Universitat Autònoma de Barcelona

Identification and analysis of risk factors associated with Lost to follow up from tuberculosis treatment in Sanatorium Hospital in Luanda

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Identification and analysis of risk factors associated with Lost to follow up from tuberculosis treatment in Sanatorium Hospital in Luanda.

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List of abbreviations

AFB: Acid Fast-Bacilli

BMC: British medical Council

CDC: Centre for Disease Control

DSS/EMG/FAA: Direcção dos Serviços de Saúde do Estado Maior General e Forças Armadas Angolanas

FP: Family of Patient

HIV: Human immunodeficiency Virus

HP: Health Professional

IEC: Information Education Communication

ISPTEC: Instituto Politécnico de tecnologias e Ciências

ISTM: Instituto Superior Técnico Militar

IGRA: Interferon Gamma Release Assay

LTFU: Loss to Follow Up

LTI: Latent TB Infection

MDR: MultiDrug resistance

MSB: Ministério da Saúde no Brasil.

N P: Number of participants

N M: Number of male

N F: Number of female

P E: Patient Expert

PNCT: Programa Nacional contra a Tuberculose (National Control Program of Tuberculose)

PNCTA: Programa Nacional contra a tuberculose em Angola (National Control Program of Tuberculose in Angola)

PT: Patient

PP: Parent of Patient

RIF: Rifampicin

RR TB: Rifampicin-Resistant Tuberculosis.

RQ: Research Question

TB: Tuberculosis

TST: Tuberculin skin test

T: Total Number

UNICEF: United Nations International Children Emergency Fund

WHO: World Health Organisation

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Summary

Tuberculosis (TB) continues to be a serious problem for public health due to the high prevalence, incidence and mortality rates caused annually in the communities. The study aim is to identify and analyse the risk factors of lost to follow up (LTFU) TB treatment in patients treated for TB in Sanatorium Hospital in Luanda. LTFU TB treatment is identified as one of the challenges to be considered in the fight against TB in Angola and is considered a major contributor to the great burden of TB disease. Moreover, it is known that lack of treatment adherence increases the risk of drug resistance, relapse and mortality rate.

The objective of this thesis is to analyse the main characteristics of TB patients who are LTFU at the Hospital Sanatorium de Luanda, as well as to understand the main factors related to LTFU. For this purpose, two studies were designed for this. In the first one, we carried out a prospective cohort study with 113 patients, who started TB treatment in Sanatorium Hospital in Luanda between August first, 2018 and September, 30th 2019 and we analysed the main characteristics of patients who were LTFU. We performed a second study with a qualitative approach focused to better understand the main factors related to LTFU TB treatment, from a perspective of patients, family members and health care providers. A total of 49 people were interviewed, and 4 focus groups were carried out.

When we analysed the variables associated with LTFU in the cohort of patients treated for TB in Hospital Sanatorium of Luanda, we observed that a severe TB presentation at the moment of diagnosis and eating less than 3 times per day were significantly associated with LTFU TB treatment (OR 9.24, 95% CI 2.18-39.04, p=0.006) and (OR 5.96, 95% CI 1.66-21.41, p=0.006). During the interviews and focus groups, we identified four main causes that lead to LTFU TB treatment: healthcare barriers, drug related problems, religious beliefs and sociodemographic variables such as lack of family support, economic factors, relocation and distance.

The conclusions of this thesis are of enormous value to understand the reasons for the loss of follow-up of patients with TB in order to be able to design measures that allow better adherence and, therefore, greater treatment success.

Resumen

La tuberculosis (TB) continúa siendo un grave problema de salud pública debido a las altas tasas de prevalencia, incidencia y mortalidad que provoca anualmente en las comunidades. El objetivo del estudio es identificar y analizar los factores de riesgo de pérdida de seguimiento del tratamiento de la TB en pacientes tratados por TB en el Hospital Sanatorium de Luanda. La pérdida de seguimiento de pacientes en tratamiento de la TB es considerado uno de los desafíos en la lucha contra la TB en Angola y se considera que contribuye de manera importante a la gran carga de enfermedad por TB. Además, se sabe que la falta de adherencia al tratamiento aumenta el riesgo de resistencia a los medicamentos, la recaída y la tasa de mortalidad.

El objetivo de esta tesis es analizar las principales características de los pacientes con TB que se pierden del seguimiento en el Hospital Sanatorium de Luanda, así como comprender los principales factores relacionados con la falta de adherencia al tratamiento. Para ello, se diseñaron dos estudios. En el primero, realizamos un estudio prospectivo de una cohorte con 113 pacientes que iniciaron tratamiento para la TB en el Hospital Sanatorio de Luanda entre el 1 de agosto de 2018 y el 30 de septiembre de 2019 y analizamos las principales características de los pacientes que abandonaron el tratamiento. Realizamos un segundo estudio con un enfoque cualitativo enfocado a comprender mejor los principales factores relacionados con la pérdida de seguimiento desde la perspectiva de los pacientes, familiares y personal sanitario. Se entrevistó a un total de 49 personas y se realizaron 4 grupos focales.

Cuando analizamos las variables asociadas a la pérdida de seguimiento en la cohorte de pacientes tratados de TB en el Hospital Sanatorio de Luanda, observamos que una presentación de TB grave en el momento del diagnóstico y comer menos de 3 veces al día se asociaron significativamente con la pérdida de seguimiento (OR 9,24, IC 95% 2,18-39,04, p=0,006) y (OR 5,96, IC 95% 1,66-21,41, p=0,006). Durante las entrevistas y grupos focales, identificamos cuatro causas principales asociadas a la pérdida de seguimiento: barreras para la atención médica, problemas relacionados con los fármacos antituberculosos, creencias religiosas y variables sociodemográficas como falta de apoyo familiar, factores económicos, reubicación y distancia al centro de salud.

Las conclusiones de esta tesis son de enorme valor para comprender los motivos de la pérdida de seguimiento de los pacientes con TB , lo que permitirá diseñar medidas que permitan una mejor adherencia y, por tanto, un mayor éxito del tratamiento.

1 Introduction

Tuberculosis (TB) continues to be a public health concern due to the high prevalence, incidence and mortality rates caused annually. In 2021, approximately 10 million new TB cases were reported worldwide with 1.5 million deaths. Moreover, the disruptions caused by the Covid-19 caused for the first time in many years a decrease in the notification rate and an increase in mortality attributed to TB.[1]

1.1 Brief description of tuberculosis

TB is an infectious disease caused by *Mycobacterium tuberculosis* (*MTB*). [2] The infection is transmitted mainly through the air from a person with active TB. The droplet nuclei traverse the mouth or nasal passages to the upper respiratory tract to eventually reach the alveoli of the lungs. There are three major factors that influence the direct transmission of TB: susceptibility of the exposed person, infectiousness of the source of infection and environment of exposure. Any exposed person may be infected by *MTB* but progression to active disease happens more frequently in more vulnerable groups such as people living with HIV, children under 5 years old, people with diabetes mellitus and those who are receiving immunosuppressive therapy.[3]

1.1.1 Incubation period

In the majority of cases, the incubation period of MTB lasts from two to ten weeks.[4] After this period, tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) became positive in most patients. In most cases, the infected person remains asymptomatic, with no signs of TB disease. This situation is called Latent TB Infection (LTI). The progression from LTI to active TB happens in around 10% of the cases, although the probability of developing an active TB increases in the presence of immunosuppression or in young children (Figure 1).

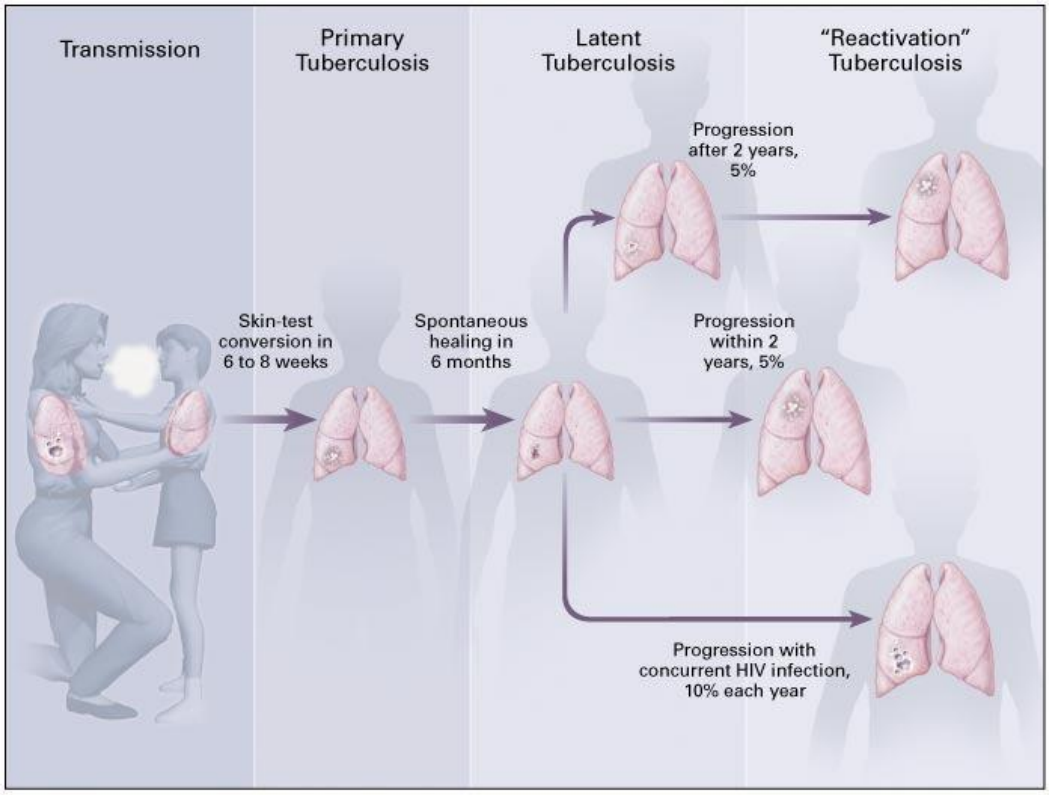


Figure 1: Tuberculosis disease progression

(Source: Small PM and Fujiwara PI, 2001)

1.1.2 Clinical manifestation of tuberculosis

Typical symptoms related to TB are mostly constitutional, such as fever, weight loss, night sweats, and asthenia. The most frequent form of TB is pulmonary TB, which typically causes chronic cough, dyspnea and haemoptysis. However, since *M. tuberculosis* may infect any organ, the clinical presentation may be very heterogeneous and depends on the affected organ.[5]

1.1.3 Diagnosis of tuberculosis

The diagnosis of TB is based on the direct detection of MTB in biological samples from the patient. Detection of Acid fast-bacilli (AFB) on sputum smear or other specimen through microscope visualisation is commonly the first test performed when TB is suspected. AFB smear test is relatively easy and quick technique, but it does not confirm a diagnosis of TB because some acid-fast-bacilli are not MTB. Therefore, the definitive diagnosis of TB is based on mycobacterial culture. However, MTB takes a long time to grow, which delays the diagnosis. Moreover, mycobacterial culture requires a high level of technological facilities,

which is not available in many settings where the burden of TB is very high. Due to these limitations, many laboratories rely on molecular techniques, such as the Xpert MTB/RIF, which allows automated detection of the existence of MTB complex and rifampicin (RIF) resistance, detecting mutations in the RIF resistance determining region (RRDR) of the gene *rpoB* with high sensitivity and giving a result in just 2 hours.[6] It is the only WHO-recommended test capable of detecting MTB complex and RIF resistance that can be used at any level, without the need for sophisticated laboratory technology. The WHO recommends its use in all patients (children and adults) with suspected TB as an initial test. It is a test that can be performed directly on a clinical sample without the need to process it previously and the only conditions required for its use are uninterrupted power supply and basic maintenance.

1.1.3.1 Immunologic diagnosis

In addition to direct tests, there are other diagnostic tests based on the detection of the immune response to mycobacterial antigens. These tests do not allow a definitive diagnosis of the disease, and only allow knowing if the person is infected with MTB, without being able to differentiate between infection and disease. Currently there are two types of immunological tests: TB skin test (TST) and Interferon-γ Release Assays (IGRAs). The TB skin test is performed by injecting subcutaneously purified protein derivatives of a mixture of various antigens common mycobacteria, which are common to both MTB and *M. bovis* (and their attenuated form Bacillus de Calvete Guarin (BCG) and non-tuberculous mycobacteria).

Once the test is done, it is necessary for patients to be visited within 48 to 72 hours to assess the skin reaction. The interpretation of the TST will vary depending on the result (degree of response generated) and the group of patients to be tested.

Figure 2: Intradermal administration of TST.

(Source: CDC, 2016).

The IGRA is an in vitro blood test which detects the release of IFN ɣ by T cells in response to specific antigens associated with the M. tuberculosis complex. [7]

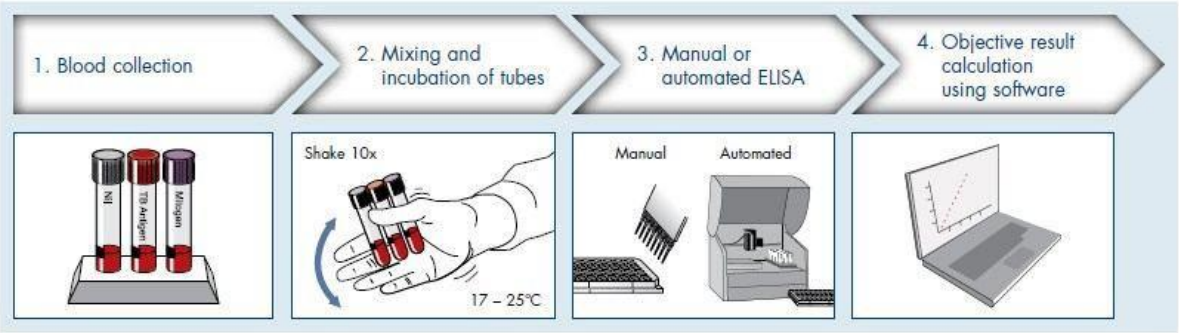


Figure 3: Blood test based on Interferon Gamma Release Assay (IGRA).

(Source: WHO, 2020).

1.1.3.2 Complementary tests

As most TB cases are pulmonary TB, performing a chest x-ray can help in the diagnosis. Pulmonary lesions may appear anywhere in the lungs, although the most common location in post primary TB cases (the most common presentation in adults) are the upper pulmonary lobes.

1.1.4 Treatment of tuberculosis

TB is a curable disease, although its treatment is complex and long-lasting. The reason for this is that the MTB is intrinsically resistant to most antibiotics classically used to treat bacterial infections. In addition, the MTB can be found in 4 different states, with different metabolic characteristics, which must be taken into account when designing a therapeutic regimen. These four phases are: metabolically active bacilli that are responsible for the development of resistance, bacilli in the acid inhibition phase that are responsible for relapses, bacilli in the sporadic multiplication phase, also responsible for relapses, and dormant bacilli. On the other hand, MTB grows slowly, which is also important in understanding the duration of treatment.

The basis of treatment for TB is based on the combination of at least 4 active drugs, to reduce the probability of the appearance of resistance.

The recommended treatment for susceptible TB is 2 months of RIF, isoniazid, ethambutol and pyrazinamide followed by 4 months of RIF and isoniazid. For RIF resistant TB (RR TB), WHO recommendations have considerably changed during the last years. Currently,

TB drugs for RR TB are classified in three groups, and a scheme composed of at least four drugs likely to be effective during 18-20 months is recommended. For the election of the drugs, Group A should be prioritise, followed by drugs included in group B and group C. For patients who have not been exposed to second line TB drugs and with no resistance to fluoroquinolone, a 9–12 month duration of bedaquiline (used for 6 months), levofloxacin/moxifloxacin, ethionamide, ethambutol, high dose of isoniazid, pyrazinamide, and clofazimine for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide is also recommended. [8] Table 1 summarised WHO classification of anti TB drugs for RR TB.

Table 1: WHO classification of anti TB drugs for Multidrug Resistant (MDR) TB

Groups	Drugs
Group: A	Levofloxacin or Moxifloxacin Bedaquiline Linezolid
Group: B	clofazimine Cycloserine or Terizidone
Group: C	Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin or Meropenem Amikacin Ethionamide or Prothionamide para-aminosalicylic acid

1.1.5 Control and prevention of tuberculosis

Infection prevention and control in settings where TB transmission is high is one of the pillars to end the global TB epidemic. The goal of TB prevention and control is to decrease the risk of TB transmission. There are many strategies for controlling and preventing TB and they are classified in three groups regarding WHO guidelines:

1.1.5.1 Administrative control:

a) To screen people with TB signs and symptoms;

b) To isolate infectious cases,

c) Respiratory hygiene

1.1.5.2 Environmental control

a) The use of upper room germicidal ultraviolet systems

b) The use of ventilation systems.

1.1.5.3 Respiratory protection

a) Using particulate respirators

Moreover, to control the TB epidemic, treating positive cases with effective anti-tuberculosis drugs as soon as possible, and to make patients adhere correctly to the treatment, are also key facts to control TB. [9]

It is also necessary to understand that education, information and communication (IEC) is essential and it helps health professionals and community leaders to better impact people. [10]

1.2 Epidemiology of tuberculosis

TB is declared as one of the global emergency diseases in the world, due to the high number of deaths it causes per year and the negative impact it lingers on families. [11] In 2020, 10 million people fell ill with TB. After COVID 19, TB is the second cause of death due to a single infectious agent. According to the latest WHO Global TB report, more than 1,3 million people died from TB, and, for the first time after many years, mortality rate due to TB increased in four of the six WHO regions. In the African region, the numbers of deaths in 2020 were stable. [12]

In 2020 approximately 10 million people were infected with TB worldwide out of which 5,6 million were men, 3,2 million were women and 1,2 million were children. We need to recall that TB is present in all countries and age groups.

1.2.1 Tuberculosis in Angola

Angola is one of the top thirty nations in the world in terms of TB burden, being included in the WHO's three high TB burden country lists (TB, TB-HIV, and MDR TB) See Figure 4.

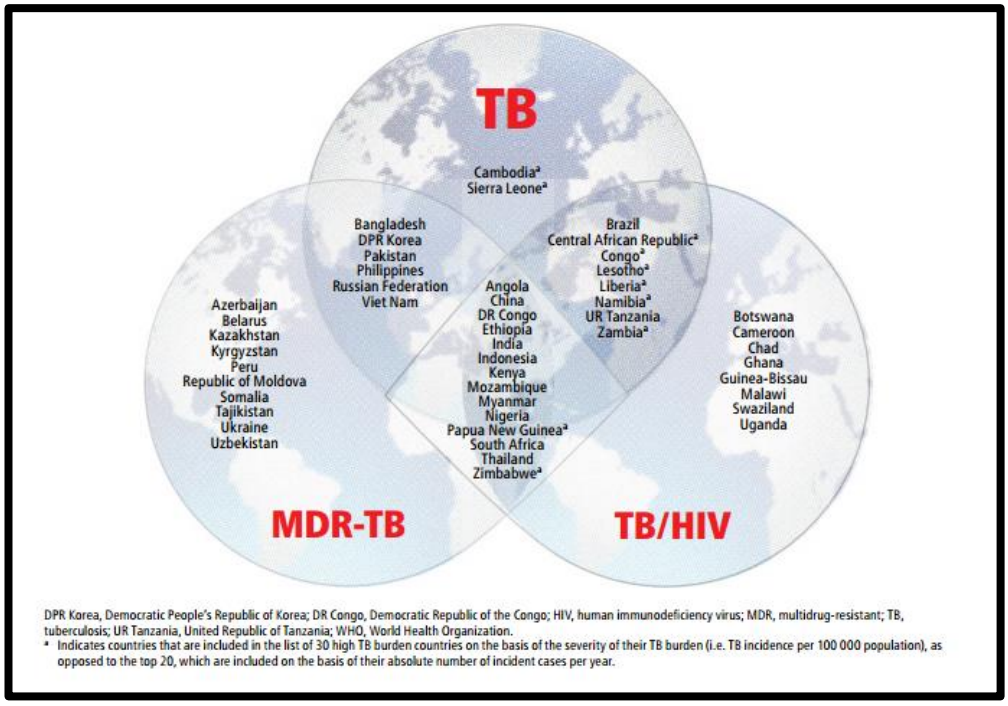


Figure 4: Countries included in the WHO's three high TB burden country lists. (TB, HIV-TB coinfection and MDR TB).

(Source: WHO Global TB Report 2015).

Based on WHO data from 2020, the estimated TB incidence is 350 (225-503) per 100.000 populations, with a treatment coverage rate of 55% [13](WHO, 2021). In 2020, Angola notified 66.058 TB cases. Trends on TB incidence and TB mortality are summarised in the Figures below.

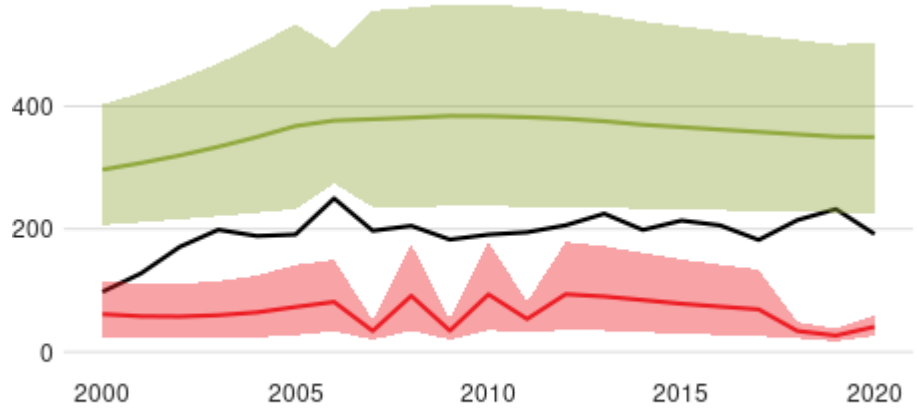


Figure 5: Incidence, new and relapse TB cases notified, HIV-positive TB incidence in Angola (Rate per 100 000 population per year)

(Source: TB country profile, WHO)

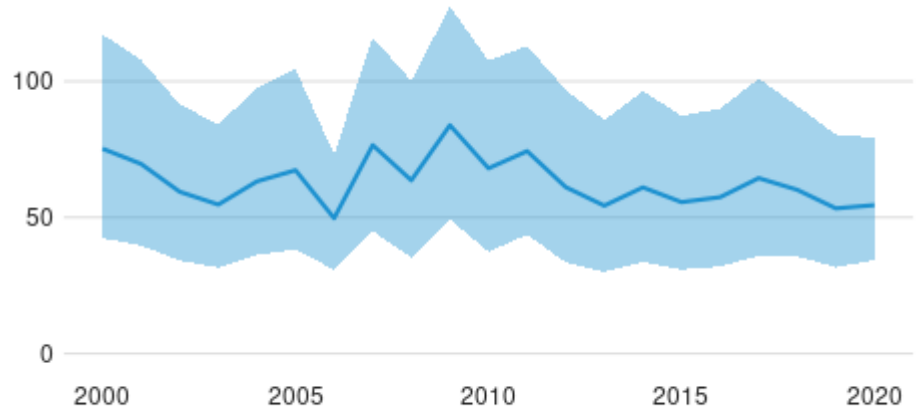


Figure 6: HIV-negative TB mortality in Angola (Rate per 100 000 population per year).

(Source: TB country profile, WHO)

1.2.1.1 Spatial distribution of TB in Angola

TB is not homogeneously distributed in Angola. Cities of Luanda, Benguela, Huambo, Bie, Moxico and Lunda-Norte have a higher prevalence and incidence rates of TB, probably due to a higher population density in those provinces. In rural areas where the incidence of TB is lower, TB poses a problem because of other factors such as a lack of health facilities, insufficient staff and qualified people.

1.2.2 TB/HIV co-infection

Of the total 63,970 reported TB cases, 45.466 (71%) in 2021 were tested for HIV, of which 5.619 (12%) were co-infected TB/HIV cases.

1.2.3 Multidrug-resistant tuberculosis (MDR TB)

Until 2014, there was no access to rapid diagnosis of TB and RIF resistance in the country. In 2014, the first Xpert MTB/RIF machine was implemented in Angola, which gave rise to the first confirmed data on MDR TB in the country. Since then, several Xpert MTB/RIF devices have been distributed throughout the country, and practically all provinces have the possibility of performing molecular diagnosis of TB and resistance to RIF. However, today there is only one laboratory with the capacity to perform mycobacterial cultures in the country. In 2020, 1.199 cases of MDR TB were reported in the country.

1.3 Lost to follow up TB treatment

Loss to follow up (LTFU) TB treatment is defined as a TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.[14] It is relevant to understand that LTFU TB treatment is identified as one of the challenges to be considered in the fight against TB worldwide. [15] and is considered a major contributor to the great burden on TB disease.

Moreover, it is known that lack of treatment adherence increases the risk of drug resistance, relapse, and mortality rate.[16]

1.3.1 Factors related with LTFU TB treatment

There are many factors that have been associated with LTFU TB treatment and the may be classified as follows:

1.3.1.1 Sociodemographic factors

Age: Several studies have observed that adolescents and elderly patients are more likely to LTFU TB treatment due to the lack of family support. [17]

Gender: There is evidence that the majority of cases of TB and TB deaths occur in male. Moreover, men are more likely to LTFU TB treatment than women. This fact has been related to some social conditions such as alcohol and drug abuse, although there might be other sociocultural factors that explain this association. [18] In some cultures, men have greater responsibilities than women for providing food and taking care of the family and this fact has been hypothesised as a reason for being LTFU. [19]

Distance to health care facility: This variable has been identified as one of the sociodemographic factors that contribute to the LTFU TB treatment in Angola. [20] It is been observed that TB patients who live far away from a TB facility have more difficulties in the treatment adherence mainly due to the cost of transportation. [22] Several studies have observed an association between distance from home to TB facilities and LTFU TB treatment. [23-24]

1.3.1.2 Community and family support

Community and family support has been identified as a very important part of the treatment process, and treatment adherence. [24] Many patients have to incur in transportation, food and treatment expenses that they are not able to afford that may be covered by family members. Lack of family and social support proved to be one of the main obstacles to continuing TB treatment.

1.3.1.3 Information and knowledge about TB

It is been observed that for patients who do not have basic knowledge of TB it is difficult to respect medication posology and frequency of attending consultations.[25] It is been hypothesized that majority of patients with lack of TB knowledge live in precontemplation. Patients in this stage are difficult to move on to contemplation, preparation, action and maintenance.

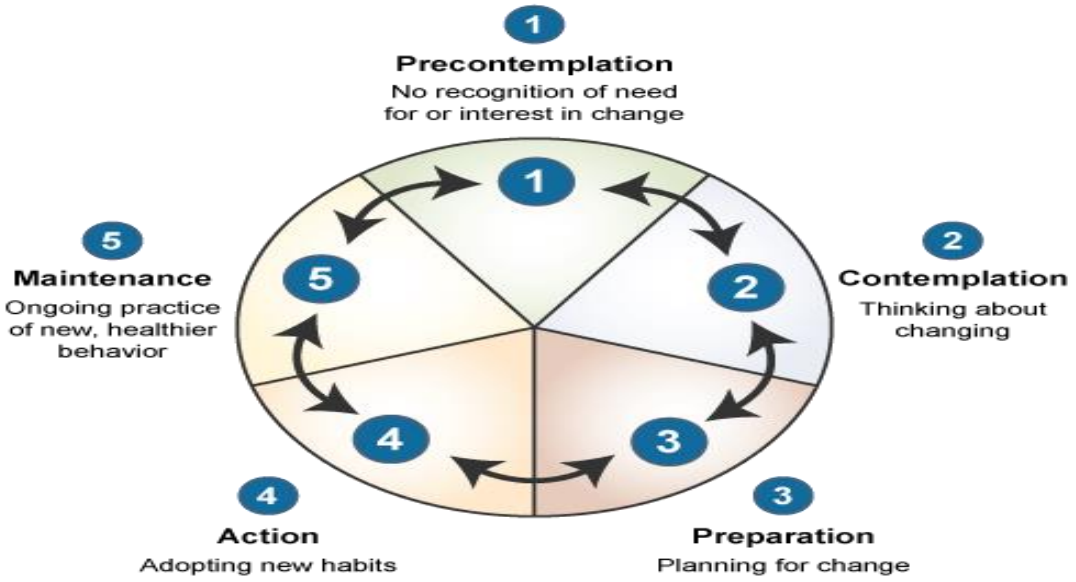


Figure 7: Stages of change

(Source SCOTT et al, 2004)

1.3.1.4 Lifestyle variables

Alcohol consumption and smoking are two individual behavioural factors that have so far been associated with LTFU TB treatment. It's been observed that the proportion of patients who abuse alcohol and smoke cigarettes is higher on LTFU TB treatment compared to those who do not use alcohol and smoke cigarettes. [26]

1.3.1.5 Level of education

Lack of basic education is one of the factors that have been observed to be related with LTFU TB treatment. It has been thought that illiterate people may have greater difficulty in understanding the recommendations, and easier to fall in misunderstandings.[27]

Unemployment

Unemployment is identified as one of the factors associated with LTFU TB treatment. It is been observed that patients who do not work are more likely to LTFU TB treatment compared to those who work.[28] Moreover, unemployment is linked to poverty and more risk of malnutrition, condition that is also related both to TB development and LTFU TB treatment due to economic difficulties.[29]

1.3.1.6 Treatment related factors

1.3.1.6.1 Adverse events

Many patients LTFU TB treatment due to adverse events related to drugs. Adverse events related to anti-TB drugs are relatively frequent, and mainly associated with second line TB drugs. For this reason, it is very important to have close monitoring and good communication between patients and health care providers. [30]

1.3.1.6.2 Duration of TB Treatment and number of pills taken per day

Duration of TB treatment is identified as one of the factors that influence patients to LTFU TB treatment, due to the negative impact that it causes on human, social, economic and psychological effects such as depression, anxiety, and stress. [31]

Currently, TB treatment lasts, at least, 6 months. Moreover, if combined drugs are not available, the number of pills per day becomes quite high. In addition, paediatric formulations are sometimes not available, making adherence difficult in children.

-Culture, ethnicity, religious beliefs and traditional doctors and Kimbandas

The cultural ethnicity values, religious beliefs, traditional doctors and Kimbandas values, also contribute to enhancing the vulnerability of people in Angola towards the LTFU TB treatment. [32]

Traditional doctor or healer is defined as a person who does not have any formal medical training but is considered by the local community as being competent to provide health care using animal, plant, mineral substances and certain other techniques based on social and cultural background. [33]

A Kimbanda is defined as a person who is accepted in the community and who provides solutions to different matters such as health and social issues that affect people's lives. Kimbanda is a Portuguese word originating from the Kimbundu language of the Bantu. The term corresponds to Nganga from the Kikongo language. [34]

Angola is made up of 18 provinces and 164 municipalities. The culture of the Angolan people depends on each province and ethnicity. In some cultures and ethnicities in Angola it is frequent that, when a person gets sick, she/he cannot go to the hospital without first consulting traditional doctors and Kimbandas to check if the illness is the result of envy that people are causing. When the conclusion is that the illness is caused by envy, it is treated by

using animals, plants and minerals substances. If a patient goes directly to a health care centre without consulting Kimbandas or traditional doctors they believe to be at risk of dying due to witchcraft.[35]

In contrast, other cultures and ethnicities in Angola allow people to visit a health care centre and start conventional treatment with health professionals. However, if there is no improvement after 2-4 weeks, family members advise the patient to LTFU treatment and to start traditional treatment. People seeking help from traditional doctors believe that the result of the treatment is better and faster compared to conventional treatment. In contrast with the recommended 6 months of TB treatment, traditional doctors complete the TB treatment in two to four weeks. This fact highlights that in countries such as Angola, where most people believe in traditional doctors and superstitions, the culture, ethnicity, religious and superstitious beliefs may make it difficult both access and adherence to TB treatment

Many religious leaders in Angola guide people to believe that when someone is sick the first step to do, even before starting treatment, is pray to God, ask for forgiveness and trust for divine healing as the bible describes in Psalms 103:1-3,

Spiritual and cultural beliefs should be regarded as distinctive strength in wellness programs, therefore, increasing the welfare of both doctors and sufferers in the midst of diseases, healing, hurt and death. Both ethnic as well as spiritual beliefs alter the patient's viewpoint regarding healthcare and their tendency to acknowledge, manage and cope up with the sickness, significance of diagnosis and the outcomes of medical treatment. These values affect the role and expectation of the patients.

1.3.1.7 Stigma and discrimination

Stigma and discrimination have also been related with LTFU TB treatment. There is evidence that, even health care providers focused on TB care, stigmatise patients.

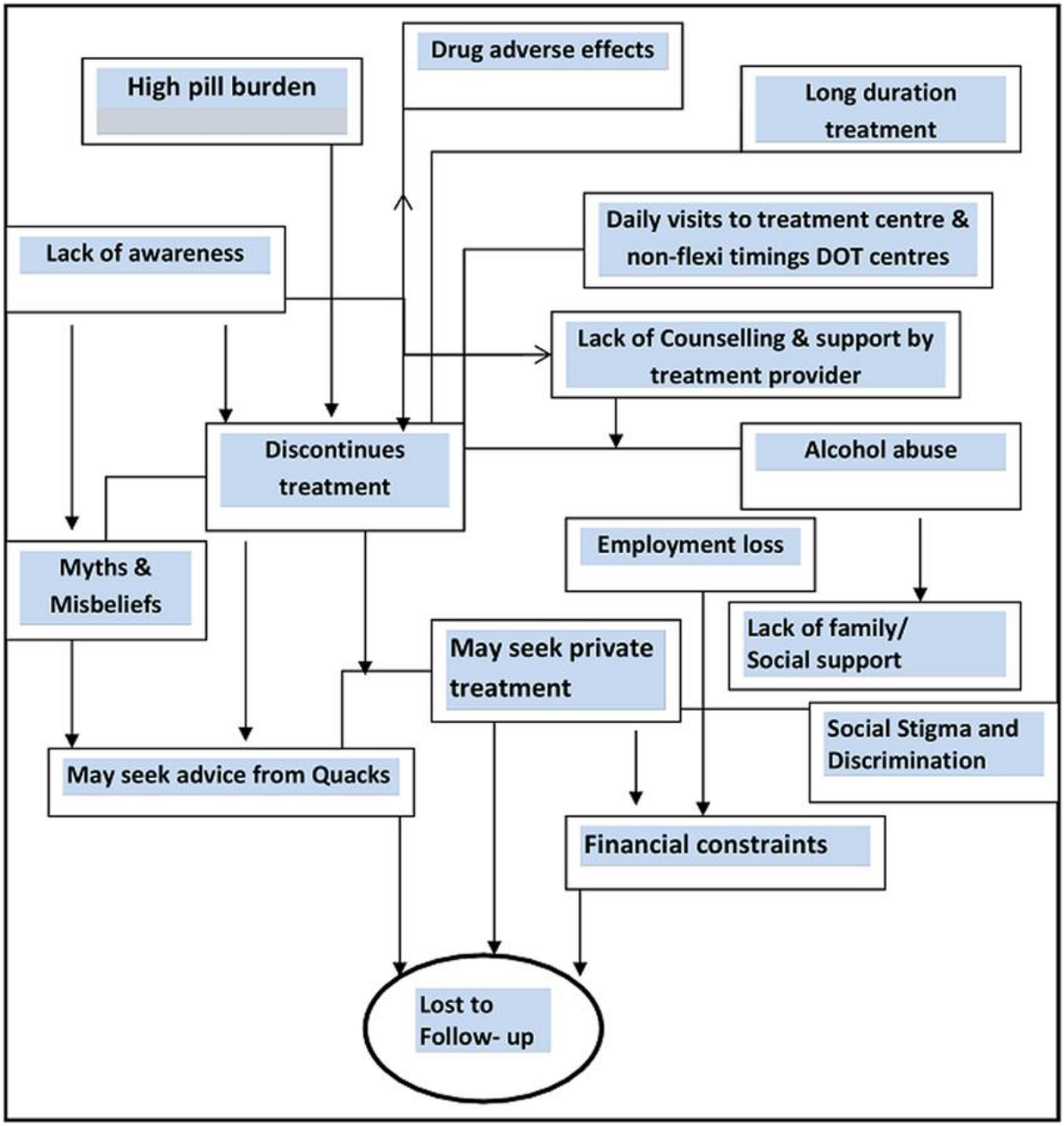


Figure 8. Factors related with lost to follow up TB treatment

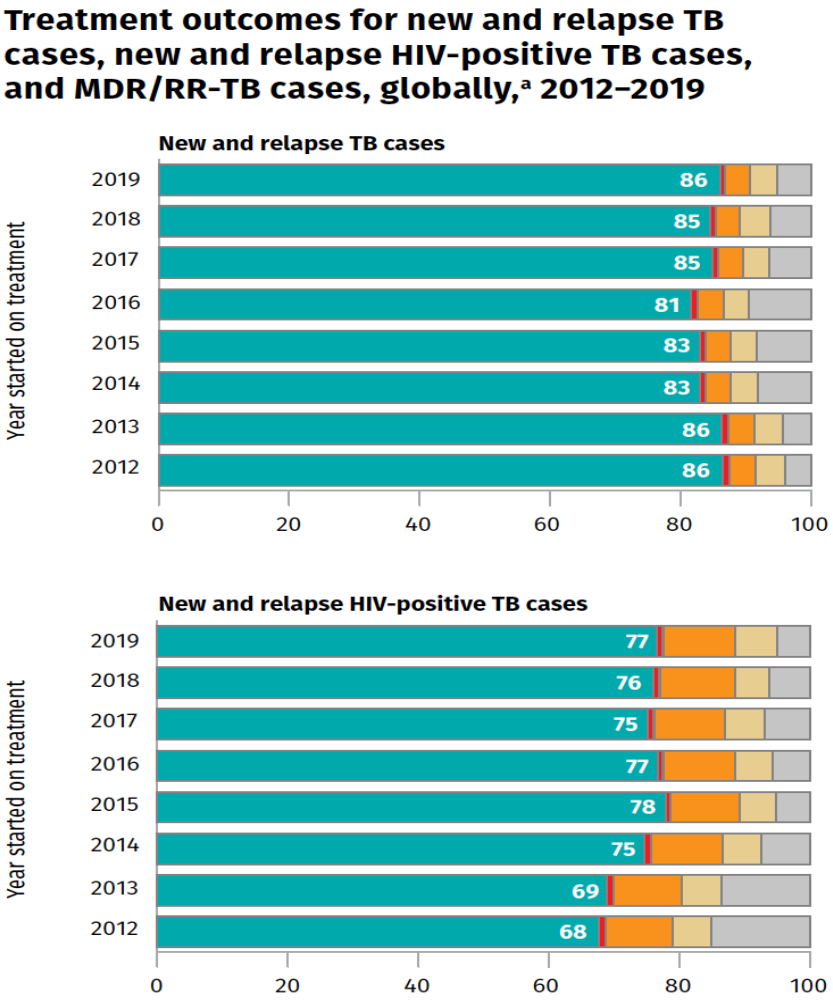
(Source: DESHMUKH et al, 2015).

1.3.2 The impact of LTFU TB treatment

Patients with TB who did not start any TB treatment or ran into interruption for almost two successive months or more are tagged as LTFU TB treatment patients.[36] Such patients continue to spread TB to the community and they are at a greater risk of evolving MDR-TB.

The proportion of patients who are LTFU for TB treatment varies regarding the country, the type of TB and the patients' population group. According to WHO, LTFU TB treatment is

slightly higher among patients living with HIV and patients with MDR TB.[37] (See figure below).



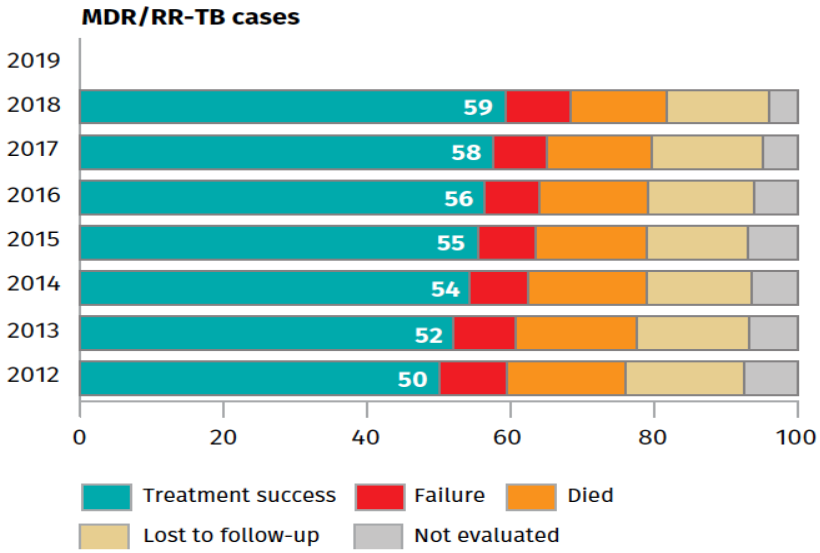


Figure 94: Treatment outcomes for new and relapse TB cases, new and relapse HIV-positive TB cases, and MDR/RR-TB cases, globally,2012–2019.

(Source: 2021, WHO Global Tuberculosis Report).

Patients who are LFTU are at a greater risk of developing drug resistance TB and they are key contributors to spreading TB to the community.[38] Hence, LTFU must be one of the primary concerns in combating TB. Every case of LTFU can be a step toward an outbreak as has been observed in different studies. [36-39]

Moreover, LTFU TB treatment results in high mortality rates [40] and increase of TB treatment cost. [41]

2 Justification of the study

Despite being a preventable and curable disease, TB continues to be a major health issue in many countries in the world, such as Angola. LTFU TB treatment is an important problem that should be addressed to achieve the Global targets and milestones for reduction the burden of TB disease. Factors associated with LTFU TB treatment may be different regarding the setting, and a good knowledge of these factors is essential to design a good national plan to control TB. A deep knowledge of the factors related with LTFU TB treatment from patients, families and health care providers may provide new insight for the requirements of an effective health care programme in Angola to manage the TB problem in the community.

3 Hypothesis

There are several sociodemographic and economic factors associated with LTFU TB treatment. Moreover, lack of information about TB transmission, treatment and prognosis may be related to LTFU. Semi Structured interviews to patients, families of TB patients and health care professionals may give a wider vision of the factors associated with LTFU TB treatment.

4 Objectives:

4.1 General objective

To identify and analyse the risk factors of LTFU TB treatment in patients treated for TB in Sanatorium Hospital in Luanda.

4.2 Specific objectives

- To describe the characteristics of the patients with TB treated with anti-tuberculosis drugs in Sanatorium Hospital in Luanda.
- To identify the socio-demographic, health lifestyle and religious beliefs factors associated with LTFU TB treatment
- To assess the relationship between clinical manifestation, adverse events and LTFU TB treatment.
- To assess and explore different perspectives in the factors related to LTFU TB treatment among patients, families, and health care providers in Sanatorium Hospital in Luanda.

5 Methods.

5.1 Analysis of risk factors associated with LTFU TB treatment in a cohort of patients treated for TB in Sanatorium Hospital in Luanda.

We carried out a prospective cohort study of patients who started TB treatment in Sanatorium Hospital in Luanda between August 1st 2018 and September, 30th 2019.

The Luanda Sanatorium Hospital is a TB referral hospital in Luanda province. Around 3.500 to 5.000 TB patients are diagnosed every year. Routine procedures for TB diagnosis in the Hospital are performed as follows: all patients with a suspected pulmonary TB are asked to collect three sputum samples. Microscopic examination for acid-fast bacilli (AFB) using Ziehl-Neelsen stain is performed in all clinical samples. A quality control on the reading of sputum smears is routinely performed according to the guidelines of the National TB Control Programme in Angola. Sputum Xpert MTB/RIF is performed as a first diagnosis method in previously treated cases and in new cases with a close contact with an MDR TB case. In cases of extrapulmonary TB, microscopic examination for AFB is performed in biological samples from the affected organ (pleural fluid, peritoneal fluid, cerebrospinal fluid, lymph nodal tissue, etc). All patients are also advised to perform a Chest-X ray. However, since the X-ray has to be paid by patients, it is not available in many cases. Patients are always offered HIV testing, which is repeated in case of a positive result. All patients are also offered a malaria rapid test. Patients are followed in the outpatient clinic every 2 weeks during the intensive phase and every 2 months during the continuation phase. In case a patient needs hospital admission, he/she is followed up on a daily basis while inpatient. Sputum smear is performed at 2, 5 and 6 months of treatment. Treatment recommendation for new cases and previously treated cases with RIF susceptibility is based on 2 months of RIF, isoniazid, pyrazinamide and ethambutol followed by 4 months of RIF and isoniazid.

5.1.1 Inclusion criteria

- Patients older than 15 years old
- Patients who started TB treatment for RIF susceptible TB based on a microbiological (sputum smear or Xpert MTB/RIF) or clinical diagnosis
- Patients who signed the informed consent.

5.1.2 Exclusion criteria

- Patients who came to the Sanatorium Hospital in Luanda in stage of coma.
- Patients treated with a second line TB drugs.

5.1.3 Data collection

At the moment of TB diagnosis, and before starting TB treatment, a structured questionnaire was carried out to all included patients. The following variables were prospectively recorded:

Demographics: gender, age at treatment initiation, place of residence, distance from the place of residence to Sanatorium Hospital in Luanda, if the patient was the house ownership, taxi fee to hospital, level of education, ethnicity, religion, employment, place and type of employment, monthly salary, and if the patient received family support.

Health/Lifestyle: smoking, alcohol consumption, and dietary habits.

TB beliefs and knowledge: belief in God as TB healer, knowledge of someone who stopped treatment due to religious reasons, knowledge of someone cured by a prayer, knowledge of TB traditional doctor, and knowledge of TB (definition, cause, transmission, clinical manifestation, diagnosis, treatment, and control and prevention).

Medical history and clinical variables: history of TB in the family, prior treatment with TB drugs, presence of symptoms (i.e. fever, cough, weight loss, night sweats, asthenia, thoracic pain, dyspnea, haemoptysis) and clinical status at diagnosis.

Diagnosis variables: Sputum smear, sputum Xpert MTB/RIF, and radiological findings. Sputum smear was graded in negative, scanty (when the sputum contains 1–9 AFB in 100 fields), 1+ (10–99 AFB in 100 fields), 2+ (1–10 AFB per field), and 3+ (more than 10 AFB per field). Xpert MTB/RIF was captured as MTB detected vs MTB not detected. In case of MTB detection, the semi quantitative assessment (high, medium, low, and very low) was also recorded. We did not record the RIF resistance since patients who had a RIF resistant TB were not included in the study. Radiological findings were captured as presence of lung infiltrates (yes/no) and the presence of lung cavities (yes/no).

Treatment variables: adverse events related to TB drugs and treatment outcome were also recorded. Definitions of these variables are described below.

5.1.4 Definition of variables

Severe TB was defined when the patient presented the following signs and/or symptoms at the moment of diagnosis: oxygen saturation below 90%, and/or massive haemoptysis (considered as 150 mL of blood expectorated in a 24-hour period, defined for patients as a half cup of blood)

Place of residence was divided in urban areas, when patients were living in the city, and suburban areas, when patients were living around the city.

Monthly salary was classified as low salary, when the average income was between 45.000 and 75.000 kwanzas per month; and medium salary, when the average income per month was between 75.000 and 175.000 kwanzas.

Patients were considered to have **TB knowledge** when they knew at least two of the 7 questions for the "TB knowledge" section of the questionnaire (definition, cause, transmission, clinical manifestation, diagnosis, treatment, and control and prevention)

Case definition: Cases were defined as new cases, in patients who were never treated with TB drugs for more than a month; and previous treated cases in patients who had received 1 month or more of anti-TB drugs in the past.

Treatment outcomes were defined on the basis of 2013 WHO recommendations (WHO, 2013)

- Cure was defined as treatment completed as recommended by the national policy and smear negative in the last month of treatment and on at least one previous occasion.
- Complete treatment was defined as patients who completed treatment as recommended by the national police without evidence of failure but no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative.
- Treatment failure: A TB patient whose sputum smear was positive at month 5 or later during treatment.
- Death: A TB patient who dies for any reason before starting or during the course of treatment.
- LTFU was defined as a patient whose treatment was interrupted for 2 consecutive months or more.

- Not evaluated: A TB patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
- Treatment success: The sum of cured and treatment completed.

5.1.5 Data analysis

Descriptive statistics are present as number and percentages in the case of categorical variables and mean (SD) or median (IQR) depending on variable normality. We used chi-square tests or Fisher’s exact tests to compare categorical variables and t-tests or Mann-Whitney tests to compare continuous variables. A two-sided P value <0.05 was considered statistically significant for all analyses. SPSS (version 22) was used to analyse variables.

For the univariate and multivariate analysis, the variable TB outcome was banded in two groups: cured and LTFU TB treatment and considered as the dependent variable. Variables with a p-value <0.20 in the univariate analysis and variables considered to be clinically important, were included in the multivariate logistic regression analysis.

5.2 Qualitative approach to identify the reason of LTFU TB treatment

5.2.1 Design

A qualitative approach was used to explore information about factors that influence patients to LTFU TB treatment. We used both semi-structured interviews and focus groups. The semi-structured interviews were selected because they allow us to learn in greater depth and in a less biased way other factors related to LTFU not detected in the previously described quantitative study. We also considered focus groups as another approach to perceive the interaction, disagreements, and dynamics among participants.

5.2.2 Setting

Participants were recruited in Sanatorium Hospital in Luanda.

5.2.3 Participants

Semi-structured interviews were addressed to TB patients who were on TB treatment at the moment of the interview, TB patients who were on TB treatment at the moment of the interview but who were LTFU TB treatment previously, TB patient experts (defined as a person with previous TB and who has been empowered with the skills, confidence and knowledge needed to play an active role in making informed decisions about their own health care and management of their clinical condition) and health professionals attending TB cases.

5.3 Semi-structured interviews

The purpose of the study was clearly informed to the participants and all of them signed the informed consent. The interviews consisted of three open questions: 1) What are the factors that influence patients to LFTU TB treatment, 2) What does happen after LTFU TB treatment and 3) What are your recommendations to improve the adherence to TB treatment. Two researchers carried out the interviews. Due to culture and religion background, where power is generally held by men, we decided that interviews with women were carried out by a woman, and interviews with men were carried out by a man, to make it easier for the interviewees to feel more comfortable and speak with fewer restrictions. Participants were guaranteed anonymity so that they could speak freely without concern for professional or personal consequences. No participants dropped out of the study. The interviews were performed in Portuguese which is the official language of Angola. Each interview lasted on average 40 minutes.

Interviews were performed until the researchers considered that no additional data were being found (data saturation).

5.3.1 Data analysis

Interviews were digitally recorded and transcribed verbatim. Written notes were also captured. The audio recorded data was transcribed, translated into English and manually coded. To analyse findings from interviews the author used a thematic analysis approach that helped to find out relevant points which contribute significantly to the study. The codes captured differences and similarities in the perceptions of participants and concepts that recurred. Emerging themes and sub themes were identified by two researchers.

5.3.2 Ethical considerations

Ethical approval was awarded from the Angolan national ethic committee. Participation in the research was voluntary and written informed consent was provided by all participants.

6 Results

6.1 Analysis of risk factors associated with LTFU in a cohort of patients treated for TB in Sanatorium Hospital in Luanda.

6.1.1 Demographic and lifestyle data

A total of 113 patients were included. Sixty-seven (59.3%) were males and 46 (40.7%) females. Most patients lived in a suburban area (90, 79.6%) and did not own their homes (86, 76.1%). Most participants were Christians (107, 94.7%). In terms of economic background, more than half of the patients had no salary (67, 59.3%) and were not working at the time of the study (67, 59.3%). Twenty-three (79.6%) patients were smokers and 39 (34.5%) consumed alcohol (65.5%). Fifty (44.2%) patients consumed less than three meals per day and the most frequent types of food they consumed were vegetables (95.6%), fruit (80.5%), fish (97.3%), and meat (85.0%). Thirty-nine (34.5%) patients were also infected by *Plasmodium sp.* at the time of TB diagnosis. Regarding comorbidities, thirty-four (30.1%) had hypertension, thirteen (11.5%) had diabetes mellitus and twenty-two (19.5%) were infected by HIV. Demographic and lifestyle data are presented in table 2.

Table 2: Demographic and lifestyle data of TB patients

	N=113 (%)
Sex, Male	67 (59.3)
Age (years), median (IQR)	30 (22-44)
Location	
Urban	23 (20.4)
Suburban	90 (79.6)
House ownership	27 (23.9)
Taxi fee to hospital	
<600 kwanzas	94 (83.2)
≥600 kwanzas	19 (16.8)
Education	
Basic incomplete	39 (34.5)
Basic complete	21 (18.6)
Medium high incomplete	27 (23.9)
Medium high complete	19 (16.8)

University	7 (6.2)
Ethnicity	
Bakongo	23 (20.4)
Umbundu	33 (29.2)
Kimbundu	51 (45.1)
Other	6 (5.3)
Religion	
Christianity	107 (94.7)
Islam	1 (0.9)
Hindu	1 (0.9)
No religion	4 (3.5)
Employment	46 (40.7)
Place of employment	
Factory	14/46 (30.4)
Market	11/46 (23.9)
Other	21/46 (45.6)
Type of employment	
Manual	42/46 (91.3)
Other	4/46 (8.7)
Salary	
Low salary (<8000 kwanzas)	40/46 (86.9)
Medium salary (≥8000 Kwanzas)	6/46 (13)
Smoking	23 (20.4)
Drinking alcohol	39 (34.5)
Comorbidities	
Asthma	7 (6.2)
Hepatitis	1 (0.9)
Diabetes	13 (11.5)
HIV	22 (19.5)
Cardiac insufficiency	8 (7.1)
Hypertension	34 (30.1)
Concomitant malaria	39 (34.5)
Number of meals per day	
One meal	3 (2.7)

Two meals	47 (41.6)
Three meals	63 (55.8)

6.1.2 Beliefs and knowledge about TB

The majority of respondents stated that they believed God could heal TB (94.7%), but only 14.2% reported knowing someone who had been cured by a prayer, and only 7.1% reported knowing someone who had stopped treatment for religious reasons.

Overall knowledge about TB was low, with (40.7%) TB patients knowing at least two of the seven questions related to TB.

6.1.3 TB symptoms and diagnosis

The most common TB symptoms were weight loss in 104 (92.0%), fever 103 (91.2%), cough 103 (91.2%), night sweats 78 (69.0%), asthenia 73 (64.6%), and thoracic pain 49 (43.4%). Ninety-eight cases were diagnosed with pulmonary TB (86.7%) and 27 (23.9%) presented a severe TB at the moment of diagnosis. Ninety out of the ninety-eight pulmonary TB were able to provide a sputum sample, and it was positive in sixty-two (68.9%) of the cases.

6.1.4 TB follow up and treatment

Ninety-nine (87.6%) patients attended at least one consultation; and 14 (12.4%) patients never came back to consultation. Regarding TB outcomes, seventy-six (67.3%) patients were cured, and 27 (23.9%) were LTFU. Table 3 shows the most frequently presenting symptoms of TB.

Table 3: Clinical findings, diagnosis, and treatment outcomes of TB patients

	N=113 (%)
History of TB in the family	26 (23.0)
Presence of symptoms and signs	
Fever	103 (91.2)
Cough	103 (91.2)
Weight loss	104 (92.0)
Night sweats	78 (69.0)
Asthenia	73 (64.6)
Thoracic pain	49 (43.4)

Dyspnea	37 (32.7)
Hemoptysis	17 (15.0)
Adenopathies	7 (6.2)
Ascites	2 (1.8)
Column deformation	9 (8.0)
Smear positive sputum	
Positive	62/90 (68.9)
Negative	28/90 (31.1)
MTB detected by Xpert MTB/RIF	22/22 (100)
Radiological finding	
Cavitation	47/72 (65.1)
Lung infiltrates	25/72 (34.7)
TB severity at admission	
Severe	27 (23.9)
Type of TB	
Pulmonary TB	98 (86.7)
Extra pulmonary	13 (11.5)
Pulmonary and extra pulmonary	2 (1.8)
Type of TB patient	
New case	100 (88.5)
Previously treated case	13 (11.5)
Presence of Adverse Events	23 (20.4)
Type of toxicity	
Skin toxicity	5/23 (21.7)
Join Pain	1/23 (4.3)
Gastrointestinal symptoms	14/23 (60.9)
Hepatic toxicity	3/23 (13)
Number of FU visits	
Never	14 (12.4)
< 2 follow-up visits	24 (21.2)
≥ 2 follow-up visits	75 (66.4)
Outcome	
Cured	76 (67.3)
Lost to follow-up	27 (23.9)

Died	5 (4.4)
Transferred	4 (3.5)
Failure	1 (0.9)

6.1.5 Variables associated with LTFU TB treatment

6.1.5.1 Univariate analysis

When we analysed the variables associated with LTFU in the univariate analysis, it was observed that men were more likely to be LTFU than women (74.1% vs 25.9%, p=0.03). No other sociodemographic variables were significantly associated with TB outcome. This information is summarized in Table 4.

Table 4: Relationship between demographic profile and LTFU TB treatment

	Cured (N=76)	LTFU (N=27)	Sig (p value)
Sex, Male	38 (50)	20 (74.1)	**0.030**
Age, years; Median (RIC)	28 (21-41)	35 (25-46)	0.226
Areas of residence			
Urban	14 (18.4)	6 (22.2)	0.668
Suburban	62 (81.6)	21 (77.8)	
House ownership	18 (23.7)	6 (22.2)	0.877
Help from family	64(84.2)	19(70.4)	0.118
Taxi fee to hospital			
600 or less	64 (84.2)	22 (81.5)	0.743
More than 600	12 (15.8)	5 (18.5)	
Education			
Basic incomplete	26 (34.2)	10 (37.1)	0.959
Basic complete	15 (19.7)	6 (22.2)	
Medium high incomplete	17 (22.4)	6 (22.2)	
Medium high complete	12 (15.8)	4 (14.8)	
University	6 (7.9)	1 (3.7)	
Ethnicity			

Bakongo	17 (22.4)	5 (18.5)	0.939
Umbundu	23 (30.3)	8 (29.6)	
Kimbundu	32 (42.1)	13 (48.1)	
Other	4 (5.3)	1 (3.7)	
Religion			
Christianity	75 (98.7)	24 (88.9)	0.093
Islam	0 (0.0)	1 (3.7)	
Hindu	0 (0.0)	1 (3.7)	
No religion	1 (1.3)	1 (3.7)	
Employment	29 (38.2)	10 (37.0)	0.918
Place of employment			
No job	47 (61.8)	17 (63.0)	0.853
Factory	10 (13.2)	2 (7.4)	
Market	8 (10.5)	3 (11.1)	
Other	11 (14.5)	5 (18.5)	
Type of employment			
No job	47 (61.8)	17 (63.0)	0.946
Manual	27 (35.5)	9 (33.3)	
Other	2 (2.6)	1 (3.7)	
Salary			
No salary	47 (61.8)	17 (63.0)	0.858
Low salary	24 (31.6)	9 (33.3)	
Medium salary	5 (6.6)	1 (3.7)	

Participants who were cured ate more often three meals per day (breakfast, lunch, and dinner) than those who were LTFU (65.8% vs. 33.3%, p=0.002). No other lifestyle/health factors were significantly related to TB outcome. Table 5 shows the relationship between health and lifestyle variables and TB outcome.

Table 5: Relationship between health/lifestyle and LTFU TB treatment

	Cured N=76 (%)	LTFU N=27 (%)	Sig (p value)
Smoking	12 (15.8)	7 (25.9)	0.243
Drinking alcohol	21 (27.6)	11 (40.7)	0.206

Comorbidities			
Asthma	4 (5.3)	2 (7.4)	0.683
Diabetes	6 (7.9)	3 (11.1)	0.611
HIV	15 (19.7)	7 (25.9)	0.500
Cardiac insufficiency	3 (3.9	2 (7.4)	0.472
Blood pressure	20 (26.3)	9 (33.3)	0.486
Malaria	26 (34.2)	8 (29.6)	0.664
Digestive disorders	16 (21.1)	3 (11.1)	0.253
Number of meals per day			
< Three meals	26 (34.2)	18 (66.6)	**0.002**
Three meals	50 (65.8)	9 (33.3)	

Regarding TB beliefs and knowledge, we observed that people who were cured believed in God as a TB healer in greater proportion than those who were LTFU (98.7% vs. 88.9%, p=0.024). No significant association was found between having knowledge about TB and TB outcome (32.9% vs. 22.2%, p=0.299). This information is summarised in Table 6.

Table 6: Relationship between TB beliefs/knowledge and LTFU TB treatment

	Cured N=76 (%)	LTFU N=27	Sig (p value)
God can heal TB	75 (98.7)	24 (88.9)	**0.024**
Knowledge of:			
Someone who stopped treatment for religion	5 (6.6)	2 (7.4)	0.883
Cured by prayer	13 (17.1)	3 (11.1)	0.460
TB knowledge	25 (32.9)	6 (22.2)	0.299

Regarding TB symptoms and diagnosis, we observed that those patients who presented as severe TB at the moment of diagnosis were more likely to LTFU TB treatment (37.0% vs. 15.8%, p=0.021). This information is summarised in Table 7.

Table 7: Relationship between TB symptoms and diagnosis and LTFU TB treatment

	Cured N=76	Lost to FU treatment	Sig (p value)

		N=27	
History of TB in the family	18 (23.7)	8 (29.6)	0.541
Prior use of TB drug recommended by doctor	75.0 (9)	25.0 (3)	0.919
Symptoms and signs			
Fever	69 (90.8)	24 (88.9)	0.774
Coughing >3weeks	67 (88.2)	26 (96.3)	0.220
Weight loss	7 (9.2)	2 (7.4)	0.776
Night sweats	48 (63.2)	21 (27.6)	0.165
Asthenia	46 (60.5)	19 (70.4)	0.363
Thoracic pain	36 (47.4)	7 (25.9)	0.052
Dyspnea	27 (35.5)	6 (22.2)	0.203
Hemoptysis	12 (15.8)	2 (7.4)	0.275
Adenopathies	5 (6.6)	1 (3.7)	0.584
Ascites	2 (2.6)	0 (0.0)	0.395
Spinal deformity	7 (9.2)	2 (7.4)	0.776
Other	34 (44.7)	13 (48.1)	0.760
Sputum smear			
Positive	41 (53.9)	15 (55.6)	0.827
Negative	21 (27.6)	6 (22.2)	
Unrealized	14 (18.4)	6 (22.2)	
Quantification of BK			
0	35 (46.1)	12 (44.4)	0.891
1+	12 (15.9)	6 (7.9)	
2+	20 (26.3)	6 (7.9)	
3+	9 (11.8)	3 (11.1)	
Chest X ray			
Cavitation	33 (50)	11 (16.7)	0.815
Lung infiltrates	17 (25.7)	5 (7.6)	
TB severity at admission			
Severe	12 (15.8)	10 (37.0)	**0.021**
Type of BT			

Pulmonary TB	66 (86.8)	25 (92.6	0.985
Extra pulmonary	8 (10.5)	2 (7.4)	
Pulmonary and extrapulmonary	2 (2.6)	0 (0.0)	
Type of TB patient			
New case	69 (90.8)	22 (81.5)	0.195
Previously treated	7 (9.2)	5 (18.5)	
Presence of adverse events	15 (19.7)	6 (7.9)	0.783
Type of adverse event			
Dermatological toxicity	4 (5.3)	1 (1.3)	0.123
Arthralgia	1 (1.3)	0 (0.0)	
Gastrointestinal toxicity	10 (13.2)	3 (3.9)	
Hepatic toxicity	0 (0.0)	2 (2.6)	

6.1.5.2 Multivariate analysis

In the multivariate analysis, we observed that a severe TB presentation at the moment of diagnosis and eating less than 3 times per day were significantly associated with LTFU TB treatment (OR 9.24, 95% CI 2.18-39.04, p=0.006) and (OR 5.96, 95% CI 1.66-21.41, p=0.006)

Table 8: Multivariate analysis of variables associated with LTFU TB treatment

	OR	95%CI	P value
Gender (male)	3.32	0.9-12.1	0.091
Eat less than 3 times a day	5.96	1.66-21.41	**0.006**
Belief in God as healer of TB	0.24	0.02-70.01	0.251
Previously treated patients	0.54	0.09-3.12	0.493
Severe TB	9.24	2.18-39.04	**0.002**
Knowledge about TB	0.25	0.04-1.34	0.107

6.2 Qualitative Analysis of risk factors associated with lost to follow up patients treated for TB in Sanatorium Hospital in Luanda.

6.2.1 Demographic and lifestyle data

6.2.1.1 *Interviews*

A total of 49 (71.0%) people were interviewed, 28 (51.8%) were patients who LTFU TB treatment, 9 (16.6%) were patients with a recent diagnosis of TB, 2 (3.7%) were expert patients, 5 (9.3%) were family members of patients who LTFU TB treatment and 5 (9.3%) were health professionals attending TB patients.

6.2.1.2 *Focus groups*

A total of 4 focus groups were carried out. The first focus group was composed for 5 parents of children with TB, the second was composed for 5 family members of patients with TB, the third and fourth focus groups were composed for 10 health professionals (5 health professionals in each group). Among the health professionals there were 2 medical doctors, 3 nurses, 1 psychologist, 1 nutritionist, 1 health promoter, 1 laboratory technician and 1 pharmacist.

6.2.2 Risk factors that influence patients to LTFU TB treatment

The themes detected in the interviews and focus groups in relation to LTFU TB treatment are listed in table 1 and are described in more detail below.

A total of 5 thematic categories related to LTFU TB treatment were detected. First one was the **health care barriers** that emerged from patients, family members and health care providers. Among health care barriers, TB patients complained about the lack of access to health care coverage as a key driver for a lack of adherence. TB patients say that they do not have enough money to buy medications or to perform radiological examinations recommended by physicians. A patient said: "*I abandoned treatment because I did not have money to buy TB drugs and to do the X-ray that the doctor requested.*" Another health care barrier mentioned by health care professionals was a lack of good communication between health care providers and TB patients and families. Health care providers explained that patients were not well informed about the importance of completing treatment despite symptoms improving, the possible adverse events or general information about TB. Furthermore, 8 patients expressed negative behaviour of healthcare providers as the main

reason to stop TB treatment: "*I abandoned treatment due to the wrong behaviours of nurses and doctors. I preferred to buy medicines from the informal market but I lost my job and I do not have money to buy medications, but I do not want to collect drugs from the public hospital*."

The second thematic category comprises **drug related factors**. Patients referred that the number of pills, the duration of TB treatment and the adverse events were causes to stop TB treatment. A 19-year-old male complained: "*I abandoned TB treatment because I discovered that the TB drugs that the hospital was giving patients were expired. I decided to not take any TB drugs from that health care centre, and I did not have money to buy the medicine. I was waiting for my mother to be paid to buy the medicine for me, but she took a long time*." A 66-year-old male mentioned: "I *abandoned treatment due to the side effects that I had in the second month. I was vomiting all the time that I took medicine. I reported the situation to the doctors, but no one paid me attention*."

Thirteen patients mentioned the **symptom improvement** as a key reason for LTFU TB treatment. A 44-year-old male mentioned: *"I abandoned treatment because I started feeling well as you know the TB treatment is long but after feeling well there is no point of continuing with treatment, then I decide to stop."*

Sociodemographic factors were detected as the fourth thematic category. The most frequent cause for a lack of treatment adherence within this category was economic factors. A 35 years old female: "*I abandoned treatment due to my financial situation. I do not work, and I have no money to buy medications, or even to pay a taxi to attend consultations. When I started the treatment in the first month, I did not have food to eat and then I decided to quit the treatment."* A female family member said: *"*P*atients abandon treatment due to the poor conditions of living. For example I am here in the hospital helping my family member but we do not have food, the hospital only gives rice and all the time that patients eat rice they start coughing not because they have TB, but because of the rice they ate."* In addition, religious belief was also reported as a driver for LTFU TB treatment: A 35 years old male: "*I abandoned treatment because my family decided to take me to the traditional doctor who said if I take TB drugs again I will die. My disease needs to be treated traditionally."* A 47 years old female: *"**I** abandoned treatment because my pastor told me that I am cured by prayer, therefore I do not need any medications and I believed him."* Moreover, 7 people addressed that the lack of family support influenced patients to LTFU TB treatment. Location and distance were another condition mentioned by patients and

family members. A 21 year old male answered: *"I abandoned the treatment because I live in prison and no one cares about me and sometimes we do not have TB drugs."*

Table 9. Risk factors that influence patients to LTFU TB treatment

Themes	Subthemes	HP	PP	FP	PE	P	T
Health barriers	Lack of access-health care coverage	0	0	1	0	2	3
	Lack of proper communication	2	0	1	0	3	6
	Behaviour of health care provider	0	0	1	0	7	8
Drug related problems	Adverse events	4	1	2	1	4	12
	Long treatment	0	0	0	0	1	1
	Expired medication	0	0	0	0	1	1
Symptoms improvement		0	0	3	0	9	13
Sociodemographic factors	Religious beliefs	1	0	0	1	3	5
	Lack of family support	3	0	0	1	3	7
	Economic factors	7	4	8	1	9	29
	Relocation and distance	0	0	0	0	2	2

*HP: Health Professional; PP: Parent of Patient; FP: Family of Patient; PE: Patient Expert; P: Patient; T: Total Number of participants

6.2.3 Impact of LTFU TB treatment

All participants in the study mentioned that symptoms worsening after stopping TB treatment. Moreover, 24 participants mentioned death as a possibility after LTFU TB treatment.

Table 10. Impact of LTFU TB treatment

Themes	Subthemes	HP	PP	FP	PE	P	T
Health deterioration	Death	9	3	6	2	4	24
	Symptoms return-worsen	9	6	8	2	24	49

*HP: Health Professional; PP: Parent of Patient; FP: Family of Patient; PE: Patient Expert; P: Patient; T: Total Number of participants

6.2.4 Recommendation from patients and families member to Health care providers and health system to improve TB treatment adherence

The main themes arising from participants regarding recommendations for improving treatment adherence are listed below:

Improvement of communication between healthcare professionals and patients: Four people mentioned the need for the close monitoring of the drug adverse effects to enhance the effectiveness of the treatment of TB. Moreover, 22 people reported that a better education about TB could support patients in continuing TB treatment. Additionally, 7 participants determined that patients wanted a significant improvement in the attitude of health care providers as a key factor to improve the treatment adherence. Thirteen people mentioned that an appropriate patient tracking and supervision is essential for better adherence and treatment completion.

Universal health care coverage: In a similar way, several people mentioned that government agencies should increase the access to health care facilities among poor citizens so they could find the appropriate treatment of TB. Apart from that, 21 participants mentioned that government agencies should offer food, free medicine and economical support to patients in an appropriate manner that may have a significant impact on the treatment quality.

Ensure a quality of care: another aspect that arise from the interviews and focus groups was the need of improve the quality of care of TB programs. Both family members and patients mentioned that it would be necessary to include other activities such as community screening, community treatment and community education programs. Moreover, patients considered that it would be necessary to include a transport service for people who live far away from health care facilities.

Table 11: Recommendations to improve TB treatment adherence

Themes	**Subthemes**	**HP**	**PP**	**FP**	**PE**	**P**	**T**
Improvement of	Close follow up of adverse events	0	0	1	0	3	4

communication between healthcare professionals and patients	Education about TB	2	0	2	1	17	22
	Improved practitioner attitudes	2	0	0	0	5	7
	Patient tracking and supervision	0	1	3	1	8	13
Universal health care coverage	Increased access to healthcare	0	0	1	2	4	7
	Nutrition and economical support	2	4	6	1	8	21
Ensure a quality of care	Improve health care qualification and quality of care	0	0	1	0	3	4

*HP: Health Professional; PP: Parent of Patient; FP: Family of Patient; PE: Patient Expert; P: Patient; T: Total Number of participants

7 Discussion

TB remains a major public health problem globally. Angola is one of the countries in sub-Saharan Africa with the highest number of TB cases. LTFU TB treatment is considered one of the most important threats that can jeopardize all efforts made by TB control programs in the most prevalent countries.

In our study we have analyzed the main characteristics of patients who LTFU TB treatment in a cohort of patients treated with first line TB drugs in the Sanatorium Hospital of Luanda. We observed that patients included in the study have approximately 25% dropout and the success rate barely reaches 70%. When these figures are compared with other experiences in countries in the sub-Saharan African region, it could be concluded that the data presented are somewhat worse. Success rates from other Subsaharan countries range 82.5% to 92.5% [42,43-44], and the average success rate for people treated with first line anti-TB drugs reported from the 2021 WHO Global report is 86%.

In order to understand the risk factors associated with the LTFU TB treatment, we have designed this work through a quantitative and qualitative analysis.

7.1 Factors related wit LTFU TB treatment

7.1.1 Biological factors and clinical presentation

Among the many risk factors, the univariate analysis revealed that being male was significantly associated with the risk of discontinuing treatment. Seventy four per cent of patients who drop out are men compared to 50% of those who were considered cured (p: 0.03). Despite everything, in the multivariate analysis, sex failed to reach statistical significance [OR 3.32, (0.9 – 12.1, p: 0.09)]

A priori there would be no biological reason to relate the male sex to failure. However, this condition has been previously described and is linked to the social sphere. Santos et al. observed that, in the Angolan society, there is a higher social pressure on man to obtain economic income to be able to support the family. This fact could justify that men could be less constant for medical controls and treatment adherence.[45] Another fact is that men usually consume more alcohol beverages or other illicit drugs than women, habits widely described as risk factors for therapeutic non-compliance. [46]

In relation to the forms of presentation of TB, we observed that with a severe TB presentation at the moment of diagnosis were significantly associated with LTFU TB treatment (OR 9.24, 95% CI 2.18-39.04, p=0.006). We did not observe other variables related to clinical presentation associated to LTFU TB treatment.

Regarding age, no significant differences were found between the groups of patients who were considered cured or those who were LTFU. In contrast to our findings, other studies have observed that older patients are at increased risk of LTFU TB treatment [47] However, this relationship is not consistent among different cohort of TB patients and other reports have observed that the age range more likely to LTFU TB treatment is younger people. [17]

7.1.2 Economic factors

The relationship between poverty and TB is well documented. Both assume a reciprocal relationship because poverty can be related to precarious health conditions and disease can produce poverty, limiting work and subsistence opportunities thus forming a vicious circle, which tends to worsen the severity and negative impact of the disease.

TB is related to unfavourable socioeconomic conditions, which usually worsen when a member of the household is ill. Catastrophic costs associated with TB (defined as all direct and indirect costs, including income loss, that exceed a 20% threshold of a household's annual income) [48] are present in more than 40% of families affected by TB, and frequently affect the most vulnerable population.

Regardless of medicines for TB being free in most settings, including Angola, there are some expenses that the patients have to incur, such as consultation fees, laboratory tests, and other indirect costs such as transportation and family accommodation. Moreover, in Angola, main meals during hospital admission are not paid by the health system and have to be afforded by patients. In the same way, in Angola, most patients do not have health insurance and have no income while they are sick and unable to work. This condition portrays that patients have to distinguish and prioritise between the treatment of the TB and food respectively. [10]

Despite the above, in our study we have not found statistically significant differences between the surrogate markers of poverty (such as salary, transport cost). It is possible that the reduced number of included patients may limit our conclusions. Moreover, the characteristics of the patients are quite homogeneous with no large differences in economic terms between patients.

7.1.3 Nutritional status

There are many studies that assess the relationship between nutrition and TB. A good nutritional status has a positive impact on the immune system of the patient. That is, a well-nourished person presents a greater protection against the disease. [49-50]

Conversely, micronutrient deficiencies and caloric protein malnutrition have been shown to increase the risk of acquiring TB [51-52]. Furthermore, it has also been reported that patients with TB who are malnourished have shown a delayed recovery and even higher mortality rates in comparison to the ones who are well nourished. [53-54]

Our study was not designed to specifically measure nutritional status but we did try to quantify at least the number of food intakes per day by understanding this variable as a surrogate marker on the nutritional status of patients. It was observed that those patients who could not guarantee less than 3 daily meals per day were associated with a greater LTFU TB treatment. Two thirds of the patients who were classified as abandonment of treatment did not manage to complete 3 meals a day. On the other hand, the vast majority of patients (85%) who guaranteed 3 meals a day, managed to complete the therapeutic scheme and subsequent clinical follow-up. The multivariate analysis showed that patients who fail to complete a minimum of 3 meals a day have a 5.96 times higher risk of LTFU TB treatment compared to those who have a complete diet (OR: 5.96, 95%CI 1.66-21.41, p:0.006).

7.1.4 Religious beliefs and traditional healers

One of the aspects that we wanted to investigate in this study is the role that religious belief plays in the different clinical outcomes of TB. In the univariate analysis, we observed that the belief that God could cure TB was positively associated with healing. Virtually, all patients who were cured believed in God's healing role in the face of disease compared to 89% in the group of patients who abandoned treatment (p:0.024). There were no other aspects of religious beliefs that had a statistically significant association with the LTFU TB treatment. In the multivariate analysis, it was not possible to observe such a difference. It has been already observed that many individuals in Angola continue to believe that gods and other supernatural creatures have a role in their physical and mental health.[55] Most of respondents (93.4%) felt that praying to God for TB healing would be successful. According to Perdigao et al, the majority of Christians agree with the idea that God can heal someone with TB.[56] In nations where religious views are highly valued, the cooperation of

community and religious leaders is vital for TB control efforts. This permits more effective and culturally appropriate outreach to at-risk populations [9]

Previous research on TB beliefs has shown that traditional healers are often the first point of contact for TB patients worldwide. [35] This fact is so relevant that the Ghanaian government created the Traditional and Alternative Medicine Act in 2010 to control the use of both traditional and alternative medicine, given the preference of certain individuals and medical conditions for traditional medicine. In several nations, regional remedies are widely used.[57] Nearly 80% of people surveyed in Kenya felt that self-treatment and herbal remedies might cure TB quicker than conventional Western medicine.[58] In addition, the qualitative investigation identified religious belief as one of the key reasons for LTFU TB treatment. Thus, it may be claimed that religious factors could have a significant impact on clinical follow up and over treatment adherence. According to Diefenbach-Elstob, religious and traditional beliefs in Balimo, region in Papua New Guinee impacted adherence to TB treatment.[59] Despite the broad embrace of Christianity by the Gogodala tribe, several people continue to practise ancient animistic practices. People were influenced by traditional and religious perspectives, with religion playing the bigger role. As a consequence of religious beliefs and confidence in God, therapeutic compliance is discouraged, and faith is promoted instead.

7.1.5 TB Knowledge

The Knowledge, Attitudes and Practices (KAP) towards TB are made up of aspects such as what the disease is, the transmission mechanism, risk factors, signs and symptoms, diagnosis, treatment and prevention. In this sense, adequate knowledge of TB patients about the disease can encourage adherence to TB treatment and, therefore, prevent the appearance of drug-resistant forms of TB; promote contact identification of people with TB; strengthen the early detection of the disease and the demand for health services of new cases. In our study, patients were assessed for general knowledge about TB. After the analysis, no significant differences were found between the level of knowledge of those patients who cured and those who were LTFU. It is worth to mention that we found a very low level of knowledge about TB, that may reflect deficient information from health care providers, as it was observed in the qualitative analysis. Moreover, we did neither observe a relationship between level of education and TB outcomes.

In the qualitative approach, six surveyed participants cited a lack of TB knowledge as a major barrier to the use of LTFU treatment. To restate, knowledge is essential for determining how to handle health issues. It has been demonstrated that a patient with TB who has a poor level of education takes longer to see a doctor compared with those who have higher educational level. [60] According to Gebreweld et al, illiterate individuals face a variety of challenges, including difficulty acquiring access to health care. [61] Therefore, while working with patients who are illiterate or have poor levels of knowledge, healthcare practitioners must establish connections, provide monitoring, and ensure a good comprehension to improve treatment adherence. However, Afshari et al. contend that insufficient patient education on the side of healthcare personnel is the major reason for long-term TB treatment failures. [62]

The great majority of those who participated in the qualitative study believed that providing patients with a good information about TB facts and the importance of TB adherence might aid those individuals in taking a more active role in their health status. Patients' commitment to therapy may be hindered because a lack of understanding, a difficult communication with health care providers, and a lacked attention and support for the patients from health institutions. [63]

It has been shown that treatments that include education and counselling are effective in increasing therapeutic adherence. [64] As a result, further training and counselling in the tried-and-true technique may be required to ensure that patients continue to adhere to their treatment regimens.

7.1.6 Lack of a proper communication between healthcare providers and patients

After conducting the qualitative analysis, it was found that lack of communication could have been one of the possible reasons justifying the abandonment of treatment. Such lack of communication between medical experts, patients, and patient families, may trigger that some patients leave prematurely their TB treatment, jeopardising the efficacy of the therapy. Ataide et al. reported comparable results in their study of HIV-TB coinfected individuals who stopped taking their treatments. [65] Poor interactions between patients and healthcare providers have been linked to negative outcomes in terms of treatment adherence and clinical follow up.

7.1.7 Drug related adverse events

The appearance of toxicity during TB treatment could be one of the factors that would have conditioned the abandonment of treatment. Despite this, in our series, the proportions of adverse events in both groups were similar, without significant differences in the toxicity profiles between the two groups. Anyway, after performing a qualitative investigation with 14 participants, it was observed that drug-related issues, such as drug related adverse events, were another cause for LTFU TB treatment. For this reason it is essential to have a good communication between patients and health care providers, and to ensure that, if any toxicity appears, there is a good and early management to avoid serious consequences, and to avoid treatment dropouts.

Moreover, main TB stakeholders mentioned that both the long treatment duration and the number of pills were other factors related with LTFU. TB treatment duration is standardized by WHO and it is essential to complete the 6 months recommended to ensure a success treatment. However, again, a good communication and a good accompaniment may help for treatment adherence. Regarding the number of pills, the fix-dose combination drugs for TB have decreased the number of daily pills. However, there are still stock breakages that cause that drugs have to be used separately, increasing the number of pills.

7.1.8 Distance to TB healthcare facilities

It is essential for TB treatment success that patients reside within an acceptable distance from healthcare facilities. [25] Patients with TB who lived within five miles of a medical centre fared better than those who lived at least 10 miles away. If a patient lives closer to the clinic, they have a better likelihood of obtaining an appointment and completing TB treatment. [66] In any case, in our series we do not find significant differences between the place of residence and LTFU TB treatment. One of the most widely used strategies to improve the adherence of patients residing far from health centers has been directly observed treatment (DOT) programs. The World Health Organization (WHO) has widely supported the implementation of the DOT as part of the DOTS strategy, which aims to favour patient compliance, and to guarantee treatment completion. In Angola, the DOT program has been evaluated in the form of a pilot program in some municipalities of the country, with the intention of being able to be implemented at the programmatic level throughout the territory. Unfortunately, the structural cost of implementing the program is high and, until today, it depends on supranational funds that make this financing an unsustainable strategy.

7.2 Study limitations

Our study has several limitations:

Despite having been designed as a prospective cohort of patients treated with anti-TB drugs, the number of patients included during the study period was lower than expected. Several changes in the direction of the Luanda Sanatorium Hospital and the difficulty of being in the country to enrol patients in the study, has had a significant impact on the final number of included patients. A higher number of patients could have result in more robust data.

Some of the patients included in the study were diagnosed they clinically, without microbiological confirmation for TB. It is possible that some of the patients included in our study did not really have TB, but rather another respiratory infection, a fact that could have influenced the treatment outcome.

The interviews were all conducted at the Hospital Sanatorium de Luanda, so patients who had dropped out and then never returned to consultations were not included. The perspective of people in the community who do not return to hospital can give another view of the reasons for LTFU.

In the qualitative study, we perform the interviews in Portuguese and the transcripts had to be translated into English for coding, which may have produced some loss of nuance.

Moreover, our study is focused on Sanatorium Hospital in Luanda, and it reflects the reality of Luanda, but it might not be applicable for the rest of the country, especially rural areas.

8 Conclusion

1. In the cohort of patients who started a first line TB regiment in the Sanatorium Hospital of Luanda, the proportion of LTFU is high (24%).

2. A severe TB presentation at the moment of diagnosis was significantly associated with LTFU TB treatment.

3. Eating less than 3 times per day were significantly associated with LTFU TB treatment.

4. The main causes that lead to LTFU TB treatment from patients, patient's family members and health care providers' perspectives were: healthcare barriers, drug related problems, religious beliefs and sociodemographic variables.

5. The main solutions suggested by TB patients, TB patient's family members and health care providers were: improvement of communication between healthcare professionals and patients, universal health care coverage and Ensure a quality of care.

9 Future perspectives

The studies that make up this thesis observe that the problem of the LTFU TB treatment is a very important issue in Angola and that it has clear causes identified by patients, relatives and health personnel. In this sense, we think that the results of this study can help to define specific strategies that could improve patient adherence. Thus, in the future, we can evaluate new strategies to improve treatment adherence. In this sense, we have planned to carry out a systematic review of the strategies implemented by other neighbouring countries and try to apply them to the Angolan context.

A growing number of nations are implementing new technologies applied to the health sector, including mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices. Appointment reminders and medication adherence programmes are two examples of the many strategies now used to reduce LTFU. Our idea is to be able to incorporate these services in the Luanda Sanatorium Hospital and to be able to analyse their impact in this context.

Since the lack of awareness of TB has been pointed out as one of the main causes for the discontinuation of treatment, we consider that it would be interesting to evaluate how an information program focused on patients could improve the problem of LTFU TB treatment.

Moreover, we have observed that a strong religious conviction could be a motivating factor to avoid the abandonment of treatment. Among the possible options to be explored, one could be the integration of religious communities and their leaders in TB programs, to incorporate messages that favour treatment adherence and clinical follow-up. Likewise, we cannot forget the powerful role played by traditional medicine and traditional healers as health referents of society; so a combined strategy among TB programs and traditional medicine could result in an important benefit that would undoubtedly revert to the health of patients.

10 Bilbiography

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11 Appendix

11.1 Appendix 1

INTERVIEWS AND FOCUS GROUP

Table 1: Category of participants and numbers

Category of participants	N. of male	N of Female	N.of P
Patients who lost to follow up TB treatment	21	17	28
New patients	4	5	9
Patients experts	0	2	2
Family of patients interviewed	2	3	5
Parents of patients in focus group 1.	2	3	5
Family in focus group 2.	2	3	5
Health professionals in focus group 1	2	3	5
Health professionals in focus group 2	1	4	5
Health professionals interviewed	2	3	5
Total	36	33	69

Table 2: Themes for the interviews and focus group

Theme for interview
Why do you abandon treatment?
What happens after quitting the treatment?
What would you recommend?

Interviews and focus group

1- **Patient 1: 27 years old, male.**

I abandoned treatment because I was feeling well and I decided to start drinking alcohol and smoking cigarettes. After two weeks I started coughing again, having fever and pain in my chest. Then I went to an informal market to buy the medicine that the hospital gave me for the first time that I went to the consultation. After feeling better I stopped the treatment again. Two weeks later I felt sick and I went to a small health care centre. They told me that I have malaria and they treated it but the cough and the fever remained. My two brothers took me to Sanatorium Hospital in a critical stage, nearly to die. I recommend the hospital to implement strategies that will help patients to take medicines in front of health professionals and to teach patients about the consequences of quitting TB drugs treatment.

2- **Patient 2: 38 years old, male.**

I abandoned treatment due to the Nurses and Doctors behaviours and also the side effects of medications such as vomit and weak body. After 3 weeks of giving up treatment, I started to vomit blood, feeling pain in my chest and having high fever. Then my family decided to bring me to the Sanatorium Hospital in a critical stage of health. I recommend Nurses and Doctors to consider the sick because one day they may get sick too.

3- **Patient 3: 66 years old, male.**

I abandoned treatment due to the side effects that I had in the second month. I was vomiting all the time that I took medicine. I reported the situation to the doctors but no one paid me

attention. After quitting the treatment I became more sick then my family brought me to the emergency unit in Sanatorium Hospital. My recommendation is that the Nurses and Doctors must take care of patients and also show responsibility to their work.

4- Patient 4: 19 years old, male

I abandoned TB treatment because I discovered that the TB drugs that the hospital was giving patients were expired. I decided to not take any TB drugs from that health care centre and I did not have money to buy the medicine. I was waiting for my mother to be paid to buy the medicine for me but she took a long time. The TB symptoms and signs came back and I was in a critical health situation including vomiting blood. A friend and family member advised me to go to Sanatorium Hospital. I recommend the health Professional especially pharmaceuticals to have more attention before distributing medicine to patients. The minister of health needs to have control of the TB drugs that hospitals are distributing to patients.

5-Patient 5: 41 years old, male.

I abandoned TB treatment because I did not have help from families and friends. I was not working and I could not buy medications, food and also I did not have money to pay for a taxi to go back to the hospital for consultation. I did not get any motivation from health professionals. After 3 weeks I felt bad and I lost memory. Someone collected me from the street and took me to the Sanatorium Hospital due to the clinical manifestation that I was presenting. My recommendation is that health professionals must have more responsibility by helping and controlling patients.

6-Patient 6: 45 years old, male,

I abandoned treatment due to the wrong behaviours of nurses and doctors. I preferred to buy medicines from the informal market but I lost my job and I do not have money to buy medications but I do not want to collect drugs from the public hospital. After one month of abandoning treatment the situation of my health was complicated day by day nearly to death. My family brought me to Sanatorium hospital by force, now I am doing medication but the nurse still misbehaves. I recommend that health professionals consider people with TB and give them value and also the health authorities need to provide good food to patients with TB not always rice. Since I am in hospital most days we eat rice. After eating rice we start coughing.

7-**Patient 7: 43 years old, male.**

I abandoned treatment after 3 weeks because I was feeling better, no more pain in my chest, no fever, cough, all the symptoms and signs gone then I decided to go back to my work as a builder. After 2 weeks of giving up the treatment I started feeling pain and coughing and difficulty breathing. I could not walk and my brother brought me to Sanatorium Hospital. I recommend the hospital to start following the patients, even calling them to find out if they're doing medication or not.

8-Patient 8: 51 years old, male.

I abandoned the treatment because I was feeling well. After 2 weeks I started vomiting blood, coughing, fever, and headache. My wife brought me to Sanatorium Hospital in critical condition. I recommend the hospital to have rigour on controlling patients who are in treatment out of the hospital and also health professionals need to give more attention to patients who are diabetics like me.

9-Patient 9: 21 years old, male

I abandoned the treatment because I live in prison and no one cares about me and sometimes we do not have TB drugs. After one month I started coughing and I went to see a doctor, he asked me to do some exams. The result of the exams that he requested was MDR. Police officers brought me to Sanatorium Hospital but even here I am still a prisoner. My recommendation is that health professionals must stop looking at prisoners like dogs. Most of the time they were putting TB drugs on the floor for me to collect, which is not good. The minister of health together with the chief of police need to review this situation.

10- Patient 10: 38 years old, male.

I abandoned the treatment because I did not have money to buy medications. When I was diagnosed, the first time they gave me medications for free to take for 2 weeks. A doctor told me that I must buy TB drugs to continue medication. After 3 weeks I became very sick and my uncle brought me to Sanatorium Hospital in critical condition. I recommend the hospital to provide medication for free to all patients.

11- Patient 11: 53 years old, male

I abandoned the treatment due to the wrong medications that the doctor gave me in the first consultation. After taking TB drugs I was feeling sicker than before. Later we discovered

that the person who prescribed the medications was not a medical doctor. My family brought me to Sanatorium Hospital in a critical stage of TB. I recommend the government to start checking the qualification of the health professionals and controlling private health care centres like where I was attending consultation.

12- Patient 12: 32 years old, male

I abandoned the treatment because I moved location from where I used to live before. I got a new job and I decided to focus on my new job rather than going to the hospital to collect the TB drugs. After 3 weeks the situation was complicated, I was very sick so my friends brought me to the Sanatorium Hospital. The doctor requested exams and from the result I found out I had MDR. I would recommend the hospital to have more control for patients and educate the population about the consequences of quitting TB treatment.

13- Patient 13: 35 years old, male.

I abandoned treatment because my family decided to take me to the traditional doctor who said if I take TB drugs again I will die. My disease needs to be treated traditionally. After a couple of days I started coughing and vomiting blood and the company that I used to work for, took me by force and transferred me to the Sanatorium Hospital in Luanda without family ethical consideration. I would recommend Health Professionals to have good communication between families and patients. In my case I found out that my family was not collaborating with health professionals.

14- Patient 14: 20 years old, male.

I abandoned treatment when I felt well after 2 months. Later on I had chest pain, fever, cough and breathing difficulty. My uncle decided to take me to the Sanatorium Hospital in critical condition of health, and nearly died. I would recommend the health authority to implement programs which will help to follow patients.

15- Patient 15: 31 years old, Female

I abandoned treatment when I was not having any more symptoms and signs of TB. After 3 weeks of giving up the treatment the symptoms came back and I decided to go to Sanatorium Hospital. I would recommend the hospital to organise the data base of patients because when I came to the hospital they did not recognise me as an old patient who abandoned TB treatment.

16-Patient 16: 24 years old 24, female.

I abandoned treatment because I was feeling well and I tried to contact the doctor but she did not respond to my calls. I went back to my normal life and activities. Three weeks later symptoms and signs came back and my parents decided to take me to the Sanatorium Hospital. I would recommend the doctors and nurses to give more attention to patients and provide good care.

17-Patient 17: 35 years old, female.

I abandoned treatment due to my financial situation. I do not work and I have no money to buy medications, or even to pay a taxi to attend consultations. When I started the treatment in the first month I did not have food to eat and then I decided to quit the treatment. After three weeks I started coughing, feeling pain in my chest and vomiting blood. My friend took me to the Sanatorium Hospital. I would recommend the government to help patients who are in need in hospitals and in the community.

18-Patient 18: 26 years old, female.

I abandoned treatment because the doctors and nurses were arrogant. From there I went back to my normal life and activities. After four weeks I was unable to stand and to walk. The symptoms and signs of TB came back and my family decided to take me to the Sanatorium Hospital. I would recommend health professionals to treat all patients well.

19-Patient 19: 30 years old, female

I abandoned treatment because I was feeling well. Three weeks later symptoms came back and my family decided to take me to Sanatorium Hospital. I would recommend nurses and doctors to teach patients about the danger of quitting treatment.

20-Patient 20: 44 years old, female

I abandoned treatment because I did not have money to buy medications, food and to pay for a taxi to attend consultations. Symptoms came back. My family brought me to the hospital in critical condition. I would recommend the hospital to help patients with medications and food.

21- Patient 21: 25 year old, male

I abandoned treatment because in 2019 and 2020 the hospital was not giving all the TB drugs to patients and I did not have money to buy medications and food to eat. I came back to the Sanatorium Hospital in a critical condition and nearly died and I developed MDR. I would recommend the minister of health to help patients with medication and food.

22- Patient 22: 22 year old, male.

I abandoned treatment because my father who was helping me with money, food and medications passed away (died), I did not have anywhere to get support and the hospital did not have medications. After 2 weeks symptoms came back. A friend of mine advised me to go to the sanatorium hospital before I die and gave me 10.000 KZ to pay for a taxi. The situation of my health was complicated and I developed MDR. I would recommend the hospital to pay more attention to patients and follow them, also the hospital needs to provide medications.

23-Patient 23: 44 years old, male

I abandoned treatment because I started feeling well as you know the TB treatment is long but after feeling well there is no point of continuing with treatment, then I decide to stop. After 3 weeks I started coughing and having a fever, my uncle helped me to go to Sanatorium Hospital. I would recommend the health authority to teach patients about TB.

24-Patient 24: 20 years old, male

I abandoned treatment because I did not have money to buy TB drugs and to do the X-ray that the doctor requested. After stopping the treatment my health situation complicated and I started vomiting blood, fever and cough. My uncle took me to Sanatorium Hospital. I would recommend the hospital to provide medication for the patients and the Doctors need to understand that some patients do not have money to pay for exams outside the hospital.

25-Patient 25: 36 years old, male

I abandoned treatment due to the amount of pills that I was taking. Four month later the TB symptoms and signs started again and I was in a critical situation and I nearly died. A friend took me to Sanatorium Hospital. I would recommend the Hospital to give more attention to patients and to teach patients about consequences of abandoning treatment.

26-Patient 26: 37 years old, male.

I abandoned treatment because I was unable to pay for taxis as well as medications. After 3 weeks I became sick again. Someone helped me to get to the hospital. I would recommend the health professionals to have more control of the patients and the hospital to provide medication.

27-Patient 27: 19 Years old, female

I abandoned treatment because I started feeling well after 2 months of treatment. Two weeks later I started feeling sick again, and my family took me to the hospital in critical condition. I would recommend health professionals to educate very well patients with TB and pay more attention to them.

28-Patient 28: 36 years old, male

I abandoned the treatment because I travelled to a different city to work. I was unable to collect the medications due to the distance. After 5 weeks I became very sick and nearly died. The company transferred me to Sanatorium Hospital. I would recommend the government to have control of the company recruitment policies.

29-New patient 29: 37 years old, female.

Patients abandon treatment because it takes 6 to 9 months and also the side effects. Some of us do not have food. Those who quit the treatment some of them die and most return to hospital in critical condition. I would recommend the minister of health to review the duration of treatment and to pay more attention to patients who present side effects.

30- New patient 30: 43 years old, female

Patients abandon treatment because of social conditions such as food, transport, and money. After giving up the treatment, some patients die and some develop MDR. I would recommend the government to provide conditions of living to the community.

31-New patient 31: 52 Years old, female.

Patients abandon treatment because the symptoms and signs go after starting treatment in the first and second month. After abandoning treatment the symptoms come back and some patients die. I would recommend the health professionals to follow patients carefully and supervise them if they are taking the medications.

32-New patient 32: 35 years old, male

Patients abandon treatment due to lack of medications, my uncle died because he could not afford to buy medicines. After abandoning treatment patients die like the way it happened with my uncle and some develop MDR. I would recommend the hospital to provide more medications.

33-New patient 33: 27 years old, male

Patients abandon treatment due to lack of information about TB. After quitting the treatment symptoms come back and families or friends take them to hospital. I would recommend the health professionals to inform patients about TB.

34-New Patients 2: 28 years old, male

Patients abandon treatment due to stigma. My friend decided to stop attending public hospitals because one nurse was calling him bad names such as death by HIV. Majority of patients after abandoning treatment the situation became more complicated and some of them died. I would recommend health professionals to avoid problems with patients and provide help to those who are in need.

35-New Patient 3: 31 years old, male

Patients abandon treatment due to economic situations such as lack of food, money to pay for transport to attend consultation. After abandonment the situation became more complicated and some patients developed MDR. I would recommend the Health Minister to provide food, transport and medications.

36-New Patient 4: 24 years old, female

Patients abandon treatment because they feel cured in the second month. After giving up, symptoms and signs come back and the family takes them to hospitals. I would recommend the health professionals to follow and provide TB information to the patients.

37-New patient 5: 33 years old, female

Patients abandoned treatment because they do not have help from the family and the health professionals do not respect those with TB. After dropping the treatment symptoms return and the patients look for health care. I would recommend families to help patients with TB and health professionals to give more consideration.

38-Patient Expert 1: 47 years old, female.

I abandoned treatment because my pastor told me that I am cured by prayer, therefore I do not need any medications and I believed him. Many patients also abandon treatment due to religion and culture. After 4 weeks symptoms and signs came back. I nearly died and my family helped me to go to hospital. I would recommend the health professionals to follow patients weekly to find out if they are taking medicine correctly.

39-Patient Expert 2: 41, female.

Patients abandon treatment due to lack of money and side effects. After abandoning most patients the symptoms come back and some of them die. I would recommend the government to provide job opportunities in the community and health professionals most find the possibility to minimise the side effects of medication.

40-Patient's family 1, female

Patients abandon treatment when they stop presenting symptoms and signs of TB they think are cured. When they give up treatment after 3 weeks symptoms and signs come back and some patients die. I would recommend health professionals to raise awareness in the community about TB.

41-Patient's family 2, female

Patients abandon treatment due to the poor conditions of living. For example I am here in the hospital helping my family member but we do not have food , the hospital only gives rice and all the time that patients eat rice they start coughing not because they have TB, but because of the rice they ate. When they stop treatment most patients become sicker and some die. I would recommend the hospital to provide food to patients and checking if patients are taking medicine correctly

42-Patient's family 3, female

Patients abandon treatment because they do not have symptoms and signs. After 3 weeks the symptoms and signs start again very intensively which result in them going back to the hospital. I would recommend the hospital to teach patients and families about the consequences of giving up treatment.

43-Patient's family 4, male

Patients abandon treatments because of the side effects. When they give up treatment the situations complicate and some patients die. I would recommend doctors and nurses to help with correct medications that will minimise the side effects.

44-Patients family 5, male

Patients abandon treatment because they do not have help. This has happened to my brother before. After giving up treatment, the situation complicated and he died. I would recommend the hospital to raise awareness in the community demonstrating the importance of family involvement during the TB treatment.

45-Parents focus group

Three women stated that children abandon treatment because parents do not have time to go to the hospital to collect medicine and attend consultations. After abandoning the treatment most of the children die. We would recommend the health professionals to start visiting patients at home.

Two men discussed that children abandon treatment because parents do not have money to pay for medications and to buy food. After abandoning treatment the situation becomes complicated and some of them die. We would recommend the government to provide job opportunities in the community and to help families with food and good health care.

46-Family focus group

A female argued that patients abandon TB treatment due to side effects of medication and lack of food. After quitting the treatment the symptoms and signs come back. I would recommend the hospital to provide food to patients and doctors to treat the side effects.

Two men revealed that patients abandon treatment due to lack of money to pay for exams which were requested by the Doctors. After giving up the treatment the symptoms return and patients are taken to hospital in critical stages. We would recommend doctors to help patients to do all the exams in the hospital.

Two women discussed that patients abandon TB treatment because of negligence especially when they are males. After giving up the treatment the symptoms come back and families take them to hospital in critical stages. This is what happens with our family members. We

would recommend the Minister of Health to implement strategies of visiting patients regularly during the treatment.

47-Health Professionals: Focus group 1

Three nurses demonstrated that patients abandon treatment due to poverty and lack of knowledge. After quitting the treatment the symptoms and signs return and families bring them back to hospital in critical stages and some of them die at home. We would recommend the Government to help the population with new job opportunities and workshops about TB.

A medical doctor and two nurses discussed that patients abandon treatment because they do not follow instructions given by the health professionals. Two weeks later the signs and symptoms come back and family members and friends bring them to hospital in critical condition. We would recommend more activities need to take place in the community to educate patients and families about TB.

A nurse and psychologist stated that patients abandon treatment due to toxicity which most of the time happens on the second week of TB treatment. The same Nurse argued that some patients abandoned treatment due to the quantity of tablets taken per week. A Psychologist stated that patients abandoned treatment due to the wrong orientation given by pastors in the churches. Majority of patients after quitting treatment the symptoms return back and are taken to emergency care and some of them die at home. We would recommend the health professional to educate people in the community about TB and organise workshops with Pastors.

48-Health Professionals: Focus group 2

A medical doctor specialist in Toxicology stated that patients abandon treatment due to side effects of medications, lack of food, lack of help from families, long time of treatment, religion and culture. After giving up treatment the symptoms return and families bring them to Sanatorium hospital in critical condition. Some patients develop MDR and die. I would recommend the health professionals to pay attention to patients who are in treatment and families must support their members when they are sick and the Minister of Health must provide teaching and seminaries.

A medical doctor specialist in public health said that patients abandon treatment due to lack of primary health care. In countries where primary health care is in place it is difficult for

patients to quit treatment. Patients who give up treatment the symptoms return and some of them die. I would recommend the Minister of Health to invest in primary health care.

A nurse discussed that patients abandon treatment because they do not have help from family, lack of money, lack of information about TB and religion. After quitting treatment the symptoms return and friends or police bring patients to hospital in critical stages. We would recommend families to support patients. Hospitals must provide medication for free and health professionals must help patients with teaching about TB.

A psychologist and nutritionist stated that patients abandon treatment because they do not have food to eat after taking pills. After dropping treatment symptoms return, some patients develop MDR and some die. We would recommend the hospital to provide food for patients.

49-Health professionals views:

A doctor from emergency care revealed that patients abandon treatment because they are not able to collect medicines at the hospital pharmacy due to the distance and they do not have money to pay for a taxi. The same doctor said that patients are not informed about TB. After quitting the treatment they return to hospital in critical condition. I would recommend the Minister of Health to help patients with medication, transport, food and workshops.

A pharmacist argued that patients abandon treatment due to negligence and lack of help from family. After giving up the treatment some patients die. I would recommend health professionals to raise more awareness in the community about TB.

A technician of the laboratory said that patients abandon treatment because the waiting list to be attended in consultations is long, sometimes patients come to the hospital doctors are not available, they need to come another day and most patients are not able to afford money to pay for a taxi to return to consultation. The same technician argued that side effects, lack of food, stigma and lack of possibility to do exams because equipment that is used to do blood count is broken. After quitting treatment patients return in critical conditions. I would recommend the hospital not to delay patient appointments, repair equipment which is broken. The government must build more hospitals for TB patients.

A nurse and health promoter demonstrated that patients abandon treatment because they are abandoned by their families and stigmata by health professionals. After giving up treatment symptoms return and many of them die. I would recommend families to help patients and health professionals to avoid stigma to patients.

11.2 Appendix 2:

Informed consent

Título do Projeto de Pesquisa: Identificação e análise de fatores que impedem os pacientes com a tuberculose de aderirem às consultas no Hospital Sanatório de Luanda.

Breve Descrição do Projeto de Pesquisa

Este estudo tem como objetivo identificar e analisar os fatores de risco que impedem os pacientes com a tuberculose de aderirem às consultas no hospital Sanatório de Luanda. O projecto enquadra-se na iniciativa e estratégias do Ministério da Saúde na melhoria da vigilância epidemiológica de acções de promoção da saúde e prevenção das doenças .

Declaração de consentimento:

Concordo em participar da pesquisa descrita acima (Alternativa: você pode fornecer uma folha informativa separada e informações verbais a que se refere aqui), e estou ciente de que estou livre para me retirar do estudo a qualquer momento. Entendo que as informações fornecidas serão tratadas confidencialmente pelo investigador e que minha identidade será protegida na publicação de quaisquer descobertas.

Nome

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Assinatura

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Data: ...../...../.....