

## Review article

**Identification of factors associated with non-adherence and discontinuation of antitubercular drugs in patients with tuberculosis**Nargiza Toktonaliev<sup>1</sup>, Iskhak Toktonaliev<sup>1</sup>, Saltanat Kadyrkulova<sup>2</sup><sup>1</sup>Department of Basic and Clinical Pharmacology (Named after Academician M.T. Nanaeva),  
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**ABSTRACT**

The effectiveness of the anti-tubercular treatment (ATT) depends on adherence to the proposed highly effective therapeutic scheme. When the patient starts ATT and fails to come to the healthcare facility for more than 30 consecutive days from the date scheduled for his return, it is considered abandonment. The objective was to identify the difficulties associated with non-adherence and abandonment of the ATT regimen and evaluate the regulation of anti-tuberculosis drugs in Kyrgyzstan. Patients with tuberculosis make the decision to abandon treatment because they are unaware of the time needed, the continuity of treatment, and for reasons of the disappearance of signs and symptoms. The use of alcohol and illicit drugs has a poor prognosis for the treatment, factors that predispose patients to abandon the treatment and prolong the drug therapy. The majority of the patients discontinue treatment because of adverse effects, contributing to the interruption of treatment, so patients should be assisted regularly. To strengthen the requirements for the quality of purchased anti-tuberculosis drugs, when drawing up the technical specification of the government decree of Kyrgyzstan, it is necessary to give preference to drugs that have been prequalified by World Health Organization or evaluated by strict regulatory authorities.

**Keywords:** Tuberculosis; anti-tubercular treatment; anti-tubercular drugs; non-adherence; adverse effects.**INTRODUCTION**

**T**uberculosis (TB) is a chronic infectious disease caused by Mycobacterium Tuberculosis, which primarily affects the lungs and may affect other organs and/or systems. Its transmission is caused by airborne transmission from an infected patient to a healthy one (1). TB requires long treatment, and it is tough to achieve a cure due to non-adherence to or abandonment of anti-tubercular treatment (ATT). TB is diagnosed by direct sputum smear microscopy, which consists of collecting sputum samples from the patient along with a chest X-ray from the same (2). The effectiveness of the ATT depends on adherence to the proposed highly effective therapeutic scheme (3). Even after treatment, the number of cases has largely increased due to the discontinuation of anti-tubercular drugs (ATD) and increased drug resistance. The best prevention strategy is early detection and the proper start of ATT, as only the affected person transmits the TB. Non-adherence and improper treatment tend to keep the patient infectious, thus maintaining the chain of transmission. Thus, low cure rates and poor adherence to ATT are one of the greatest difficulties in controlling TB (4). There are many reasons for non-adherence and abandonment of treatment, increasing resistance such as lack of information about TB in patients and their families, use of alcohol and illicit drugs, and problems inherent to the medication.

One of the main obstacles faced by patients is drug adherence due to adverse effects (AEs), prolonged therapy time, and the early perception of a cure, which weakens adherence and contributes to treatment abandonment. Therefore, strategies are needed to minimize the difficulties encountered. One of the main goals in the control of TB is the reduction of the rates of abandonment of treatment because its interruption will lead to greater dissemination and the patients will remain as sources of infection and thus contribute to drug resistance to increase the time and cost of treatment and compromising the quality of life in patients (5).

When the patient starts ATT and fails to come to the healthcare facility for more than 30 consecutive days from the date scheduled for his return, it is considered abandonment (6). The objective was to identify the difficulties associated with non-adherence and abandonment of the ATT regimen and evaluate the regulation of anti-tuberculosis drugs in Kyrgyzstan.

**Treatment and adherence**

The standard treatment regimen includes ATT such as isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, followed by isoniazid and rifampicin with ethambutol in areas of high resistance, or without ethambutol for four months (3). This regimen can poorly affect patients' adherence to treatment (7).

Drug	Recommended dose in mg/kg body weight (range)			
	Daily regimen		3 times weekly regimen	
<b>Isoniazid</b>	<b>Dose</b>	<b>Range</b>	<b>Dose</b>	<b>Range</b>
Children	10	(7-15)		
Adults	5	(4-6)	10	(8-12)
	Maximum 300 mg/day		Maximum 900 mg/dose	
<b>Rifampicin</b>				
Children	15	(10-20)		
Adults	10	(8-12)	10	(8-12)
	Maximum 600 mg/day		Maximum 600 mg/dose	
<b>Pyrazinamide</b>				
Children	35	(30-40)		
Adults	25	(20-30)	35	(30-40)
	Maximum 2000 mg/day		Maximum 3000 mg/dose	
<b>Ethambutol</b>				
Children	20	(15-25)		
Adults	15	(15-20)	30	(25-35)
	Maximum 1000 mg/day (children) and 1600 mg/day (adults)		Maximum 2400 mg/dose	

**Fig. 1:** Recommended dosages of anti-tubercular drugs in children and adults

Poor adherence may develop drug resistance and develop the chance of relapse (8, 9). Recommended dosages of anti-tubercular drugs in children and adults are presented in Fig. 1. At the beginning of the treatment, there is an expressive improvement of the symptoms, the patient returns to normal weight, the fatigue decreases, and the appetite returns, that is, an improvement in the general condition, but it does not mean a cure, and the therapeutic scheme must be followed through to the end. For this reason, daily and continuous treatment is fundamental for the cure of the pathology, followed by confirmation by laboratory tests.

The main factors that lead patients to non-adherence and abandonment of treatment were divided into three categories:

- The lack of information about TB in patients and their families
- Use of alcohol and illicit drugs
- Inherent problems with medications

One of the main limitations for fighting and curing the disease is the abandonment of treatment, which increases the cost of following up on patients and also implies a lower chance of cure, besides facilitating the development of resistant bacilli, which can lead to an outcome such as multidrug resistance, new abandonment or death. The knowledge of the month of its occurrence is an important issue in the control of dropouts. The study showed that the dropouts occurred during the first 5 months of disease treatment (6).

If the treatment is adequate and correct, the disease is curable in practically 100% of the cases caused by susceptible bacilli. Some measures must be taken until

there is negativity of the bacteria in the organism, such as: covering the mouth with the arm or handkerchief when coughing, and keeping the environment sunlight and well-ventilated, because the air circulation enables the dispersion of the infecting particles.

#### **The lack of information about the TB in patients and their families**

One of the factors that influence the abandonment of treatment is the lack of information on family members. The educational activities are directed to the family members, being relevant to the patient's rehabilitation process. Once the family becomes a source of support for the treatment of TB, enabling adherence. Detailed information about the pathology of the diagnosed person, as well as knowing the importance of taking the treatment to obtain a cure, the potential AEs, and the consequences of treatment irregularity have a greater propensity for treatment adherence. Knowledge about the pathology, the duration of the prescribed treatment, the importance of regularity in the use of ATD, and knowledge of the consequences of treatment discontinuation are important information for ATT adherence (10). A factor that may influence adherence to the therapeutic regimen is the lack of knowledge about the pathology since TB can generate psychological and social changes in the patients (5).

Some studies revealed that patients with TB make the decision to abandon treatment because they are unaware of the time needed, the continuity of treatment, and for reasons of the disappearance of signs and symptoms (11).

Multiple factors that directly affect the patient in relation to therapeutic adherence determine the

person's behavior in relation to the recommendations regarding the ATT. Different factors are related to socioeconomic conditions, the disease, the therapy, the relationship of healthcare professionals with the patient, as well as the patient himself. Healthcare professionals ignore patients' perspectives by putting their own when addressing the issue of adherence/non-adherence to ATT. The interaction and communication between the healthcare professional and the patient tend to be lower, jeopardizing adherence to treatment (11). When patients have doubts about the treatment, seeking health care services becomes one of the positive factors for successful adherence to the therapeutic scheme (12).

Undoubtedly, information about ATT is necessary for patients to continue taking their medications. It is still noted that many studies point to the failure of healthcare professionals in relation to the correct guidance to patients. All the research showed that most patients receive information about TB at the moment of diagnosis, and there are no lectures and group meetings that can contribute to broader knowledge about the disease, alerting about the importance of completing the treatment, increasing the risk of discontinuation and not being able to achieve the discontinuation control goals. One of the factors that influence the abandonment of treatment is the lack of information for family members. The educational activities directed to family members are relevant to the patient's rehabilitation process. Once the family becomes a source of support for the treatment of the disease, enabling adherence (10).

### **Use of alcohol and illicit drugs**

The consumption of alcoholic beverages and the use of drugs in excess impairs the proper functioning of the body of any individual, especially when it is compromised by some diseases. ATT is associated with alcohol use, which increases the chance of medication intolerance, and may be considered one of the causes for abandonment. One of the issues that raise the low adherence of users of alcoholic beverages and chemical dependents, their clinical condition, and they also face strong social exclusion, and psychological and emotional conflicts that are situations that worsen due to the lack of family support (1).

The use of alcohol and illicit drugs has a poor prognosis for the treatment of TB, factors that predispose patients to abandon the treatment and prolong the drug therapy. Part of the patients who do not use alcohol and drugs end up developing withdrawal crises, returning to use, and abandoning treatment, while others do not leave their addictions and end up not adhering to treatment properly (4).

These patients are irregular in taking daily medications, do not complete the therapeutic scheme, and only return to the health unit when they feel

unwell, where they often become multidrug-resistant TB (13).

### **Inherent problems with medications**

There are several problems related to levels of adherence to treatment, such as incorrect or irregular use of the medication, forgetfulness, lack of motivation, anxiety about possible AEs, frustration with the healthcare team, anxiety about complex regimens, amount of medication, and emotional factors.

The majority of the patients discontinue treatment because of AEs, contributing to the interruption of treatment, so patients should be assisted regularly. The healthcare team should warn patients about the AEs of medications, and that information about the reactions of the medications during treatment should be clarified to avoid future abandonment (4).

Most of the patients reported AEs to ATT have suffered from the AEs of the drugs, presented by pain and burning sensation in the stomach, nausea, vomiting, and body pains throughout the body. It was observed that the signs and symptoms generated by AE, which is stronger than the symptoms of the disease, lead people to abandon treatment (11).

One of the determinants of adherence to ATT is the patient's relationship with the health care professional. Adherence is a complex concept when we consider the therapeutic recommendations (14). Identifying AEs, performing specific care in the face of AEs, confirming the dose of the drugs used, excluding other causes for the signs and symptoms presented, estimating the severity of the AEs, suspending the drugs responsible for the adverse symptoms and reintroducing gradually according to the resolution of the condition (11).

The approximation of healthcare professionals to the social context of patients is a complementary way that raises the possibility of early identification of treatment abandonment, the use of an accessible language to the treatment of patients, and individualizing education about the importance of not interrupting treatment (15).

### **Analysis of the regulation of anti-tuberculosis drugs in the Kyrgyzstan**

According to the Law of the Kyrgyzstan 'On Public Procurement' No 72, dated April 03, 2015 (16); and other by-laws including the Order of the Ministry of Finance of the Kyrgyzstan "About approval of regulatory legal acts in the sphere of public procurements" dated October 14, 2015 No. 175-p (17), procurement of ATD is carried out on a competitive basis. In this article, as a purchasing party, we will consider the example of the National Center of Phthysiology. According to the above Law, the purchasing party develops a public procurement plan with an indication of the budget for the next fiscal

year and places it on the public procurement web portal (18). Before starting the procurement procedure, a list of necessary ATD is compiled, then the needs are calculated, taking into account the stocks available on the balance sheet and the number of ATD consumers. To do this, an inventory of the balances is carried out monthly with the provision of a report on the balances of the ATD in the National Center of Phthisiology. Next, a technical specification is compiled for the purchased ATD.

In accordance with the Law of the Kyrgyzstan "On Circulation of medicines" No. 165 dated August 02, 2017 (19), drugs and medical devices with state registration can be imported into the territory of the Kyrgyzstan, since the presence of a registration certificate gives the right to the circulation of the drug on the market of the Kyrgyzstan, as well as serial quality control of drugs, including laboratory tests. Therefore, when drawing up a technical specification for purchased ATD, a necessary condition is the availability of a registration certificate issued by the authorized body of the Department of Medicines and Medical Devices under the Ministry of Health of Kyrgyzstan.

In addition, upon arrival in the country, each delivered batch of medicines undergoes a quality assessment procedure, including laboratory tests with the issuance of an opinion on the quality of a specific batch of medicines. The quality assessment procedure is carried out in accordance with the 'About approval of the Procedure for evaluating the quality of medicines' dated July 05, 2018 No. 312 (20).

However, in addition to the above requirements, in order to provide high-quality medicines, it is desirable to have in the technical specification a requirement for the prequalification assessment of the World Health Organization or other strict regulatory authorities such as the Food and Drug Administration, European Medicines Agency, Pharmaceuticals, and Medical Devices Agency, Swiss Agency for Therapeutic Products, and Medicines and Healthcare products Regulatory Agency, because the World Health Organization prequalification assessment process is based on strict regulatory principles and includes data on safety, efficiency, and quality of medicines, as well as an audit of the company for compliance with the rules of good distribution practice. Further, after the tender for the purchase of TB drugs and the conclusion of a contract for the supply of ATD, drugs are delivered to the central warehouse of the National Center of Phthisiology.

## CONCLUSION

Adherence to the ATT is essential for the control of its transmission. Treatment abandonment is a challenge for public health due to several related factors, where in this research we identified the main difficulties in adhering to treatment such as the lack of information

about TB in patients and their families, the Use of alcohol and illicit drugs, and inherent problems with medications. In order to strengthen the requirements for the quality of purchased ATD, when drawing up the technical specification of the government decree of the Kyrgyzstan, it is necessary to give preference to drugs that have been prequalified by World Health Organization or drugs that have been evaluated by strict regulatory authorities. The orientation to the patient regarding the AEs of medication and to their families the pertinent information to the correct and adequate treatment and the importance of welcoming them to the patient. We must take into consideration the social and clinical repercussions that the disease causes related to the decrease in quality of life, where it reflects negatively on family life, work, and social activities in general.

For the effectiveness in adherence and the reduction of discontinuation, it is necessary to have a professional bond with the patient and his family in the care and follow-up so that health actions can be taken to increase adherence to the therapeutic scheme. Patients should be helped to accept their diagnosis and encouraged to continue the treatment, and mechanisms should be created to increase adherence and improve their quality of life.

## CONFLICT OF INTEREST

None.

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