UNIVERSITAS INDONESIA

PATIENT ADHERENCE IN MDR-TB PATIENTS DURING PRIMARY TB TREATMENT: ITS ASSOCIATION WITH PATIENT COMPLIANCE

SKRIPSI

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A final project report presented to Universitas Indonesia
in partial fulfilment of the requirements for the
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STATEMENT OF ORIGINALITY

This final project (undergraduate) is of my own composition.

Any and all outside resources, whether quoted or referenced,

have been stated as such.

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ENDORSEMENT PAGE

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Research title	: Patient Adherence in MDR-TB Patients during Primary TB Treatment: Its Association with Patient Compliance

Has successfully been scrutinized in front of The Board of Examiners and accepted as a prerequisite towards attaining the *Sarjana Kedokteran* (Bachelor of Medicine) degree from the Faculty of Medicine, Universitas Indonesia.

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Jakarta, 20 May 2011
The Author

AGREEMENT OF FINAL YEAR PROJECT PUBLICATION FOR ACADEMIC PURPOSES

As an academic member of Universitas Indonesia, I, the undersigned:

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Date: 27 May 2011
Signed,

(Alberta Jesslyn Gunardi)

ABSTRAK

Pengarang : Alberta Jesslyn Gunardi
Program Studi : Pendidikan Dokter
Judul : Kepatuhan Pasien Meneruskan Pengobatan pada Pasien MDR-TB selama Pengobatan TB Pertama: Hubungan dengan Kepatuhan Pasien Makan Obat Sesuai Jadwal

Kemunculan dari MDR-TB telah menjadi masalah kesehatan yang penting dan mengancam kontrol TB sedunia. Beberapa faktor resiko dihubungkan dengan perkembangan MDR-TB pada pasien yang pernah menjalani pengobatan TB, termasuk kepatuhan pasien meneruskan pengobatan. Penilitian ini ditujukan untuk mencari bagaimana kepatuhan pasien MDR-TB meneruskan pengobatan sewaktu pengobatan TB yang pertama kali. Selain itu hubungan dengan kepatuhan pasien makan obat sesuai jadwal juga diteliti. Penilitian ini menggunakan metode *cross sectional* dengan mewawancarai pasien MDR-TB di RS Persahabatan, Jakarta selama bulan Desember 2009 sampai Agustus 2010 (n=50). Hasil menunjukan bahwa mayoritas pasien patuh meneruskan pengobatan terhadap pengobatan TB yang pertama kali. Penelitian ini menemukan bahwa tidak adanya hubungan antara kepatuhan pasien meneruskan pengobatan dan kepatuhan pasien makan obat sesuai jadwal sewaktu pengobatan TB yang pertama kali.

Kata kunci : TB, MDR-TB, Kepatuhan Pasien Meneruskan Pengobatan, Kepatuhan Pasien Makan Obat Sesuai Jadwal

ABSTRACT

Author : Alberta Jesslyn Gunardi
Study Program : Medicine
Title : Patient Adherence in MDR-TB Patients during Primary TB Treatment: Its Association with Patient Compliance

The emergence of MDR-TB has become an important health issue and threatens TB control worldwide. Various risk factors are identified to contribute the development of MDR-TB from previous TB treatment, including patient adherence. This study aims to find out how the MDR-TB patient adherence during their primary TB treatment. In addition, the association with patient compliance is analyzed. This is a cross-sectional study by interview to MDR-TB patients in Persahabatan Hospital, Jakarta during December 2009 until August 2010 (n=50). Results show that majority of the patients adhere to their primary TB treatment. This study finds there is no association between patient adherence and compliance during primary TB treatment.

Keywords : TB, MDR-TB, Patient Adherence, Patient Compliance

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CHAPTER 1: INTRODUCTION

1.1 Background

Tuberculosis as an infectious disease is one of the top ten leading cause of death in the world. Around one third of the world's population is currently infected with *Mycobacterium tuberculosis*, the causal agent of this disease.[1] It is also responsible for 1,7 million deaths in 2009.[2] Indonesia is categorized as the third high burden countries of TB after India and China by WHO with the number of patients about 10% of the total number of TB patients worldwide.[3,4]

In addition, the emergence of multidrug-resistant tuberculosis (MDR-TB) has become an important health problem and threatens TB control worldwide. In order to be categorized as MDR-TB, the *M. tuberculosis* should be resistant to at least isoniazid (H) and rifampicin (R), the two most powerful anti-TB drugs, with or without resistant to other anti-TB drugs.

There were an estimated 440.000 new MDR-TB cases in 2008 and 150.000 deaths from MDR-TB.[2] However, MDR-TB can also be a continuation from TB. According to 2010 Global Report on Surveillance and Response, five of the countries: Azerbaijan, Kazakhstan, Republic of Moldova, Tajikistan and Uzbekistan, reported that MDR-TB proportions of 50% or more among previously treated TB cases.[5] In Indonesia, about 17% of MDR-TB cases are among previously treated TB cases.[6]

Annually, more than 400.000 cases of MDR-TB come out. These MDR-TB cases are resulted from under investments in basic activities to control TB, transmission of drug-resistant strains, and poor management of anti-TB drugs[7]. Those interfere genetic strains and make mutation of resistance in the chromosome spontaneously.

Mario Raviglione as WHO's director of Stop TB Department said lack of inspection control and diagnostics, and poor treatment adherence have increased

occurrences of multi-drug resistant TB.[8] According to Johnson et al, in a study of positive AFB smear of pulmonary TB patients found a high incidence of drug resistance in previous treatment defaulters.[9] Not only patient adherence that can influence the occurrences of resistance, but also patient compliance. Adherence and compliance are usually thought to have the same meaning. However, in this study, patient adherence means that the patient continues the medical treatment after the initial phase or the first 2 months to the continuation phase.

1.2 Identification of Problems

Based on the background that has been explained above, there are several research questions arises and this study wants to identify:

1. How is the MDR-TB patient adherence during primary TB treatment?
2. How is the MDR-TB patient compliance during primary TB treatment?
3. Does patient adherence associate with patient compliance in MDR-TB patients during primary TB treatment?

1.3 Research Scope

This study only includes subjects who are MDR-TB patient who are at the time of interview undergoing MDR-TB treatment in MDR-TB Clinic, Persahabatan Hospital, East Jakarta. This limited population is chosen because they are enrolled to the pilot project of MDR-TB treatment in Indonesia. Thus, organized data of the MDR-TB patient is available.

This project is part of a bigger project by a six members group. Each member investigates one or more risk factors that may contribute to the development of TB towards MDR-TB. This study only accounts patient adherence and patient compliance as the possible risk factors.

This study investigates the patient adherence during the primary TB treatment. In addition, this study also looks into the association between patient adherence and patient compliance during the primary TB treatment.

1.4 Hypothesis

This study compares patient adherence and compliance in primary TB treatment. Thus, hypothesis of this study is formulated as follows:

H1: Patient adherence associates with patient compliance in primary TB treatment.

1.5 Research Objective

1.5.1 General Objective

1. Identify and analyze patient adherence during primary TB treatment as contributing factor that may lead to development of TB towards MDR-TB

1.5.2 Specific Objectives

1. To describe MDR-TB patient adherence during primary TB treatment
2. To describe MDR-TB patient compliance during primary TB treatment
3. To find out the association between patient adherence and compliance in MDR-TB patients during primary TB treatment

1.6 Research Benefit

1.6.1 Benefit for Researchers

1. To develop an interest in the research field
2. To gain experience and knowledge in doing research
3. To train and apply effective communication skill within society
4. To gain more knowledge about MDR-TB such as its epidemiology, treatment and etc
5. To know about MDR-TB patient adherence and compliance

1.6.2 Benefits for University

1. To hold the principle of tri dharma of higher institution while perfoming the functions of the institution as a means for education, research and community service

2. To contribute to the vision of Faculty of Medicine University of Indonesia to be one of the research faculty of medicine in Asia Pacific 2010 and top 80 in the world in 2014

3. To take a part in giving rise to Faculty of Medicine University of Indonesia's graduates as seven stars doctors, which is one of them is researcher

1.6.3 Benefits for Clinician

1. To give empirical data for future clinicians, general practitioners and specialists to be used in daily clinical practice

1.6.4 Benefit for Community

1. To give the society more knowledge about MDR-TB
2. To give the society suggestion to comply and adhere to TB treatment

1.6.5 Benefit for Government & Policy Makers

1. To give recommendation for government & policy makers to shape national TB management program.

CHAPTER 2: LITERATURE REVIEW

2.1 TB

Tuberculosis as one of the oldest diseases known to affect humans is a major cause of death worldwide. This disease mostly affects the lungs, although other organs are involved in up to 33% of cases. Transmission is usually through the airborne spread of droplet produced by patients with infectious pulmonary tuberculosis. Where the waxy outer coat of mycobacteria allows them to withstand drying and therefore survive for long periods of time in air and house dust.[10]

2.1.1 Etiology

Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the *M. tuberculosis* complex, the most common and important agent of human disease is *M. tuberculosis*. The complex also includes *M. bovis*, *M. caprae*, *M. africanum*, *M. microti, M. pinnipedii*, and *M. canettii*.[11]

M. tuberculosis is a rod-shaped, non-spore-forming, thin aerobic bacterium. Mycobacteria, including *M. tuberculosis*, are often neutral on Gram's staining. However, once stained, the bacteria cannot be decolorized by acid alcohol. This characteristic is classified as acid-fast bacteria (AFB).[12]

Acid fastness is due to the organisms' high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. In the mycobacterial cell wall, lipids are linked to underlying arabinogalactan and peptidoglycan. This structure confers very low permeability of the cell wall, thus reducing the effectiveness of most antibiotics. Another molecule in the mycobacterial cell wall, lipoarabinomannan, is involved in the pathogen-host interaction and facilitates the survival of *M. tuberculosis* within macrophages.[10]

2.1.2 Pathophysiology

Tuberculosis is transmitted from person to person in airborne droplets. It is highly contagious, individuals living with an infected person have a 33% risk of developing the infection.[13] The microorganism is contained by the inflammatory and immune response systems and no clinical disease develops in immunocompetent individuals. Microorganisms reside in the lung periphery, usually in the upper lobe. Once the bacteria are inspired into the lung, they multiply and cause lung inflammation. Some bacteria migrate through the lymphatics and become resided in the lymph nodes, where they meet lymphocytes and initiate the immune response.

Inflammation in the lung triggers neutrophils and alveolar macrophages to migrate to that area. These cells then swallow the bacteria and begin the process of body's defense mechanisms which is to isolate the bacteria. However, the bacterium is successful as a pathogen because it can survive within macrophages, resist lysosomal killing, and multiply within the cell. In defense, macrophages and lymphocytes release interferon, which inhibits the replication of the microorganism and encourages more macrophages to attack the bacterium. The infected macrophages can also activate cytotoxic T cells (CD8).

Neutrophils, lymphocytes, and macrophages seal off the colonies of bacteria, forming a granulomatous lesion called a tubercle. Then, infected tissues within the tubercle will die and form caseation necrosis. Collagenous scar tissue then grows around the tubercle. The immune response is complete after 10 days or more to prevent further multiplication of the bacteria.

Once the bacteria are isolated in the tubercles and immunity develops, tuberculosis may remain dormant for life. However, if the immune system is impaired or if live bacteria escape into the bronchi, active disease occurs and may spread through the blood and lymphatics to other organs.

2.1.3 Clinical Manifestation

In many infected individuals, tuberculosis is asymptomatic. In others, symptoms develop so gradually that they are not noticed until the disease is progressing. However, symptoms can appear in immunosuppressed individuals within weeks of exposure to the bacteria. Common clinical manifestations include fatigue, weight loss, lethargy, anorexia, a low-grade & remittent fever (usually occurs in the afternoon and then subsiding) and night sweats.[14] A cough that produces purulent sputum will develop slowly and become more frequent over several weeks or months. Dyspnea, chest pain, and hemoptysis may also present as the disease worsen.

2.1.4 TB Treatment

The purposes of TB treatment are to cure patient, prevent death, relaps, complication, microorganism resistance to anti-TB drug and break transmission chain.

Table 2.1 Type, characteristic, and dose of anti-TB drug (first-line)[15]

Type	Characteristic	Recommended Dose (mg/kg)	
		Daily	3 x a week
Isoniazid (H)	Bactericidal	5 (4-6)	10 (8-12)
Rifampicin (R)	Bactericidal	10 (8-12)	10 (8-12)
Pirazinamine (Z)	Bactericidal	25 (20-30)	35 (30-40)
Streptomycin (S)	Bactericidal	15 (12-18)	-
Ethambutol (E)	Bacteriostatic	15 (15-20)	30 (20-35)

Five major drugs which are considered the first-line agents for the treatment of tuberculosis is summarized in Table 2.1. These agent are recommended on the basis of their bactericidal activity (ability to rapidly reduce the number of viable organisms and render patients noninfectious) and their sterilizing activity (ability to kill all bacteria and sterilize the affected organ).[11]

Basically, the short cousse tuberculosis treatment are divided into an initial (bactericidal) and continuation (sterilizing) phases. During the initial phase, the majority of tubercle bacteria are killed. As a result, the symptoms are resolved and the patient become noninfectious. The continuation phase is to eliminate persisting mycobacteria and prevent relapse.

Usually after the 2 months of initial phase, the patients will have sputum-culture conversion to become negative result. For these patients, the continuation phase needed is only for 4 months. However, for the delayed sputum-culture conversion patients, the sputum culture result is still positive after 2 months, they should have their treatment extended by 3 months. As a result, they have a total course of 9 months.

Table 2.2 Guidelines of anti-TB drug used by *Program Nasional Penanggulangan Tuberkulosis* in Indonesia[4]

Combination	Initial Phase	Continuation Phase
Category 1	2HRZE	4(HR)3
Category 2	2HRZES/HRZE	5(HR)3E3
Additional	HRZE	-
Children	2HRZ	4HR

The anti-TB drug should be given in combination of several drugs (Table 2.2), in adequate amount and appropriate dose according to the treatment category (Table 2.3). Monotherapy of anti-TB drug should be avoided because it can develop resistance. To ensure the patients will adhere and comply to the treatment, DOTS (Directly Observed Treatment Strategy) should be supervised by PMO (*Pengawas Menelan Obat*).

Table 2.3 Categories of anti-TB drug[4]

Category 1	Category 2	Category 3
New Patient with positive AFB smear of lung TB	Relapse	New patient with negative sputum smear and extra-pulmonary TB
Patient with negative AFB smear of lung TB but has positive thorax x-ray	Failure	
Extrapulmonary TB patient	Retreatment after default	

Additional category is given to the patient with positive AFB smear who still has positive AFB smear at the end of initial phase of the treatment.

Classification of TB patients according to the history of treatment:

a. New Cases

Patients who have never got anti tuberculosis drug or have got anti tuberculosis drug less than 1 month.

b. Relapse

TB patients who have got TB treatment completely and have been declared cured and diagnosed again with positive AFB smear.

c. Default

Patients who have got TB treatment more than 1 month and stop the treatment for 2 months or more and come with positive AFB smear.

d. Failure

Patients who still have positive AFB smear or become positive again at one month before the end and at the end of treatment.

e. Transfer In

Transferred patients from health service units which has other TB register to continue the TB treatment.

f. Others

Is not included in above criteria. In this class includes chronic case, patients with positive AFB smear after done with TB retreatment.[4,15]

2.2 MDR-TB

M. tuberculosis strains resistant to individual drugs due to spontaneous point mutations in the mycobacterial genome. Because there is no cross-resistance among the commonly used drugs, the probability that a strain will be resistant to two drugs is the product of the probabilities of resistance to each drug and thus is low.

Table 2.4 Genetic sites for drug resistance in TB[16,17]

Drug	Target	Gene
Isoniazid	Catalase-peroxidase eznyme	katG
	Enoyl acp reductase	inhA
	Alkyl hydroperoxidase reductase	ahpC
	Oxidative stress regulator	oxyR
Rifampicin	RNA polymerase subunit B	rpoB
Pyrazinamide	Pyrazinamidase	pncA
Streptpmycin	Ribosomal protein subunit 12	rpsL
	16s ribosomal RNA	rrs
	Aminoglycoside phosphotransferase gene	strA
Ethambutol	Arabinosyl transferase	Emb A, B and C

Drug-resistant tuberculosis may be either primary or acquired. Primary drug resistance is that in a strain infecting a patient who has not previously been treated. Acquired resistance develops during treatment with an inappropriate regimen. Worldwide, MDR tuberculosis is a serious problem in some regions, especially in the former Soviet Union and parts of Asia.[11]

Although its causes are microbial, clinical and programmatic, drug-resistant TB is essentially a man-made phenomenon. An inadequate or poorly administered treatment regimen allows a drug-resistant strain to become the dominant strain in a patient infected with TB. Table 2.5 summarizes the common causes of inadequate treatment.

Table 2.5 Causes of inadequate antituberculosis treatment[18]

Health-Care Providers: Inadequate Regimens	Drugs: Inadequate Supply/Quality	Patients: Inadequate Drug Intake
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOTS)
Noncompliance with guidelines	Unavailability of certain drugs	Lack of information
Absence of guidelines	Poor storage conditions	Lack of money
No monitoring of treatment	Wrong dose or Combination	Lack of transportation
Poorly organized or funded TB control programs		Adverse effects
		Social barriers
		Malabsorption
		Substance dependency disorders

Ongoing transmission of established drug-resistant strains in a population is also a significant source of new drug-resistant cases.

2.3 Patient Adherence and Compliance

Adherence to therapy in TB patients is a major determinant of their outcomes, development of drug resistance or not.[19,20] In Pakistan, non-adherence rate are often high and can lead to relapse, and the development of drug-resistance strains, which are harder and more expensive to treat.[21] Moreover, in Harrison also stated that the tubercle bacteria infecting patients who do not adhere to the prescribed drugs are likely to become drug resistant.[11]

According to Manders et al, interruption of treatment leads to relapse and transmission to other individuals, and is also the most important underlying cause for the development of drug-resistant strains of *Mycobacterium tuberculosis*.[22] The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance reported that the retreatment case status was significantly associated with both MDR-TB and any drug resistance.[23]

In fact, patient adherence & compliance is influenced not only by the patients themselves but also by the doctor who prescribes the drugs, the nurses and other healthcare personnel who supervise administration of drugs and monitor patient's progress. In addition, the program director is also an important actor because they selects the suitable chemotherapy regimens, manages drug supplies and supervises the program.

Some patient characteristics that are more commonly associated with non-adherence behaviour are homelessness, alcohol or substance abuse, behavioral problems, mental retardation, and lack of social or family support. A study in Nigeria found about 30% of TB population are mental disorders and none of these were recognized by the healthcare personnel.[24] However, it is still difficult to indentify non-adherence patients because the reason for poor adherence is not only multifactorial and complex but also various from patient characteristic to

qualities of the social and economic environment.[19] In general, age, sex, marital status, ethnicity and education levels are not reliable predictors. [25]

Failure to adhere (non-adherence) with anti-TB chemotherapy means that the patient fails to continue the TB treatment after having the initial phase of the treatment. Failure to comply (non-compliance) with anti-TB chemotherapy may be manifested in various ways in developing countries:

1. Total absence of treatment, due to lack of drugs more often than to the patient's absolute refusal to take them.
2. Treatment duration does not conform to the treatment considered necessary (too short or too long).
3. Patient takes the drugs irregularly, with more or less frequent omissions of one drug or of all of them.
4. Drugs taken at an incorrect dose (too high or too low).
5. Drugs taken at an ineffective dose, either because of an error in the prescription, because of a drug interaction not taken into consideration, or because of a spontaneous decision by the patient.
6. Drugs not taken in accordance with a correct schedule (patient takes the drugs several times during the day at meal-times, for example, when the prescription says only once on an empty stomach in the morning).[26]

Some studies found out the reason why the patient is not adhere and comply to the TB treatment program. Some patient reported stopping medication due to adverse effects while others reported that they were not informed about side effects and what to do to encounter them.[27] Some patient poorly understood the long treatment period.[17] According to Mishra et al, better communication between healthcare personnels and patients is essential for improving treatment adherence and compliance in TB treatment.[28]

2.3.1 DOTS Affecting Patient Adherence and Compliance

In the early 1990s, WHO and IUATLD (International Union Against Tuberculosis and Lung Disease) had developed a TB control strategy known as DOTS (Directly

Observed Treatment Strategy) and had been proven as a cost-efective prevention. DOTS, if well implemented, not only can change the contaginous cases to become not contagious but also prevent the development of MDR-TB.[4] DOTS can improve the adherence and compliance of tuberculosis patients.[29] If DOTS as a strategy to control TB is properly implemented, cure rates of 85% can be achieved.[22]

DOTS has 5 key elements:[30]

1. Political commitment with increased and sustained financing
2. Case detection through quality-assured bacteriology
3. Standardized treatment, with supervision and patient support
4. Effective drug supply and management system
5. Monitoring and evaluation system, and impact measurement

One component of DOTS is standardized treatment of anti-TB drug with direct supervision. To ensure the regularity of treatment, *PMO* (*Pengawas Minum Obat*) is required. The role of *PMO* are:

- Overseeing the TB patients to swallow the medication regularly until the end of the treatment
- Encouraging the patients so they want to take medication regularly
- Reminding the patients to check the sputum at the appointed time
- Providing counseling to the family members of TB patients who have suspicious symptoms of TB to immediately go to the Health Services Unit

The important informations that *PMO* should understand about to be conveyed to the patients and their families:[4]

- TB can be cured with regular medical treatment
- TB is not a hereditary disease nor a curse
- TB transmission, suspicious symptoms and its prevention
- How to take the medication (intensive and continue phase)
- The importance of supervision so the patient have medication regularly
- Possible side effects of drugs

2.4 Conceptual Framework

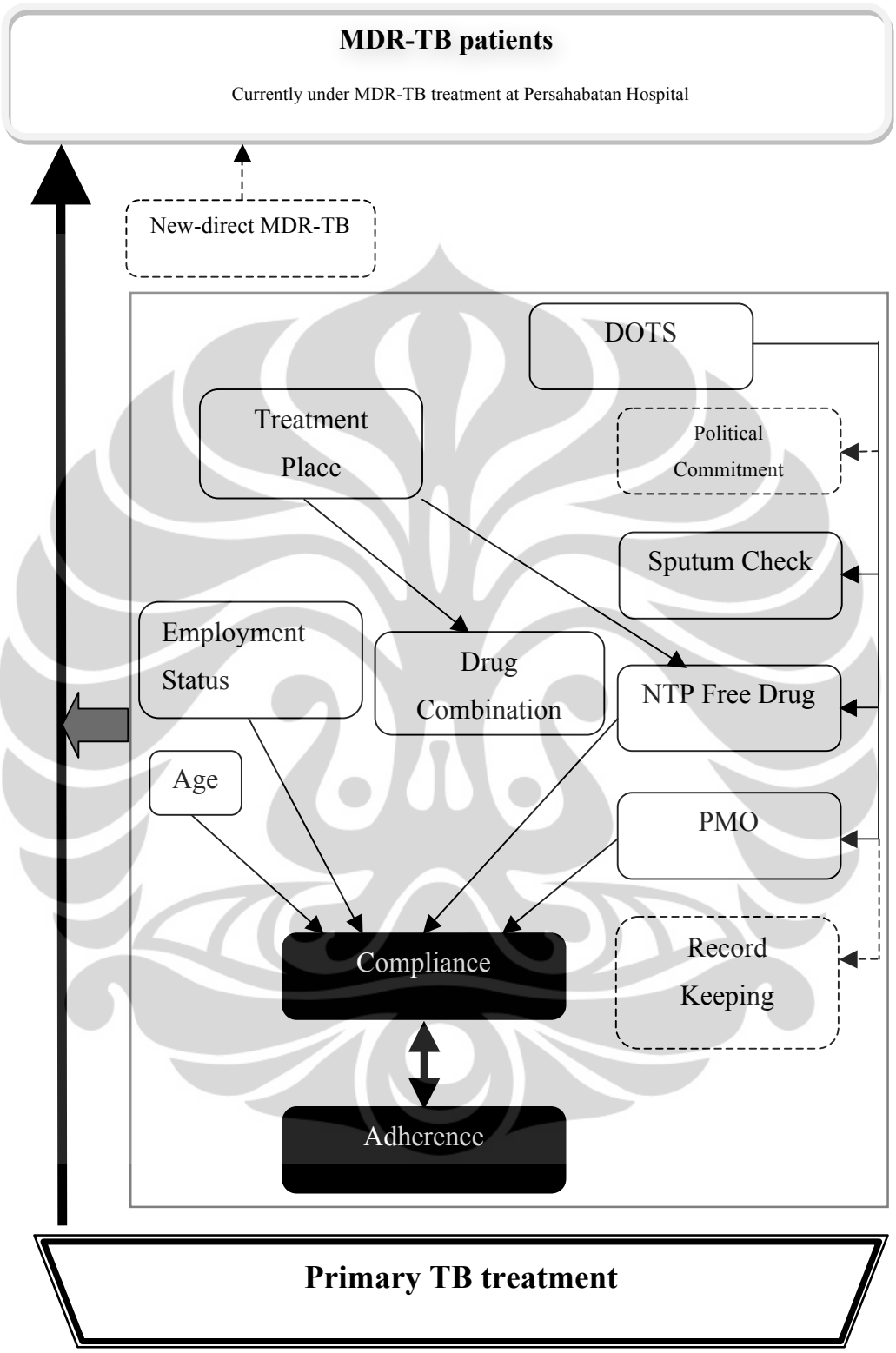

Figure 2.1 Conceptual Framework

Note:

- Dashed boxes and arrows indicate variables that are not included in this group study.
- Boxes highlighted in black indicate variables analyzed in this particular study.
- Boxes highlighted in white indicate variable analyzed by other members of the group.
- Arrows between the boxes direct independent to dependent variables.

CHAPTER 3: RESEARCH METHODS

3.1 Study Design

This is an observational study aimed investigate the variables at one particular time, thus this study utilizes a cross sectional design by surveys done in clinical series part-taking the MDR-TB pilot project in Persahabatan Hospital, Jakarta.

3.2 Time and Place of Study

This study is conducted from March 2009 to May 2011 in Jakarta, Indonesia. The interview is carried out at Persahabatan Hospital, Jl. Persahabatan Raya No. 1, Pondok Kelapa, East Jakarta. The rest of the process is conducted at Faculty of Medicine Universitas Indonesia, Jl. Salemba Raya 6, Central Jakarta.

3.3 Data Source

This study utilizes primary data obtained from deep interview with the subjects. The interview is done by six people. In addition, secondary data from medical record is observed for confirmation.

3.4 Population & Sample

The target population of this study is MDR-TB patients in Indonesia who has been treated by primary TB treatment. The studied population is MDR-TB patients in Persahabatan Hospital.

This study uses convenience sampling method as only limited valid data is available. In Indonesia, only at least two centers could confirm the MDR-TB cases, one of them is Faculty of Medicine Universitas Indonesia-Persahabatan Hospital. The majority of MDR-TB patient are undergoing treatment initiated by WHO in MDR-TB Clinic in Persahabatan Hospital.

3.5 Sampling Criteria

This study applies some inclusion and exclusion criteria for the subjects.

3.5.1 Inclusion criteria

1. MDR-TB patient who previously received TB treatment
2. MDR-TB patient under MDR-TB treatment at MDR-TB clinic, Persahabatan Hospital.

3.5.2 Exclusion criteria

1. New case of MDR-TB patient who are not arising from previous TB treatment
2. Incomplete information written in patient's medical records
3. Patient is not available
4. Patients or patients' family do not want to participate in this study

3.6 Data Sampling

The formula used to calculate the minimal sample size is the formula to determine the proportion of health problem in the population. Minimum sampling size is calculated as below.

Equation 3.1 Minimum Sample Size for Cross-Sectional Study

$$n = \frac{\{(Z_1 - \alpha)^2 \times p \times (1 - p)\}}{d^2}$$

where,

n = raw minimum sample size

(Z_1-α) is already determined 1.96 for α=5%

p= general prevalence of MDR TB cases developed from TB cases

d= acceptable error of the researcher

In Indonesia, the prevalence of MDR TB cases developed from TB cases is estimated by WHO in 2006 to be in range from 8.1% to 26%. This study estimates that the prevalence is 15%, based on comparison to other countries with high burden of MDR-TB.

$$n = \frac{\{(1.96)^2 \times 15\% \times (1 - 15\%)\}}{0.1^2}$$

$$n = 48.9804 \approx 49$$

This study utilizes convenient sampling, for the lack of availability of valid data, to fulfill the minimum sample size.

3.7 Variable Identification

All variables in this study are nominal variables. The first variable is patient adherence. The second variable is patient compliance. This study will describe the patient adherence and compliance during primary TB treatment. This study is a two way study which means the first variable can determine the outcome of the second variable and vice versa.

3.8 Data Analysis Plan

3.8.1 Data Collection

Data collection is done through direct deep interview to the subjects and confirmation by reviewing the medical record. The data collection is conducted at MDR-TB Klinik, Persahabatan Hospital, East Jakarta during December 2009 until August 2010. A permission letter, dated 24 November 2009, is signed by the Chairwoman of Research Module team for necessary authorization in the hospital, dr. Erlina Burhan. The questionaire will be attached at appendix.

3.8.2 Data Processing

The results of interview are written down in the form filled by the interviewer. The data is compiled in table using Microsoft Excel. Then, the data is statistically processed by SPSS 11.5.

3.8.3 Data presentation

The data is presented in chart and table with necessary explanations.

3.8.4 Data Analysis

The data is analyzed by descriptive and comparative statistic method. This study describes the patient adherence and compliance during primary TB treatment using descriptive statistic method. The association of the patient adherence and compliance is determined by chi-square test.

3.8.5 Data Interpretation

The association between patient adherence and patient compliance will be known after the data is interpreted.

3.8.6 Results Report

The result of this study is written in this report and will be presented in front of supervisor and examiner board.

3.8.7 Research Ethics

An ethic clearance has been filed and approved on 22 November 2009 by Prof. DR. Purwantyastuti, MD, MSc, SpFK. All of the candidates for subjects would first receive explanation about the background and the objectives of the research by verbal description prior to the interview. If candidate agrees to participate in this study, the subject is then required to sign an informed consent.

3.9 Operational Definition

Tuberculosis (TB) is any of the infectious diseases of humans and other animals due to species of *Mycobacterium* and marked by formation of tubercles and caseous necrosis in tisues of any organ. In humans, the lung is the major site of infection and the usual portal through which infection reaches other organs.

Multidrug-resistant TB (MDR-TB) is TB that is resistant to at least Isoniazid (INH) and Rifampicin (RIF).

Primary TB Treatment is defined as the first treatment obtained by TB patients subsequent to the earliest diagnosis of TB.

Adherence is defined as patients' attitude to obey the TB treatment program by still continuing the treatment after the initial phase of the treatment.

Compliance is defined as patients' attitude to obey the regulations of anti-TB treatment, including taking the drugs in correct dose regularly at designated length of treatment, according to the correct schedule.

Table 3.1 List of Variables

Variable	Measuring Device	Methods of Measurement	Value Measured	Type of Data
Patient Adherence	Questionnaire	Interview	Adhere Not adhere	Nominal
Patient Compliance	Questionnaire	Interview	Comply Not comply	Nominal

CHAPTER 4: RESULTS & DISCUSSIONS

4.1 Patient Adherence during Primary TB Treatment

This study describes the patient adherence during their primary TB treatment of MDR-TB patient. From 50 MDR-TB patients, the number of patients who adhere to the primary TB treatment is 72%. This number is much higher for about 2.5 times than the patients who do not adhere to the primary TB treatment.

In a study conducted in India by Johnson et al found 45 of the 48 defaulters showing drug resistance.[9] However, this study observes from different angle. This study finds out the limited population of MDR-TB patient behaviour when they had their primary TB treatment. It is found that the number of non-adherence patients who are now MDR-TB patient is low for only 28% of subjects. This finding happens maybe due to the facts that MDR-TB is caused by many possibilities, not only due to patient adherence. It can be caused by inadequate regimens such as inappropriate guidelines and absence of guidelines; and inadequate supply of drugs such as poor quality and wrong dose or combination. A history of relapse was also found to be associated with drug resistance.[9] The MDR-TB can also come up due to the failure of previous treatment.

Through in depth interview with the subjects this study finds out some reasons why the patient do not adhere to the treatment. There are 7 from 14 patients (50%) who do not adhere said they already felt well, no more cough and the other symptoms relief so they thought that they were already cured. The other 2 patients said that they couldn't afford the laboratory test and medication. Another patient said the doctor only give medication for the first two months and didn't tell to come back or to continue the treatment. A patient said the side effects were too bothersome and another said he/she wasn't cured. Unfortunately, there are two subjects who didn't explain the reason why they do not adhere to the treatment.

The reasons found in this study are almost similar with other study conducted in Uzbekistan. Botha et al found that the patient lack of proper information about TB

and its treatment.[31] This happens due to poor communication between the patients and the healthcare personnels. Al-Zubaidi also found that 37 from 93 subjects didn't adhere to the treatment or default due to they thought that they were cured because of clinical improvement.[32]

4.2 Patient Compliance during Primary TB Treatment

This study also describes the patient compliance during their primary TB treatment of MDR-TB patient. The number of patient who comply to the primary TB treatment is slightly higher than the patient who do not comply to the treatment. From 50 patients, the patient who comply is 54% while the patient who do not comply is 46%.

This study describes the patient compliance during the primary TB treatment. The result of this study is almost equal between the MDR-TB patient who comply and do not comply to the primary TB treatment. Another study conducted in Nepal assessed the risk factor of multidrug-resistant TB. It is found that the number of patient who did not comply to the previous treatment is 67%.[33] This happen maybe cause by the same reason as why the adherence number is low in this study such as inappropriate drug dose or combination.

This study also finds out the reason why the subject do not comply to the primary TB treatment. The majority of patients, 9 subjects, said they forgot to take the drugs. The second most reason for 6 subjects is the patient felt well. The other 4 subjects said the medication was not available in drug store. The rest 4 subjects said the side effects of drugs were too bothersome.

However, not only patients themselves but also healthcare personnels are important factors that affect the patient compliance. Healthcare personnels should educate patient about the treatment as a whole included the duration, side effects, and the outcome if the patient suddenly stop or not comply to the treatment.

4.3 Patient Adherence in Relation to Patient Compliance during Primary TB Treatment

This study also describes the combination of patient adherence and compliance to the primary TB treatment in Figure 4.3. The majority of patients adhere and comply during primary TB treatment. The second most is the patients who adhere but not comply during primary TB treatment.

Figure 4.1 Patient Adherence and Compliance

Note: $n = 50$.

This study wants to find out the association between patient adherence and compliance during primary TB treatment. Thus, the chi-square test is conducted using SPSS 11.5.

Table 4.3 indicates that there is no significant association between patient adherence and compliance during primary TB treatment because $\chi^2 = 0.972$, $p > 0.05$.

Table 4.1 Association between Patient Adherence and Patient Compliance in MDR-TB Patients during Primary TB Treatment

Count (% to total *n*)	**Comply**	**Not Comply**	Total
Adhere	**21 (42%)**	**15 (30%)**	36 (72%)
Not Adhere	**6 (12%)**	**8 (16%)**	14 (28%)
Total	27 (54%)	23 (46%)	50 (100%)

Note: Comparative test using chi-square test, $\chi^2 = 0.972$ ($p > 0.05$ not significant), df = 1.

This study found there was 15 patients who adhere but not comply to the primary TB treatment. This happens due to patient forgetfulness (40%), felt well (26,7%), medication was not available (20%) and side effects (13,3%). There are also 6 patients who did not adhere but comply to the primary TB treatment. Two of them (33,3%) said the reason was due to economy problem. Unfortunately, the other two (33,3%) did not explain why this happened. One of them (16,7) said she felt well so she thought she was already cured. The other (16,7%) said he was not cured so he stopped taking the medicine.

Patient adherence and compliance can be improved by DOTS (Directly Observed Treatment Strategy). A study in Nigeria already confirmed that DOTS improves the rates of adherence and compliance.[34] Another study also stated that the administration of anti-TB drug under *PMO* leads to significant reductions in the frequency of drug-resistance.[35]

4.4 Limitation of the study

This study employs guided interview, including asking open questions and in-depth interview. Hence, variability of interviewer may happen although it has been prevented with briefing. Misleading questions may lead to different answers.

Data obtained for this study are based on the recounted information on medical history from the subjects. This data is highly dependent on patients' memory as well as patients' perceived understanding of the disease. A confirmatory review of medical records has been done to minimize subjects' recounting bias.

This study only observes limited number MDR-TB patients from MDR-TB clinic in Persabahatan Hospital. This may result in underestimation and bias to the data obtained.

This study is designed in cross sectional study. It can only observe comparative relation between two variables instead of correlative relation.

CHAPTER 5: CONCLUSION & SUGGESTION

5.1 Conclusion

1. The number of adherence in MDR-TB patient during primary TB treatment is 72%.

2. The number of compliance and non-compliance in MDR-TB patient during primary TB treatment is almost equal.

3. There is no association between patient adherence and compliance in primary TB treatment.

5.2 Suggestion

5.2.1 Future Studies

Epidemiological research could be done in more than one centre and bigger sample size. A case control study should be conducted to be able to identify the risk factors that contribute to the development of TB towards MDR-TB.

5.2.2 Policy Makers

The healthcare personnels should have a good communication with patient and educate the patient well about TB treatment to prevent the development of resistance. Availability of *Pengawas Minum Obat* will ensure and support the patient adherence and compliance to the treatment. Thus, the MDR-TB can be prevented.

5.2.3 Research Module

The duration of research should be extended so that the study can be conducted in cohort method.

APPENDIX A: PERMISSION LETTER

UNIVERSITAS INDONESIA
FACULTY OF MEDICINE
INTERNATIONAL CLASS PROGRAM
IASTH Building, 5th Floor
Jl. Salemba Raya No. 4, Jakarta Pusat 10430, Phone : 62-21 - 3902408, 3903004, 31909005
Fax. : 62-21-3903004, 3902408 email : international@fk.ui.ac.id

24 November 2009

Nomor : 4610 /PT.02/FK-KI/F/XI/2009
Lampiran :
Perihal : Permohonan izin penelitian

Kepada Yth

Ketua Departemen Pulmonologi dan Ilmu Kedokteran Respirasi FKUI

Di RS.Persahabatan
Jakarta

Dengan hormat,

Bersama in kami mengajukan permohonan melakukan penelitian bagi mahasiswa modul Riset FKUI Kelas Internasional (daftar nama terlampir),yang akan melakukan penelitian di Departemen yang Saudara Pimpin mulai dari Desember 2009 - Febeuari 2010.

Sebagai informasi Judul Penelitian Mereka ***Adherence,Compliance,Dosage & Choces of Antimycobacterial Drugs Combination,Age and Referral System n Relation with TB Treatment that Leads to Conversion to MDR-TB***,dengan supervisor Prof.Dr.dr.Purwantyastuti,MSc,Sp.FK dan dr. Erlina Burhan,Sp.P

Besar harapan kami saudara dapat mengijinkan mahasiswa kami, atas perhatian dan kerja samanya kami sampaikan terima kasih.

Ketua Modul Research,

Dr.dr.Saptawati Bardosono,Msc

Tembusan:
1. Arsip

APPENDIX B: ETHICAL CLEARANCE

UNIVERSITAS INDONESIA
FAKULTAS KEDOKTERAN

Jalan Salemba Raya No. 6 Jakarta Pusat
Pos Box 1358 Jakarta 10430
Kampus Salemba Telp. 31930371, 31930373, 3922977, 3927360, 3912477, 3153236, Fax. : 31930372, 3157288, e-mail : office@fk.ui.ac.id

KAJIAN ETIK
USULAN RISET MAHASISWA MODUL RISET
FAKULTAS KEDOKTERAN UNIVERSITAS INDONESIA

Nama Pengkaji : Prof. Dr. dr. Purwantyastuti SpFK. MSc.
Judul Usulan Riset :
Adherence, Compliance, Dosage & Choices of Antimycobacterial Drug Combination, Age and Referral System in Relation with TB Treatment that Leads to Conversion to MDR TB.
Nama tim peneliti : Alberta Sedyahtera, Alberta Jesslyn Gunardi, Anindya Pradipta Susanto, Nicolaus Widyo Pramono, Mentia Agustari, Tiesy Fabiola

1. Apakah alasan/motivasi untuk melakukan penelitian ditulis dengan jelas?
   Ya / Tidak
2. Apakah tujuan untuk melakukan penelitian ditulis dengan jelas?
   Ya / Tidak
3. Apakah manfaat dari hasil penelitian ditulis dengan jelas?
   Ya / Tidak
4. Adakah masalah etik yang mungkin akan dihadapi?
   Ada / Tidak
5. Bila penelitian ini menggunakan subyek manusia, apakah penelitian di laboratorium dan/atau percobaan pada hewan harus dilakukan terlebih dahulu?
   Ya / Tidak
6. Bila penelitian ini menggunakan subyek manusia, adakah bahaya potensial yang langsung atau tidak langsung, segera atau kemudian dan cara-cara untuk mencegah atau mengatasi kejadian (termasuk rasa nyeri dan keluhan lain)?
   Ada / Tidak ada
7. Bila penelitian ini menggunakan subyek manusia, adakah dilampirkan contoh surat persetujuan penderita dan rincian informasi yang akan diberikan kepada subyek penelitian)? Ada / Tidak
8. Apakah tim peneliti sudah menjelaskan mengenai penjagaan kerahasiaan data subyek dalam informasi yang diberikan untuk calon subyek penelitiannya? Sudah / Belum

Penelitian ini disetujui / tidak disetujui untuk dilaksanakan, dengan / tanpa perbaikan.

Jakarta, 22/11/09
Tanda tangan Pengkaji Etik:

Prof DR PURWANTYASTUTI, MD, MSc, SpFK

APPENDIX C: INFORMED CONSENT

Formulir Persetujuan untuk Berpartisipasi dalam Riset

Tuberkulosis, atau TB adalah infeksi bakterial yang mnyebabkan lebih banyak kematian di dunia daripada penyakit infeksi lainnya. Hampir 2 milyar orang yang terinfeksi dengan Tuberkulosis di dunia. Tetapi, karena banyak faktor, banyak pasien TB tidak dirawat dengan baik. Hal ini menyebabkan timbulnya MDR-TB atau Multidrug Resistant Tuberculosis. Riset mengenai perubahan dari TB menjadi MDR-TB sedang berkembang pada saat ini.

Anda adalah sample dari riset ini, dan saya memohon kesediaan Anda untuk mengikuti riset ini sebagai partisipan. Setiap data yang diambil akan dijaga kerahasiaannya.

Riset ini adalah bagian dari program pendidikan dokter umum di Fakultas Kedokteran Universits Indonesia.

Terima kasih

Tim Riset MDR-TB

Saya, yang menandatangani formulir ini:

Nama :

Umur :

Telepon:

Telah mendapatkan penjelasan dan mengerti mengenai riset ini, serta menyatakan bahwa saya secara sukarela bersedia untuk mengikuti riset ini dan informasi yang akan diambil dapat digunakan utnuk keperluan riset beserta mengikuti prosedur riset sesuai ketentuan.

Contact person : Albert Sedjahtera 085263574572

APPENDIX D: QUESTIONNAIRE

Particulars

Name	
DOB	
Address	
Contact No.	

Do you know TB can be cured?	Yes No	Adh Comp
How do you know? Who told you?		

First Time Diagnosed TB		
Time/Month-Year (diagnosis or commencement of treatment)		ALL
Attending Physician		
Did you feel the presence of PMO is helpful for you?		DOTS Comp Adh
Have you ever skipped the medication in <u>initial phase</u> (even once)	Yes No	Comp

Frequency of skip		Comp
Why did you skip the medication	Lazy Forget Side effect Feel well, no more coughs and other symptoms Feel tired, tidak sembuh-sembuh Related to medicine (finish stock, expensive)	Comp
Have you ever skipped the medication in continuation phase (even once)	Yes No	Comp
Frequency of skip		Comp
Why did you skip the medication	Lazy Forget Side effect Feel well, no more coughs and other symptoms Feel tired, tidak sembuh-sembuh Related to medicine (finish stock, expensive)	Comp
Was there sputum check after initial phase	Yes No	ALL
Did you continue to take medication after initial phase	Yes No	Adh
If no, why did you stop take medication	Doctor did not give medication Can't afford the expensive medication	Adh

	Feel well, no more coughs and other symptoms Lazy to take medication	
Do you have activities other than your job?	Side job…….. Hobby…….. Sports……	
Did you smoke regularly before you were diagnosed TB?	Yes No	
Have you ever smoked after diagnosed with TB/during medication?	Yes No Frequency: less 1 pack/day 1 or more packs/day Duration:	

Other Remarks: (eg: drinking habits)

Subsequent Time Diagnosed TB		
Brief History: Time, Place, Medications, PMO, Adherence, Compliance		
Most Recent Time Diagnosed TB		
Time/Month-Year (diagnosis or commencement of treatment)		ALL
Attending Physician		
Have you ever skipped the medication in <u>initial phase</u>	Yes No	Comp

(even once)		
Frequency of skip		Comp
Why did you skip the medication	Lazy Forget Side effect Feel well, no more coughs and other symptoms Feel tired, tidak sembuh-sembuh Related to medicine (finish stock, expensive)	Comp
Have you ever skipped the medication in continuation phase (even once)	Yes No	Comp
Frequency of skip		Comp
Why did you skip the medication	Lazy Forget Side effect Feel well, no more coughs and other symptoms Feel tired, tidak sembuh-sembuh Related to medicine (finish stock, expensive)	Comp
Was there sputum check after initial phase	Yes No	ALL
Did you continue to take medication after initial phase	Yes No	Adh
If no, why did you stop take	Doctor did not give medication	Adh

medication	Can't afford the expensive medication Feel well, no more coughs and other symptoms Lazy to take medication	
Do you have activities other than your job?	Side job…….. Hobby…….. Sports……	
Did you smoke regularly before you were diagnosed TB?	Yes No	
Have you ever smoked after diagnosed with TB/during medication?	Yes No Frequency: s 1 pack/day 1 or more packs/day Duration:	

Other Remarks: (eg: drinking habits)

APPENDIX E: RAW DATA TABULATION

No	Name	Adherence	Reason	Compliance	Reason
1	NID	Yes		Yes	
2	D	Yes		No	Forgot to Take Medicine
3	MY	No	Feel Well	No	Forgot to Take Medicine
4	S	Yes		No	Side Effects Are Too Bothersome
5	J	Yes		No	Side Effects Are Too Bothersome
6	S	Yes		Yes	
7	R	Yes		Yes	
8	R	No	Economy	Yes	
9	BH	Yes		Yes	
10	E	Yes		Yes	
11	S	Yes		No	Feel Well Enough
12	IH	Yes		Yes	
13	ES	Yes		No	Ran Out of Medicine
14	H	Yes		Yes	
15	H	Yes		Yes	
16	ANM	Yes		Yes	
17	J	Yes		Yes	
18	AS	Yes		Yes	
19	A	No	Side Effect	No	Feel Well Enough
20	M	Yes		Yes	
21	S	Yes		No	Forgot to Take Medicine
22	AY	No	Economy	Yes	
23	M	Yes		No	Ran Out of Medicine
24	A	Yes		Yes	
25	M	Yes		Yes	
26	F	Yes		No	Feel Well Enough
27	EJ	Yes		Yes	

28	HS	No	No Answer	Yes	
29	AS	Yes		Yes	
30	DS	Yes		No	Feel Well Enough
31	NE	Yes		No	Forgot to Take Medicine
32	S	Yes		No	Forgot to Take Medicine
33	Z	No	Doctor didn't give medication	No	Side Effects Are Too Bothersome
34	R	No	Feel Well	No	Forgot to Take Medicine
35	A	Yes		Yes	
36	C	Yes		No	Feel Well Enough
37	DM	No	Feel Well	Yes	
38	R	No	Feel Well	No	Side Effects Are Too Bothersome
39	N	Yes		Yes	
40	L	No	Feel Well	No	Forgot to Take Medicine
41	YT	Yes		No	Forgot to Take Medicine
42	M	Yes		Yes	
43	S	No	Feel Well	No	Feel Well Enough
44	Y	Yes		No	Forgot to Take Medicine
45	DHL	No	Not Cured	Yes	
46	G	Yes		Yes	
47	RA	No	Feel Well	No	Ran Out of Medicine
48	J	Yes		No	Ran Out of Medicine
49	R	Yes		Yes	
50	SEW	No	No Answer	Yes	

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