having a severe disease with a prognosis shorter than 6 months.

Withdrawal criteria: (1) unwilling to continue participating in the study; (2) non-compliance such as stopping the drugs for longer than 2 months; (3) developing diseases that meet the exclusion criteria after enrollment; (4) moving or travelling and thus missing the scheduled laboratory tests in the first two months; and (5) death that is not caused by anti-TB drug-induced ADRs.

Study protocol

This study protocol was based on the National Tuberculosis Prevention and Control Planning and the Guideline for TB Diagnosis and Treatment in China[24], which consists of four main steps: TB diagnosis and patient enrollment, baseline investigation and patient training, anti-TB treatment and follow-up, clinical outcome and ADRs judgement. A flow chart of the study design and procedures is shown in Figure 1.

TB diagnosis and patient enrollment

Potential subjects will be recruited from Zhenjiang, Changshu, Taixing, and Jurong between January 2019 and December 2020 and diagnosed based on Chinese national TB diagnostic guidelines (WS288-2017), which rely on clinical judgement based on symptoms, chest radiography, tuberculin skin tests, and smear microscopy.

If newly diagnosed TB patients meet the inclusion criteria, the doctors will explain the study to the patients and invite them to participate. If the patients agree, informed consent will be signed by the patient or a surrogate.

Baseline investigation and patient training

TB patients who have been recruited will complete the baseline questionnaire, including personal history of diseases and smoking and drinking habits, and undergo anthropometric measurements (weight and height). The patients will also be subjected to blood collection and laboratory tests, including routine blood tests and liver function and hepatitis B surface antigen tests. The residual blood sample of each patient will be separated into plasma and blood cells according to the standard laboratory protocol and then immediately frozen at −40℃.

The enrolled TB patients will receive training and counselling about medication knowledge and self-monitoring knowledge, for example, the importance of scheduled liver function tests, how to fill out the self-recorded diaries, what uncomfortable symptoms need to be recorded, and how to get consulting services.

Anti-TB treatment and follow-up

Once diagnosed with TB, patients will begin to receive standardized anti-TB treatment according to the WHO guidelines for the treatment of drug-susceptible and drug-resistant TB[25, 26]. For example, in patients with drug-susceptible pulmonary TB, isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) will be given for 2 months in the intensive phase, and then, INH and RIF, for the 4 months of the continuation phase. The doctors can decide whether hospitalization admission is needed according to the patient's condition. Inpatients after discharge and other patients who do not need hospitalization admission will receive community- or home-based DOTS regimens. The doctors can also change or adjust the medication according to the patient's condition during the treatment period.

After initiating the anti-TB treatment, all patients will be followed up until finishing treatment unless they withdraw. Patients will be asked to record personal drug use and signs and/or symptoms of discomfort or unfavorable feelings in the self-recorded diaries. During the first two months, patients will receive scheduled outpatient follow-up and liver function tests every two weeks in the designated hospital according to the local free-TB service policy. If patients exhibit unbearable discomfort or some symptoms of suspected hepatitis (such as anorexia, nausea, vomiting, malaise, or tea-colored urine) or other diseases, they should see a doctor and undergo examinations. After the first two months, patients can volunteer to go to the hospital for medical examinations.

During the treatment, if suspicious ADEs emerge, the local supervising doctors will conduct investigations to rule out other possible causes and fill out the relevant questionnaire. If the scheduled laboratory tests of the patients without any discomfort show an abnormality, the ADE investigation procedure will also be activated. Furthermore, the local supervising doctors will be required to actively contact the patients and check their self-recorded diaries for signs and/or symptoms of ADEs/ADRs and drug use. Additionally, the residual blood sample of each patient after the scheduled laboratory tests will be preserved and frozen at −40℃.

Every TB patient in Jiangsu Province has a special outpatient medical record, which is used to record all of the treatment behaviors of patients throughout the treatment period, including basic personal information, diagnosis, medication history, laboratory test, and suspicious ADEs/ADRs. In addition, every local supervising doctor will be provided with a registration and management card for every TB patient, which will be used to record basic personal information, patient management methods and treatment outcomes. Both the medical record and the management card are based on the patient's China ID number.

Clinical outcome and ADRs judgement

When all TB patients finish treatment, the local supervising doctors will comprehensively judge the patient's treatment outcomes according to their symptoms and signs, various clinical examinations, drug use, etc., and record them on the management card of every patient. The outpatient medical record and the management card will be collected and converted into an electronic database.

Based on medication records, symptoms, signs, laboratory test results, relevant investigations and self-recorded diaries, local supervising doctors will be able to judge ADEs preliminarily. Experts from the ADRs monitoring center will regularly review and verify the judgements and classify all of the ADEs into 8 categories as follows[6, 27]: (1) liver dysfunction, including elevated transaminase and jaundice; (2) gastrointestinal reactions, including nausea, vomiting and diarrhea; (3) drug allergy, including pruritus and rash; (4) arthralgia or muscle pain; (5) nervous system disorders, including sleep disorders, dizziness, headache, tinnitus and hearing loss; (6) hematologic system disorders, including anemia and leukopenia; (7) renal impairment, including decline of renal function, positive urine protein and renal failure; and (8) others. Finally, the experts will conduct causality assessments based on the WHO-UMC causality assessment system[28] and the Roussel Uclaf Causality Assessment Method (RUCAM)[29] and judge some ADEs as ADRs according to the criteria.

Anti-TB drug-induced hepatotoxicity (ATDH) is defined as (1) an increase in alanine aminotransferase (ALT) levels greater than two times the upper limit of normal (ULN) with/without a combined increase in aspartate aminotransferase (AST) and total bilirubin levels provided one of them was greater than two times the ULN during the treatment[30] or (2) the causality assessment result is highly probable, probable or possible. The severity of hepatotoxicity is classified into mild, moderate and severe according to the WHO toxicity classification standards[31]. The clinical types of hepatotoxicity are classified into hepatocellular, cholestatic or mixed types based on the ratio (R) of elevation of baseline ALT to baseline alkaline phosphatase[30].

Sample size calculation

The sample size calculation was based on the genetic susceptibility study to be carried out in the future. We were interested in calculating the sample size needed for an effect size (odds ratio) of 2.0 with at least 90 percent power under the dominance model, where the minor allele frequency was set at 10%, with a type Ⅰ error level of 0.05 under a matched case-control study design. The incidence of ATDH in Chinese anti-TB treatment patients is 11.9%[16]. The Quanto statistical program (version 1.2.4, University of Southern California, USA)[32] was used to calculate the sample size of a genetic susceptibility study for ATDH. The calculated sample size was 253 ATDH cases. This number of cases can be obtained from 2126 (253/11.9%) TB patients who finished anti-TB treatment. Based on our previous ADACS cohort, and considering a loss of follow-up rate of 4%, a participation rate of eligible subjects of 71.2%, and an exclusion rate of 2.4%[16, 21], the calculated sample size was 3187 TB patients. Therefore, we set the target sample size to 3200 newly diagnosed TB patients.

Data analysis plan

Continuous variables will be described as the mean ± standard deviation or as median with interquartile range, and differences between groups will be analyzed by one-way analysis of variance or nonparametric tests. Blood biochemical indicators in different groups at different times will be compared using variance analysis of repeated measures data. Categorized variables will be expressed as numbers and percentages and analyzed by χ^2 tests or a logistic regression model. The incidence of different ADEs/ADRs will be reported by descriptive statistics, and subgroup analysis will be used to provide descriptive results for different groups of patients. A matched nested case-control study will be used to analyze the influencing factors on the incidence. Multivariate conditional logistic regression analysis will be used to estimate the association between various factors and the risk of ADRs by odds ratios (ORs) and 95% confidence intervals (CIs), with potential confounders as covariates. All analyses were performed using SPSS for Windows (version 20.0, IBM Inc., Chicago, IL, USA). A two-tailed P value <0.05 will be considered significant.

Ethics and dissemination

Ethical approval

This study is an observational research study conducted in a real-world medical environment and has been approved by the ethics committee of Nanjing Medical University. Written informed consent will be signed by every patient or a surrogate before enrollment. Patients can withdraw from the study at any point with no effect on their clinical care. The patients' blood sample in this study will come from the residual blood samples after routine laboratory tests, which will not increase the amount of blood taken or the number of blood samples taken. All data will be kept anonymous and managed with confidentially.

Dissemination

The findings of the study will be published in peer-reviewed journals and will be presented at national and international conferences.

Discussion

China is one of the 20 highest TB-burdened countries[1], and in 2010, TB was more prevalent in rural areas (163/100000) than urban ones (73/100000)[33], which is one of the causes of unfavorable treatment outcomes[34]. A previous study showed that patients from rural areas were less aware of ADRs than those from urban areas[35]. Therefore, in the case of many rural TB patients in China, a key issue in treatment success is to improve their self-reporting rates of ADEs/ADRs. Furthermore, the potential of patient self-reporting has been described in the literature as a noteworthy source of new information about early detection of new, rare and serious ADRs[36]. The information provided by patient reports can also be significant in ADR detection[37]. However, patient self-reporting rates and awareness are still low[38]. In recent years, many electronic methods have been used to increase reporting rates, especially in cancer treatment[39-41], but those methods are obviously inappropriate for Chinese rural patients in a developing country. In the present study, a method combining active self-recorded diaries and passive scheduled laboratory tests was used to enhance the identification of adverse reactions. In our previous ADACS cohort study, active self-recorded diaries were used in TB patients during treatment, which were simple, practical and easy to maintain[16]. The local supervising doctors regularly checked and reviewed the patient records and timely identified some problems. In addition, the local free-TB service policy, especially free liver function tests in the first two months, also facilitates the timely detection of ADEs/ADRs. Most ADRs induced by anti-TB drugs occur within the first two months of treatment[6, 42], including MDR-TB treatment[43]. Therefore, our approach may be a good way to identify ADEs/ADRs during home-based anti-TB treatment.

One of the purposes of ADR monitoring is to identify risk factors that may predispose, induce or influence the development, severity and incidence of adverse reactions in population samples, such as genetics, racial differences, diets, diseases, prescribing practices, cultures of drug use and traditions of the people[44]. Our study will not only evaluate the incidence of ADEs/ADRs but will also collect samples for future research on risk factors for ADEs/ADRs, such as genetic polymorphisms. The sample size calculation of this protocol was based on studies of genetic analyses of ATDH. In previous studies, the sample sizes used have been relatively small (ranging from 8[45] to 461[46]), which makes it difficult to achieve an adequate statistical power. Furthermore, too small a sample size to detect true evidence for an association increases false negative rates and reduces the reliability of a study[47], which is one of the reasons for heterogeneity of results between different studies. Additionally, plasma specimens collected at different time points during treatment from each patient are also important for ADR studies. Previous studies have shown that oxidative stress, and more broadly, disturbances in redox homeostasis alongside mitochondrial dysfunction, may contribute to the hepatotoxicity induced by first-line anti-TB drugs[48]. A rat study suggested that INH may initiate its toxicity in liver mitochondria through interactions with electron transfer chains, lipid peroxidation, mitochondrial membrane potential decline and cytochrome c expulsion, which ultimately leads to cell death[49]. The activity of glutathione in ATDH patients is reduced and the level of malondialdehyde is increased[50]. In addition, plasma specimens could be used to study the relationships among the changes in blood drug concentration, oxidative stress index and ADRs, which facilitate the study of mechanisms from the perspective of the population.

The HATTAR study will be conducted similarly to our previous population-based cohort study, which provides a good technical basis for us to carry out some new research. However, there are still two limitations in our study. One limitation is that we will recruit all eligible patients, including the floating population, who will add uncertainty to the follow-up. The floating population is a high-risk group not only for tuberculosis infection[51] but also for treatment failure or drug-resistance[52]. Although the risk of being lost to follow-up of this population is high, risk factor studies of ADRs in this population are still helpful in improving treatment adherence. In addition, considering safety and practical necessity, rechallenge with the drug suspected of causing the ADRs will not be done in this study. Furthermore, among the first line anti-TB drugs prescribed, INH, RIF and PZA are potentially hepatotoxic[31]. Under the combination therapy strategy, it is difficult to judge which drug or drug combination is the main causative agent leading to ADRs.

Contributors SWT and HQP obtained the research funding and is the principal investigator of the study. MMY, HQP and LHL conceived and designed this study. MMY and HQP drafted the manuscript. XMH, HBC, BLT, WPL, HGY and SWT all participated in the final design of the study and revisions of this manuscript.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The ethics committees of Nanjing Medical University (NMU 2018-579).

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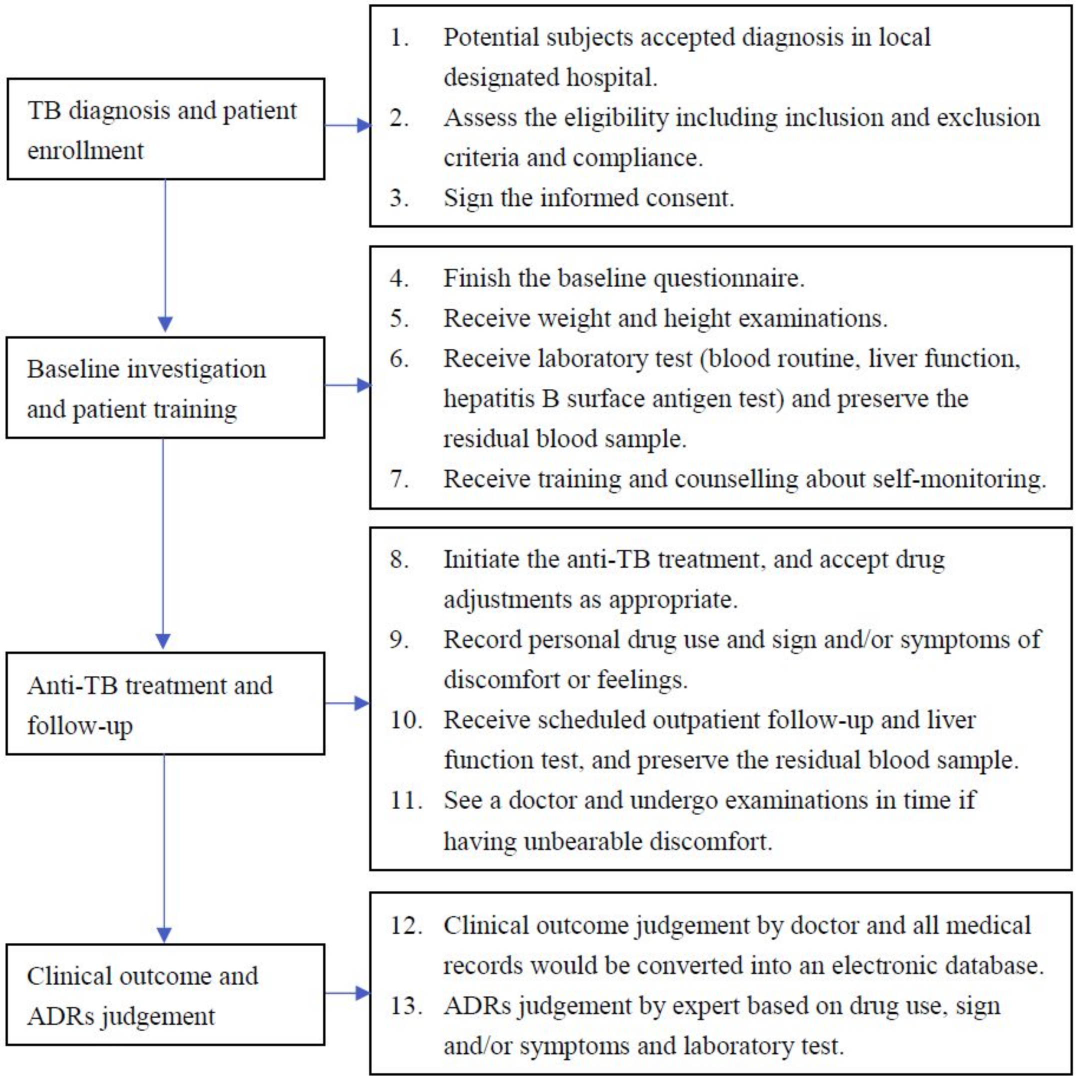

Figure 1 Flow chart of study design and procedures. TB, tuberculosis; ADRs, adverse drug reactions.

The Home-based Anti-Tuberculosis Treatment Adverse Reactions (HATTAR) study: a protocol for a prospective observational study

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The Home-based Anti-Tuberculosis Treatment Adverse Reactions (HATTAR) study: a protocol for a prospective observational study

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ABSTRACT

Introduction Tuberculosis (TB) continues to be an important public health problem throughout much of the world. Drug treatment is the only effective treatment method, but adverse drug events (ADEs) and adverse drug reactions (ADRs) can affect medication adherence. As the number of drug-resistant TB patients and the number of anti-TB drugs have increased, it is necessary to explore the risk factors for ADEs/ADRs in order to reduce their occurrence. This study aims to build a home-based anti-TB treatment cohort and to recognize the incidences, prognosis and risk factors of anti-TB drug-induced ADEs/ADR in real-world experiences.

Methods and analysis This study is a multicentre, prospective observational cohort study. The study population will consist of 3200 newly diagnosed TB patients between January 2019 and December 2020. After initiating the anti-TB treatment, all patients will be followed up until finishing treatment unless they withdraw, and we will record personal drug use and signs and/or symptoms of discomfort. Patients will receive scheduled laboratory tests in designated hospitals every two weeks during the first two months, and the residual blood sample after conducting the laboratory tests will be preserved. The ADEs/ADRs will be placed into 8 categories: liver dysfunction, gastrointestinal reactions, drug allergy, arthralgia or muscle pain, nervous system disorders, hematologic system disorders, renal impairment and others.

Ethics and dissemination This study protocol has been approved by the ethics committees of Nanjing Medical University. All patients will give written informed consent before enrollment. The findings of the study will be published in peer-reviewed journals and will be presented at national and international conferences.

Keywords

Anti-tuberculosis treatment, adverse drug reactions, prospective observational study

Strengths and limitations of this study

- This is a prospective study design with a home-based, large-scale consecutive anti-TB treatment cohort under real-world experiences in China.
- A method combining active self-recorded diaries and passive scheduled laboratory tests will be used to enhance the identification of adverse reactions.
- The residual blood sample after the laboratory tests will be preserved for future research.
- A limitation is that it will recruit the potential eligible patients, including a floating population, who will add uncertainty to the follow up.

Introduction

Tuberculosis (TB) is one of the top 10 causes of death and the leading cause from a single infectious agent. In 2017, approximately 10.0 million people developed TB disease, and TB caused an estimated 1.3 million deaths[1]. Drug treatment is the only effective treatment method for TB, and the World Health Organization (WHO) has implemented a standardized directly observed treatment, the short-course (DOTS)/Stop TB Strategy, to improve TB prevention and control. Although the WHO set the global target rate for a successful treatment outcome at 85%[2], the treatment success rate remains low, at 82% for all TB patients and 55% for drug-resistant TB (DR-TB) patients[1]. Many factors have influenced the treatment success rate, such as sociodemographic and socioeconomic factors, nutrition, HIV, drug resistance, and strategies for TB management including DOTS[3]. Additionally, effective chemotherapy is largely based on patients' willingness to comply with the prescribed regimen, and adverse drug events (ADEs) and adverse drug reactions (ADRs) are significant factors affecting the adherence of patients to medications[4]. According to WHO, an ADE is defined as any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment[5]; and an ADR is any response to a drug that is noxious and unintended and that occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function[6]. Long-term anti-TB combination regimens could lead to various types and levels of ADEs/ADRs, which could subsequently lead to treatment discontinuation or interruption, treatment time extension and an increased risk for developing drug resistance, treatment failure and relapse[7]. All of these negative consequences have posed a challenge to TB treatment and have implications for TB control.

Amongst the various ADEs/ADRs, the most common ones induced by first-line anti-TB drugs are hepatotoxicity, gastrointestinal disorders, allergic reactions, arthralgia, neurological disorders[8], while in multidrug-resistant TB (MDR-TB) patients, common types are arthralgia, gastrointestinal disorders, hypothyroidism, dermatologic disorders, hematologic disorders, hepatotoxicity, ototoxicity, and nervous system or psychiatric disorders[9]. TB patients treated by second-line anti-TB drugs in the context of high HIV coinfection had more severe ADEs/ADRs, and the most common severe type reported was hearing loss or ototoxicity[10]. Women, patients of an advanced age and recurrent TB patients were found to be at a higher risk of leukopenia[11]. As problems such as DR-TB, MDR-TB, extensively drug-resistant TB (XDR-TB), and a recently emerging threat by a totally drug-resistant TB (TDR-TB) are increasing in prevalence, several novel drugs will cause a significant shift in the landscape of TB treatment but can cause some other ADEs/ADRs. For example, bedaquiline and delamanid can prolong cardiac QTc[12, 13]. The majority of TB patients receive community-based or home-based treatment; however, most studies of ADRs are hospital-based[9-11]. Treatment interruption due to ADEs/ADRs could decrease the chance of a cure[14] and lead to patient loss to follow-up, further increasing the development of drug resistance[15]. Additionally, community-based care for MDR-TB patients is more effective than care in a central specialized hospital[16]. Home-based care could increase MDR-TB treatment success[16] and has potential in improving treatment outcomes[17]. Therefore, it is necessary to strengthen research on ADEs/ADRs in home-based anti-TB treatment.

Between October 2007 and June 2008, a cohort of Anti-tuberculosis Drugs induced Adverse Reactions in China National Tuberculosis Prevention and Control Scheme Study (ADACS) was established by us in China[18]. Based on this cohort, ADRs and genetic susceptibility in anti-TB treatment patients were widely studied[8, 19-23], which made a great contribution to the pharmacoepidemiology of Chinese TB patients. However, two limitations cannot be ignored. First, blood samples were collected with FTA cards, which could not be used in subsequent high-throughput genomics studies and led to the inability to conduct serum marker studies. The combination of chemical, biological, and large-scale observational health data is critical to predict ADRs in both individual patients and global populations[24]. In addition, serum or plasma samples obtained both before and during treatment of all subjects are also needed to enable future studies of new proteomic, metabonomic and other soluble biomarkers or predictors of drug induced hepatotoxicity[25]. Second, only sputum smear-positive pulmonary TB patients treated with the DOTS strategy were included, and the percentage of bacteriologically confirmed cases amongst total new and relapsed pulmonary TB cases was only 32% in 2017[1]. Thus, it is necessary to study ADRs in other types of patients. In addition to first-line drugs, the number of second-line drugs and new drugs for treating different types of DR-TB patients are also gradually increasing[12], and ADRs induced by those drugs still need further study. Thus far, there are no other similar new cohorts in China that can satisfy the need for a study of ADEs/ADRs.

For these reasons, we plan to establish a new prospective observational cohort, the Home-based Anti-Tuberculosis Treatment Adverse Reactions (HATTAR) study, based on newly diagnosed TB patients receiving home-based anti-TB treatment in China, and to recognize the incidences, prognosis and risk factors of anti-TB drug-induced ADRs in real-world experiences. The goals are as follows:

(1) To complete an epidemiological survey of anti-TB treatment patients, including baseline characteristics, diagnosis and treatment, clinical outcomes, ADEs/ADRs, risk factors, and to evaluate the incidence of various ADEs/ADRs in this population.

(2) To build a biological specimen bank for future research, including plasma and blood cells at different treatment times and incorporating existing routine biochemical test results.

(3) To explore demographic factors, genetic variants and environmental risk factors relevant to anti-TB induced ADEs/ADRs, and their interactions.

Methods and analysis

Study design

This is a multicentre, prospective observational cohort study of Chinese patients being treated for TB, sponsored by Nanjing Medical University. The participating hospitals are two infectious disease hospitals and two local designated TB diagnosis and treatment centres in general hospitals located in Jiangsu Province of China.

Study population

Recruitment of a baseline cohort of 3200 newly diagnosed TB patients will be conducted between January 2019 and December 2020. The patients will be followed up until finishing anti-TB treatment.

Newly diagnosed TB patients who are ready to receive anti-TB treatment, are willing to join the study and sign the informed consent form or have a surrogate do so will be included in this study.

Exclusion criteria: (1) having a psychiatric disease and unable to fill out the self-recorded diaries during the anti-TB treatment and (2) having a severe disease with a life-expectancy shorter than 6 months.

Withdrawal criteria: (1) unwilling to continue participating in the study; (2) loss to follow-up (stopping the drugs for longer than 2 months); (3) developing serious diseases that prevent them from continuing anti-TB treatment; (4) moving or travelling and thus missing all the scheduled laboratory tests in the first two months; and (5) death that is not caused by TB or anti-TB drug-induced ADRs.

Study protocol

This study protocol was based on the National Tuberculosis Prevention and Control Planning and the Guideline for TB Diagnosis and Treatment in China[26], which consists of four main steps: TB diagnosis and patient enrollment, baseline investigation and patient training, anti-TB treatment and follow-up, clinical outcome and ADRs classification. A flow chart of the study design and procedures is shown in Figure 1.

TB diagnosis and patient enrollment

Potential subjects will be recruited from Zhenjiang, Changshu, Taixing, and Jurong between January 2019 and December 2020 and diagnosed based on Chinese national TB diagnostic guidelines (WS288-2017), which rely on clinical judgement based on symptoms, chest radiography, tuberculin skin tests, and smear microscopy.

If newly diagnosed TB patients meet the inclusion criteria, the doctors will explain the study to the patients and invite them to participate. If the patients agree, informed consent will be signed by the patient or a surrogate.

Baseline investigation and patient training

TB patients who have been recruited will complete the baseline questionnaire, including personal history of diseases and smoking and drinking habits, and undergo anthropometric measurements (weight and height). The patients will also be subjected to blood collection and laboratory tests, including routine blood tests and liver function and hepatitis B surface antigen tests. The residual blood sample of each patient will be separated into plasma and blood cells according to the standard laboratory protocol and then immediately frozen at −40℃.

The enrolled TB patients will receive training and counselling about medication knowledge and self-monitoring knowledge, for example, the importance of scheduled liver function tests, how to fill out the self-recorded diaries, what uncomfortable symptoms need to be recorded, and how to get consulting services.

Anti-TB treatment and follow-up

Once diagnosed with TB, patients will begin to receive standardized anti-TB treatment according to the WHO guidelines for the treatment of drug-susceptible and drug-resistant TB[27, 28]. For example, in patients with drug-susceptible pulmonary TB, isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) will be given for 2 months in the intensive phase, and then, INH and RIF, for the 4 months of the continuation phase. The doctors can decide whether hospitalization admission is needed according to the patient's condition. Inpatients after discharge and other patients who do not need hospitalization admission will receive community- or home-based DOTS regimens. The doctors can also change or adjust the medication according to the patient's condition during the treatment period.

After initiating the anti-TB treatment, all patients will be followed up until finishing treatment unless they withdraw. Patients will be asked to record personal drug use and signs and/or symptoms of discomfort or unfavorable feelings in the self-recorded diaries. During the first two months, patients will receive scheduled outpatient follow-up and liver function tests every two weeks in the designated hospital according to the local free-TB service policy. If patients exhibit unbearable discomfort or some symptoms of suspected hepatitis (such as anorexia, nausea, vomiting, malaise, or tea-colored urine) or other diseases, they should see a doctor and undergo examinations. After the first two months, patients can volunteer to go to the hospital for medical examinations.

During the treatment, if suspicious ADEs emerge, the local supervising doctors will conduct investigations to rule out other possible causes and fill out the relevant questionnaire. If the scheduled laboratory tests of the patients without any discomfort show an abnormality, the ADE investigation procedure will also be activated. Furthermore, the local supervising doctors will be required to actively contact the patients and check their self-recorded diaries for signs and/or symptoms of ADEs/ADRs and drug use. Additionally, the residual blood sample of each patient after the scheduled laboratory tests will be preserved and frozen at −40°C.

Every TB patient in Jiangsu Province has a special outpatient medical record, which is used to record all of the treatment behaviors of patients throughout the treatment period, including basic personal information, diagnosis, medication history, laboratory test, and suspicious ADEs/ADRs. In addition, every local supervising doctor will be provided with a registration and management card for every TB patient, which will be used to record basic personal information, patient management methods and treatment outcomes. Both the medical record and the management card are based on the patient's China ID number.

Clinical outcome and ADRs classification

When all TB patients finish treatment, the local supervising doctors will comprehensively judge the patient's treatment outcomes according to the WHO definitions (cured, treatment completed, treatment failed, died, lost to follow-up, not evaluated, treatment success), and record them on the management card of every patient. The outpatient medical record and the management card will be collected and converted into an electronic database.

Based on medication records, symptoms, signs, laboratory test results, relevant investigations and self-recorded diaries, local supervising doctors will be able to judge ADEs preliminarily. Experts from the ADRs monitoring centre will regularly review and verify the judgements and classify all of the ADEs into 8 categories as follows[8, 29]: (1) liver dysfunction, including elevated transaminase and jaundice; (2) gastrointestinal reactions, including nausea, vomiting and diarrhea; (3) drug allergy, including pruritus and rash; (4) arthralgia or muscle pain; (5) nervous system disorders, including sleep disorders, dizziness, headache, tinnitus and hearing loss; (6) hematologic system disorders, including anemia and leukopenia; (7) renal impairment, including decline of renal function, positive urine protein and renal failure; and (8) cardiac injury, including QT prolongation; (9) others. Finally, the experts will conduct causality assessments based on the WHO-UMC causality assessment system[30] and the Roussel Uclaf Causality Assessment Method (RUCAM)[31] and judge some ADEs as ADRs according to the criteria.

Anti-TB drug-induced hepatotoxicity (ATDH) is defined as (1) an increase in alanine aminotransferase (ALT) levels greater than two times the upper limit of normal (ULN) with/without a combined increase in aspartate aminotransferase (AST) and total bilirubin levels provided one of them was greater than two times the ULN during the treatment[32] or (2) the causality assessment result is highly probable, probable or possible. The severity of hepatotoxicity is classified into mild, moderate and severe according to the WHO toxicity classification standards[33]. The clinical types of hepatotoxicity are classified into hepatocellular, cholestatic or mixed types based on the ratio (R) of elevation of baseline ALT to baseline alkaline phosphatase[32].

Sample size calculation

The sample size calculation was based on the genetic susceptibility study to be carried out in the future. We were interested in calculating the sample size needed for an effect size (odds ratio) of 1.8 with at least 90 percent power under the dominance model, where the minor allele frequency was set at 10%, with a type Ⅰ error level of 0.05 under a matched case-control study design. The incidence of ATDH in Chinese anti-TB treatment patients is 11.9%[18]. The Quanto statistical programme (version 1.2.4, University of Southern California, USA)[34] was used to calculate the sample size of a genetic susceptibility study for ATDH. The calculated sample size was 354 ATDH cases. This number of cases can be obtained from 2975 (354/11.9%) TB patients who finished anti-TB treatment. Considering a withdrawal or loss of follow-up rate of 6%[23], the calculated sample size was 3165 TB patients. Therefore, we set the target sample size to 3200 newly diagnosed TB patients. Based on our previous ADACS cohort, and setting the exclusion rate to 2.4% and the participation rate of eligible subjects to 71.2%[23], at least 4600 newly diagnosed TB patients will be needed within two years. According to the number of newly diagnosed TB patients in each hospital per year (600 patients per hospital), the total number of TB patients in four hospitals is almost 2400 per year, which fully meets the sample size requirement in two years.

Data analysis plan

Continuous variables will be described as the mean ± standard deviation or as median with interquartile range, and differences between groups will be analyzed by one-way analysis of variance or nonparametric tests. Blood biochemical indicators in different groups at different times will be compared using variance analysis of repeated measures data. Categorized variables will be expressed as numbers and percentages and analyzed by χ^2 tests or a logistic regression model. The incidence of different ADEs/ADRs will be reported by descriptive statistics, and subgroup analysis will be used to provide descriptive results for different groups of patients. Unmatched nested case-control study will be used to analyze the influencing factors on the incidence of ADRs (including ATDH).Patients who fulfilled the ATDH criteria will be assigned to the case group, whereas controls will be selected from those with sustained normal liver function through the whole therapy. Furthermore, matched nested case-control study will be used to explore the role of genetic variations (single nucleotide polymorphisms, SNPs) in susceptibility to ATDH. For each ATDH case, two controls will be selected randomly and matched for the place of sample collection, age (within 5 years), sex and treatment history. Multivariate conditional logistic regression analysis will be used to estimate the association between various factors and the risk of ADRs by odds ratios (ORs) and 95% confidence intervals (CIs), with potential confounders as covariates. The Cox proportional-hazards regression model will be used in the analysis of time-to-event data. Bonferroni correction method will be applied to adjust the P value for multiple comparisons. All analyses will be performed using SPSS for Windows (version 20.0, IBM Inc., Chicago, IL, USA). A two-tailed *P* value <0.05 will be considered significant.

Patient and public involvement

Patients or public were not involved in the development of the research question and study design or conducting the present study. All participants will be informed of the results through post or email.

Ethics and dissemination

Ethical approval

This study is an observational research study conducted in a real-world medical environment and has been approved by the ethics committee of Nanjing Medical University. Written informed consent will be signed by every patient or a surrogate before enrollment. Patients can withdraw from the study at any point with no effect on their clinical care. The patients' blood sample in this study will come from the residual blood samples after routine laboratory tests, which will not increase the amount of blood taken or the number of blood samples taken. All data will be kept anonymous and managed with confidentially.

Dissemination

The findings of the study will be published in peer-reviewed journals and will be presented at national and international conferences.

Discussion

China is one of the 20 highest TB-burdened countries[1], and in 2010, TB was more prevalent in rural areas (163/100000) than urban ones (73/100000)[35], which is one of the causes of unfavorable treatment outcomes[36]. A previous study showed that patients from rural areas were less aware of ADRs than those from urban areas[37]. Therefore, in the case of many rural TB patients in China, a key issue in treatment success is to improve their self-reporting rates of ADEs/ADRs. Furthermore, the potential of patient self-reporting has been described in the literature as a noteworthy source of new information about early detection of new, rare and serious ADRs[38]. The information provided by patient reports can also be significant in ADR detection[39]. However, patient self-reporting rates and awareness are still low[40]. In recent years, many electronic methods have been used to increase reporting rates, especially in cancer treatment[41-43], but those methods are obviously inappropriate for Chinese rural patients in a developing country. In the present study, a method combining active self-recorded diaries and passive scheduled laboratory tests was used to enhance the identification of adverse reactions. In our previous ADACS cohort study, active self-recorded diaries were used in TB patients during treatment, which were simple, practical and easy to maintain[18]. The local supervising doctors regularly checked and reviewed the patient records and timely identified some problems. In addition, the local free-TB service policy, especially free liver function tests in the first two months, also facilitates the timely detection of ADEs/ADRs. Most ADRs induced by anti-TB drugs occur within the first two months of treatment[8, 44]. Therefore, our approach may be a good way to identify ADEs/ADRs during home-based anti-TB treatment.

One of the purposes of ADR monitoring is to identify risk factors that may predispose, induce or influence the development, severity and incidence of adverse reactions in population samples, such as genetics, racial differences, diets, diseases, prescribing practices, cultures of drug use and traditions of the people[45]. Our study will not only evaluate the incidence of ADEs/ADRs but will also collect samples for future research on risk factors for ADEs/ADRs, such as genetic polymorphisms. The sample size calculation of this protocol was based on studies of genetic analyses of ATDH. In previous studies, the sample sizes used have been relatively small (ranging from 8[46] to 461[47]), which makes it difficult to achieve an adequate statistical power.

Furthermore, too small a sample size to detect true evidence for an association increases false negative rates and reduces the reliability of a study[48], which is one of the reasons for heterogeneity of results between different studies. Additionally, plasma specimens collected at different time points during treatment from each patient are also important for ADR studies. Previous studies have shown that oxidative stress, and more broadly, disturbances in redox homeostasis alongside mitochondrial dysfunction, may contribute to the hepatotoxicity induced by first-line anti-TB drugs[49]. A rat study suggested that INH may initiate its toxicity in liver mitochondria through interactions with electron transfer chains, lipid peroxidation, mitochondrial membrane potential decline and cytochrome c expulsion, which ultimately leads to cell death[50]. The activity of glutathione in ATDH patients is reduced and the level of malondialdehyde is increased[51]. In addition, plasma specimens could be used to study the relationships amongst the changes in blood drug concentration, oxidative stress index and ADRs, which facilitate the study of mechanisms from the perspective of the population.

The HATTAR study will be conducted similarly to our previous population-based cohort study, which provides a good technical basis for us to carry out some new research. However, there are still two limitations in our study. One limitation is that we will recruit the potential eligible patients, including the floating population (namely, people who engage in partial temporary relocation, whose registration of legal residence remains in their original place of habitation and who are ineligible for permanent residence in the locale into which they moved[52]), who will add uncertainty to the follow-up. The floating population is a high-risk group not only for tuberculosis infection[53] but also for treatment failure or drug-resistance[54]. Although the risk of being lost to follow-up of this population is high, risk factor studies of ADRs in this population are still helpful in improving treatment adherence. In addition, considering safety and practical necessity, rechallenge with the drug suspected of causing the ADRs will not be done in this study. Furthermore, amongst the first line anti-TB drugs prescribed, INH, RIF and PZA are potentially hepatotoxic[33]. Under the combination therapy strategy, it is difficult to judge which drug or drug combination is the main causative agent leading to ADRs.

Contributors SWT and HQP obtained the research funding and is the principal investigator of the study. MMY, HQP and LHL conceived and designed this study. MMY and HQP drafted the manuscript. XMH, HBC, BLT, WPL, HGY and SWT all participated in the final design of the study and revisions of this manuscript.
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Competing interests None declared.
Patient consent Obtained.
Ethics approval The ethics committees of Nanjing Medical University (NMU 2018-579).

Figure 1 Flow chart of study design and procedures. TB, tuberculosis; ADRs, adverse drug reactions.

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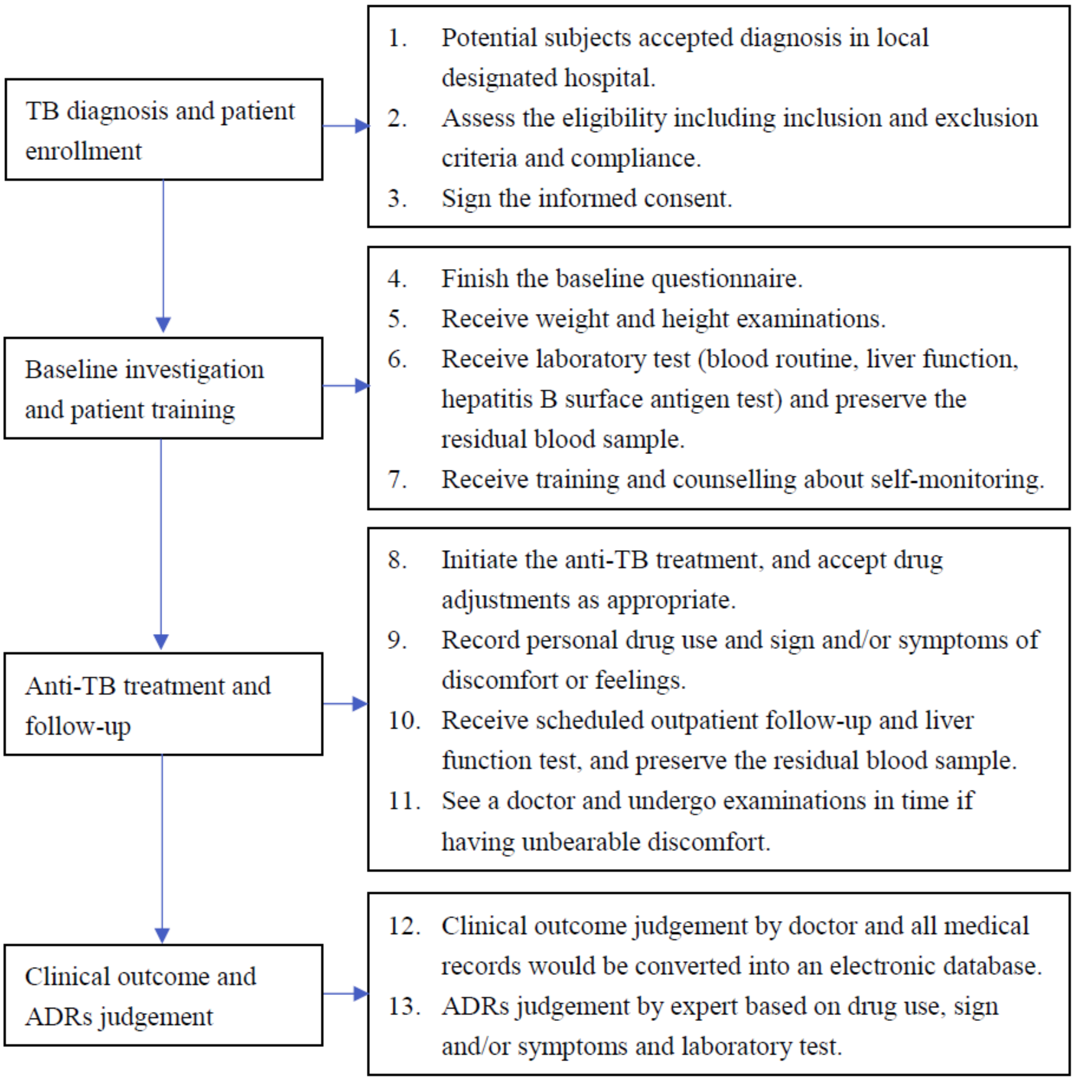

Figure 1 Flow chart of study design and procedures. TB, tuberculosis; ADRs, adverse drug reactions.