COST-EFFECTIVENESS OF A PROTOCOL FOR TUBERCULOSIS DIAGNOSIS IN PEOPLE LIVING WITH HIV: AN ECONOMIC STUDY ALONGSIDE A PRAGMATIC CLINICAL TRIAL IN BRAZIL

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I, Noêmia Teixeira de Siqueira Filha, confirm that the work presented in this thesis is my own. When information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Tuberculosis (TB) is the main opportunistic infection and the main cause of death in people living with HIV (PLHIV). Brazil is among the 30 countries with the highest TB/HIV burden worldwide and the disease is responsible for about 13% of all deaths in PLHIV in the country. Brazil is committed to the goals stated by international organisations and launched The National Plan to end TB, highlighting some of the main challenges that need to be overcome in the next 18 years. These include the expansion of gene Xpert for the diagnosis of TB, the introduction of new technologies for TB diagnosis and treatment and the strengthening of policies for TB control in PLHIV. The aim of the present study was to evaluate the cost-effectiveness of a protocol for TB diagnosis in PLHIV in Brazil. Four specific objectives were identified in order to achieve this aim: (1) to perform a review of the literature to evaluate gaps in costing studies and economic evaluations addressing TB/HIV co-infection; (2) to estimate the costs of PLHIV, with or without active or latent TB, from the symptomatic phase until the first year of treatment from the perspective of the Brazilian public health system; (3) to estimate direct and indirect costs of TB/HIV and latent TB/HIV co-infection (LTBI/HIV) from the patient perspective during the pre-diagnosis and treatment period; and (4) to perform an interim analysis of the cost-effectiveness of a protocol for TB diagnosis in PLHIV as part of a pragmatic clinical trial in Brazil. The literature review shows a gap in the scientific evidence on cost and cost-effectiveness of TB diagnosis in PLHIV, with a concentration of studies in African countries. The cost study from the health system perspective shows that TB/HIV co-infected patients incurred in higher costs when compared with HIV/AIDS and LTBI/HIV patients for the whole pathway of care. The total mean cost for the TB/HIV category was almost 6 times higher than the HIV or AIDS category (US$ 6,210 *vs* US$ 1,612). The cost study from the patient perspective indicates that TB/HIV co-infected patients can face catastrophic costs during the diagnosis and treatment period, with indirect costs representing a higher proportion of total costs, at 52.4%. The modelling study suggests that the protocol for TB diagnosis in PLHIV, including screening by clinical algorithm and complementary tests, such as gene Xpert is a cost saving intervention when compared with routine hospital referral. The findings from this study can contribute to supporting strategies to improve TB diagnosis in PLHIV, reducing costs from the health system perspective and preventing catastrophic costs faced by TB/HIV patients.

ABBREVIATIONS

ART	Antiretroviral therapy
ARV	Antiretroviral
BCR	Benefit-cost ratio
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CHOICE	Choosing Interventions that are Cost–Effective
CONITEC	National Committee for Technology Incorporation/Comissao Nacional de Incorporacao de Tecnologias no SUS
CPH	Correia Picanco Hospital
CUA	Cost-utility analysis
CXR	Chest X-ray
DALYs	Disability Adjusted Life Years
DOTS	Direct Observed Treatment Strategy
IGRAs	Gama-interferon
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
ICER	Incremental cost-effectiveness ratio
IPT	Isoniazid preventive treatment
LF-LAM	lateral flow lipoarabinomannan
LTBI	Latent TB infection
LTBI/HIV	Latent tuberculosis and HIV co-infection
LYS	Life-years saved
NPV	Net present value
PEPFAR	The United State President's Emergency Plan for AIDS Relief
PLHIV	People living with HIV
PrEP	Pre-exposure prophylaxis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSA	Probabilistic sensitivity analysis
PTB	Pulmonary tuberculosis
QALY	Quality Adjusted Life Years

SAE	Specialised Care Services/Servico de Atendimento Especializado
SC	Sputum culture
SDGs	Sustainable Development Goals
SSM	Sputum smear microscopy
SUS	Unified Health System/Sistema Único de Saúde
SINAN	National Disease Notification System /Sistema Nacional de Agravos de Notificacao
TasP	Treatment as Prevention
TB	Tuberculosis
TB/HIV	Tuberculosis and HIV co-infection
TST	Tuberculin skin tests
UNAIDS	United Nations Programme on HIV/AIDS
UN	United Nations
WHO	World Health Organization
Xpert MTB/RIF	Xpert Mycobacterium tuberculosis/Rifampicin resistant
YLD	Years of life with a disability
YLL	Years of life lost

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Appendix

CHAPTER 1. INTRODUCTION

1.1 Background

Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) co-infection occurs when people have HIV infection, and either latent TB (LTBI) or active TB disease [1]. Globally, the risk of People Living with HIV (PLHIV) developing TB is 26 times greater than those who are HIV negative [a], which makes TB the most common opportunistic infection among PLHIV. TB is also the leading cause of death among PLHIV, accounting for 390,000 deaths in 2015, worldwide[2]. The interaction between the two pathogens accelerates the progression of HIV disease, increasing the risk of death in co-infected patients[3].

The lack of, or delays in, TB diagnosis and treatment also explain the high mortality rate among co-infected patients. TB diagnosis can be difficult due to the paucibacillary[b] nature of the disease in PLHIV. Furthermore, TB may modify clinical and radiological features in PLHIV with a high degree of immunodeficiency. As a result, many co-infected patients present atypical or absent findings in pulmonary radiography. Also, they are more likely to have sputum smear negative tests[c] leading to a greater risk of undiagnosed cases [4,5]. Owing to the limitations in co-infection diagnosis, many patients die without receiving TB treatment [6,7].

Studies have shown that a significant number of TB cases remain undiagnosed in PLHIV during routine care. Autopsy studies in PLHIV have found a significant number of undiagnosed and untreated TB cases. In Brazil, a post-mortem analysis in PLHIV found 67% (6/9) of undiagnosed TB ante-mortem [8]. Another autopsy study carried out in South Africa found evidence of TB in 47% (16/34) of the decedents and 38% (6/16) of them had not started TB treatment ante-mortem [9]. Another recent systematic review of post-mortem studies addressing resource-limited settings found that TB remained undiagnosed at death in 45.8% of TB cases [10].

Other epidemiological studies also have found failure to diagnose TB and, consequently, delay in TB treatment in co-infected patients. A survey conducted in South Africa diagnosed TB in 9% of PLHIV, with 5% of them being previously undiagnosed [11]. Another study conducted in

[a] Incidence rate ratio (IRR) = probability of developing TB among PLHIV divided by probability of developing TB among HIV negative people. Globally, the mean and median IRR in 2014 was 26 (range = 24 - 28) and 23 (interquartile interval = 14 - 36), respectively.
[b] Low bacillary counts.
[c] Patients with clinical and/or radiological evidence of pulmonary TB, but repeatedly sputum smear microscopy test negative.

Brazil found an association between sputum smear negative disease and delay in TB treatment (Odds Ratio: 1.90; 95% CI: 1.02-3.58; *P-value*: 0.0438). The time interval between the onset of cough and the initiation of treatment for TB ranged from 1 to 552 days, with a median of 41 days [12].

The World Health Organization (WHO) has recommended various algorithms to improve TB diagnosis in PLHIV. The first one is intensified TB case finding through a clinical algorithm based on cough, fever, night sweats and weight loss. The protocol recommends further clinical assessment and TB tests in PLHIV with at least one of these symptoms [13]. The screening based on these clinical symptoms was the best detector of TB in PLHIV, with a sensitivity of about 79% [14]. Another recommendation is the rapid molecular Xpert MTB/RIF test for the detection of TB and rifampicin resistance. Currently, 15 TB and TB/HIV high burden countries[d] have adopted Xpert as the initial tests for people with signs and symptoms of pulmonary TB [15]. The urine lateral flow lipoarabinomannan (LF-LAM) assay is another option to diagnose pulmonary and extrapulmonary TB. WHO recommends the tests for PLHIV with unknown CD4 count, CD4 ≤ 100cells/μL, or seriously ill patients regardless of CD4 [2].

Prevention of TB in PLHIV is also an important discussion among experts and the main WHO recommendations are treatment with antiretroviral therapy (ART) and isoniazid preventive treatment (IPT). A meta-analysis found a strong association between ART and reduction of TB incidence for any category of CD4 count, but especially for early ART initiation (CD4 ≥350 cell/ μL) [16]. WHO highlights the significance of ART in reducing TB morbidity and mortality in PLHIV [17]. IPT is part of the three 'I's strategy (IPT, intensified case finding, and TB infection control) to prevent TB in PLHIV. WHO emphasises that all PLHIV who are unlikely to have TB should perform the treatment, regardless of the tuberculin skin test result (TST) [13,18].

Although there are innumerable challenges to be faced in the fight against TB/HIV co-infection, global efforts have achieved positive results. Worldwide, the scale-up of collaborative TB/HIV activities has saved 6.5 million lives; 55% of notified TB cases have a known HIV status; and ART coverage achieved 78% of TB/HIV co-infected patients. The main challenges are still to decrease the number of TB deaths in PLHIV and increase the offer of

[d] WHO has defined a list of high TB/HIV burden countries for the period 2016–2020 based on the severity of their TB burden (i.e. TB incidence per 100 000 population), on the absolute number of incident cases per year. The list includes 30 countries: Botswana, Cameroon, Chad, Ghana, Guinea-Bissau, Malawi, Swaziland, Uganda, Brazil, Central African Republic, Congo, Lesotho, Liberia, Namibia, UR Tanzania, Zambia, Angola, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Papua New Guinea, South Africa, Thailand, Zimbabwe. Some of these countries are also classified as a high burden for TB and multidrug resistant TB [15] .

ART and IPT to this population [19]. The management of these challenges will be imperative to end the TB and HIV epidemics by 2030, as stated in the Sustainable Development Goals (SDGs) [20].

Health economic evaluation also plays an important role in supporting the achievement of the SDGs in a sustainable way, especially with the reduction in the amount of funding available to deal with both epidemics in recent years. Furthermore, the majority of high TB/HIV burden countries face resource constraints, both financial and human. Thus, the use of evidence provided by this type of study becomes essential to support the decision-making process. There is a vast literature on cost and cost-effectiveness studies addressing TB/HIV co-infection. However, most of the studies have been conducted in African countries. There is a lack of information in the recent literature on TB/HIV in Brazil and other Latin American countries. A clinical trial on TB diagnosis provided a chance to fill this gap in the literature on clinical and economic evaluation. The next section provides more details about the clinical trial.

In order to fill this gap in the literature addressing TB/HIV co-infection and provide information regarding cost-effectiveness of algorithms for TB diagnosis in PLHIV, this study aimed to evaluate the cost-effectiveness of a protocol for TB diagnosis in PLHIV in a Brazilian city.

The current thesis provides important information for the Brazilian National TB and HIV programmes and points the way for further research. As a high TB/HIV burden country currently facing a severe economic crisis with reduction in investments in the health sector, Brazil increasingly needs to make use of health economic evaluation in the decision-making process. The results provided by this study can guide public health policies to prevent TB in PLHIV and reduce delays in TB diagnosis in PLHIV and, consequently, AIDS related-deaths. In addition, the study can contribute to improving TB diagnosis in PLHIV and support strategies to reduce costs from the health system perspective and prevent catastrophic costs faced by TB/HIV patients, thus setting the country on track to achieve the goals stated by the United Nations (UN), WHO and Stop TB partnership [20–22].

To develop the scope for the cost and cost-effectiveness analyses presented in this thesis, two literature reviews were conducted. The reviews investigated the current gap in cost and cost-effectiveness studies addressing TB/HIV co-infection and guided the methodology applied in this thesis. The next step was the investigation of costs involved in the diagnosis and treatment of PLHIV, TB/HIV and LTBI/HIV co-infection. The study investigated the cost from the health

system perspective during the pre-diagnosis and treatment period and supported the development of the cost-effectiveness study. Another study developed in the current thesis was a cost analysis of TB/HIV and LTBI/HIV co-infection from the patient perspective. An analysis was also conducted for the pre-diagnosis and treatment periods. Finally, a cost-effectiveness analysis of a protocol for TB diagnosis in PLHIV was conducted with the development of a decision analytic model. The cost-effectiveness analysis was conducted from the health system perspective and the main outcome was the cost per Disability Adjusted Life Years (DALYs) averted. All cost and cost-effectiveness analyses presented in this thesis used two years of primary data collection alongside a pragmatic clinical trial.

1.2. A pragmatic clinical trial to assess the effectiveness of different screening and diagnostic methods for TB disease in PLHIV in the city of Recife, Brazil

A three-year pragmatic clinical trial with individual randomisation led by epidemiologists from the Oswald Cruz Foundation (FIOCRUZ), the Federal University of Pernambuco, the University of Pernambuco and the London School of Hygiene and Tropical Medicine started in March 2014. The trial was developed as an opportunity to answer the Brazilian MoH's main questions regarding the cost-effectiveness of different methods of TB diagnosis and TB prevention in HIV-infected patients using ART. The trial took place in the Correia Picanco Hospital (CPH) in the city of Recife, state of Pernambuco, Northeast region of Brazil. The hospital is the main HIV/AIDS referral service in the state and is responsible for the care of 60% of all individuals with HIV and AIDS in Pernambuco. The hospital carries out almost 3,000 outpatient appointments a month and covers emergency and inpatient care. Patients were recruited until March 2017 and will be followed-up for one year. After the end of the follow-up period, the epidemiological and economic team will be able to run the final analysis of the clinical trial. The economic study was conducted alongside the pragmatic clinical trial between March 2014 and March 2016 (Trials' Protocol provided in Appendix).

The aim of the trial was to evaluate the effectiveness and cost-effectiveness of a protocol for TB diagnosis in PLHIV. The epidemiological study compared the mortality rate due to TB among PLHIV who have been diagnosed using a TB protocol with the mortality rate of those who are diagnosed within the routine referral services.

The algorithms for TB diagnosis assessed were:

- Algorithm 1: routine hospital referral
- Algorithm 2: TB screening by a clinical algorithm (cough, fever, night sweats and weight loss) plus gene Xpert and other routine tests, such as SSM, CXR and SC.

In the first algorithm, routine hospital referral, patients were investigated for TB in a non-standardised way. Doctors asked or did not ask about TB symptoms at the first or subsequent appointments. The gene Xpert test was not available at routine hospital appointments and TB diagnosis was made through conventional tests (i.e. SSM, SC). In the second algorithm, a screening for TB by clinical algorithm was performed at every patient appointment at CPH. In patients who presented at least one symptom during the screening, the final diagnosis was performed using gene Xpert, if patients presented at least 2ml of sputum, or other conventional tests. The study population was composed of HIV-infected individuals aged 18 years or over, attending Correia Picanço Hospital before initiating ART. Those who were currently undergoing TB treatment or have done so in the last 3 months, as well as those previously diagnosed or diagnosed during the trial with multidrug resistant tuberculosis (MDR/TB), were excluded from the trial.

The sample size for the epidemiological study was calculated for the primary analysis and used the mortality rate estimated by a cohort study of TB/HIV co-infected treated in the hospital where the trial was conducted [23]. The sample size was determined using the following parameters:

(1) Mortality rate in one year (80% survival rate in 400 days): 20% [23]
(2) Proportion exposed and unexposed: 2:1
(3) Study power: 80%
(4) Alpha error: 5%
(5) Relative Risk (RR) = 0.5 comparing the rate in both groups, reduction of 50% (assumption)

The sample size was calculated using the command "*sampi"* in *STATA* 12, and the parameters above. A sample size of 847 patients was estimated for the whole trial (565 intervention and 282 control group). Considering 40% of losses in the follow up, the final sample was 1,412 patients.

A randomisation list was prepared by a statistician and generated by a computer. The allocation at random was performed when patients come for their first appointment. A nurse assigned

them to one of the interventions by selecting a number (1, 2) from a prepared envelope containing the random letters.

It was expected that the randomization ensured similar distribution across groups of the factors associated with mortality due TB. At the beginning of the trial the baseline characteristics was assessed as well as during the follow up. An independent statistician assessed the data to check differences of gender, age, CD4 and other characteristics. In the case of imbalance, such characteristics were considered as confounders during the analysis – at the end of the trial.

The sequence of steps for the pragmatic clinical trial followed the guidance proposed by Pocock, 1983 [24]:

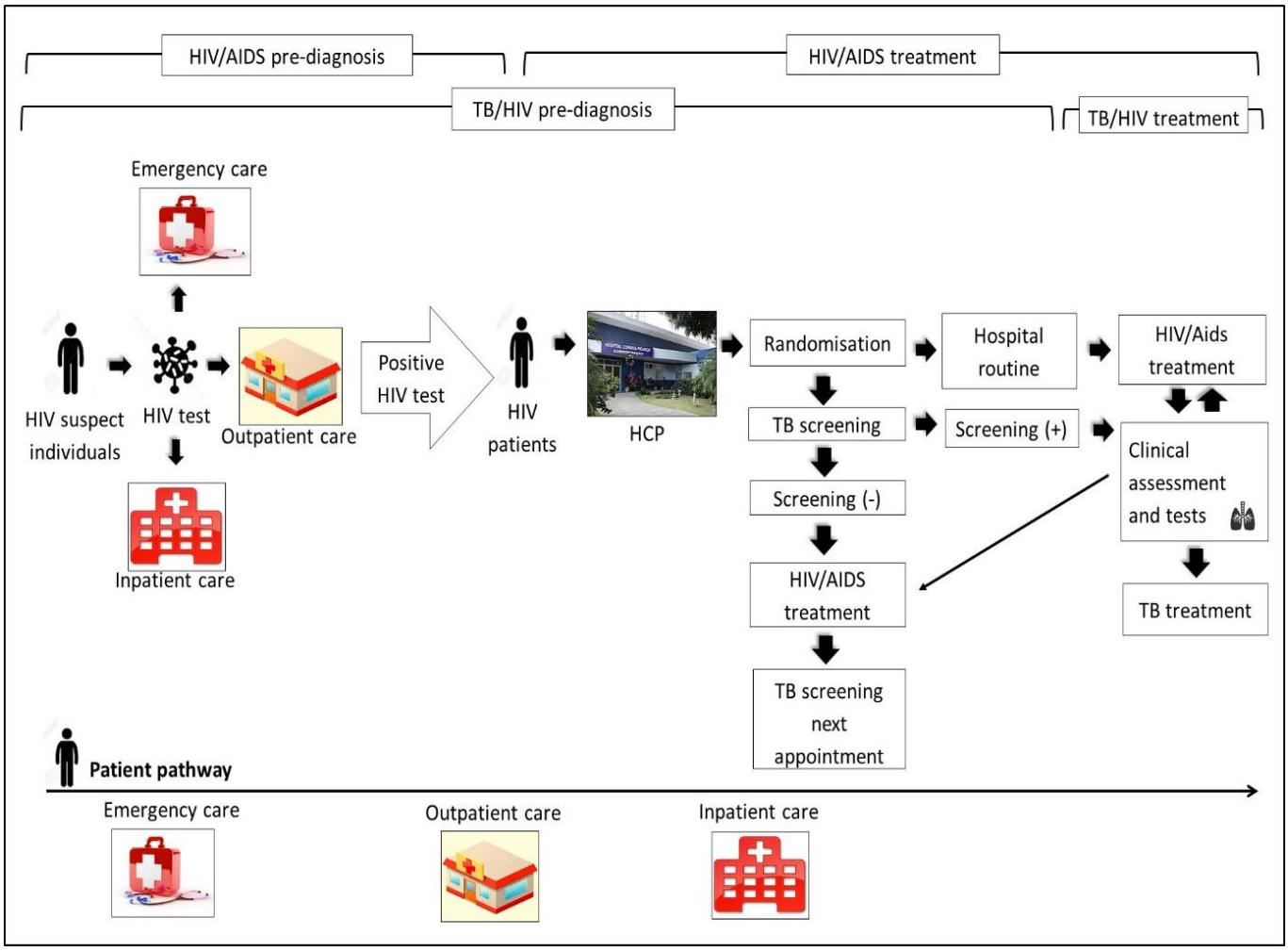
(1) Patient requires treatment: identify appropriate patients and ensure that they were representative of the disease under investigation (PLHIV)
(2) Patient eligible for inclusion in the trial: eligibility criteria checked based on the protocol (inclusion criteria: PLHIV, aged 18 years or over, ART naive), excluded patients who did not match the criteria (exclusion criteria: patients undergoing TB treatment currently or in the last 3 months; patients treated in the private service and registered at CPH only to collect antiretrovirals; patients transferred to other health services during follow-up; patients with diagnosed MDR/TB).
(3) Medical staff willing to accept randomisation: four nurses, three infectious disease specialists and one pulmonologist based at CPH were invited and agreed to participate in the clinical trial and followed Algorithm 2. The other medical staff followed routine hospital referral, Algorithm 1.
(4) Patient consent was obtained: eligible patients were approached by a nurse and received an explanation about the purpose of the clinical trial, those who agreed to take part signed an informed consent form.
(5) Patients formally entered in trial: nurses conducted a first interview and collected information on patient name, date of birth, affiliation, address and investigator's initials. They also assigned a trial number to each patient.
(6) Algorithm 1 or 2 assigned from the randomisation list: a randomisation list was prepared by a statistician and was generated by computer. A nurse, who was not involved in the patient treatment, assigned the patient to one arm of the trial by selecting a number (0- routine/ 1-intervention) from a prepared envelope containing the random

numbers. The nurse did not know the order of the random numbers and were unable to predict the next assigned treatment.

(7) Initial questionnaires: the first interview for the costing study was performed after patient registration at CPH. On this occasion, a questionnaire was used to collect demographic, socio-economic characteristics, lifestyle habits (i.e. use of alcohol and illicit drugs), information on HIV diagnosis and previous history of TB disease. Another questionnaire was applied asking about the use of medical resources at CPH and other public health services. The questionnaire also collected information regarding direct (transport, food, caregiver) and indirect costs (income and time loss) for diagnosis and treatment from the perspective of patients and families. Subsequent interviews were conducted at every regular appointment the patient had at CPH. Patient notes were reviewed to complement and capture the use of resources from the health system perspective.

(8) Patients followed Algorithm 1 or 2 pathways: we followed up the entire pathway of care of HIV or AIDS patients from the pre-diagnosis and treatment periods. Pre-diagnosis was the period between the onset of HIV or TB symptoms until HIV or TB diagnosis. The treatment period for HIV/AIDS patients was the period from the beginning of treatment with prophylactic drugs and/or ART until one year after starting this treatment or death before one year of follow-up. For those patients who were diagnosed with TB or received IPT during the study period, treatment period was the time from the beginning of TB or TBL treatment until cure, death or treatment abandonment. Figure 1 shows the patient pathway during the pre-diagnosis and treatment period.

Figure 1. Patient pathway during the pre-diagnosis and treatment period.



1.3 Aims and Objectives

The overall aim of this study was to evaluate the cost-effectiveness of a protocol for TB diagnosis in PLHIV in Brazil. To achieve this aim, this study encompassed four specific objectives:

- To perform a literature review to evaluate gaps in costing studies and economic evaluations addressing TB/HIV co-infection;
- To estimate the costs of PLHIV with or without active or latent TB, from the symptomatic phase until the first year of treatment from the perspective of the Brazilian public health system;
- To estimate direct and indirect costs of TB/HIV and LTBI/HIV co-infection from the patient perspective during the pre-diagnosis and treatment period;

- To perform an interim analysis of a pragmatic clinical trial in Brazil to assess the cost-effectiveness of a protocol for TB diagnosis in PLHIV.

1.4 Thesis structure

The next chapters are organised as follow. Chapter two presents a background on HIV/AIDS and TB/HIV epidemics around the globe. The chapter provides information about the epidemiological profile of both epidemics, discusses the UN Goals and funding available to achieve these goals. The chapter also presents the Brazilian scenario: epidemiological profile, financing, organisation of the Brazilian Health System to assist PLHIV and current algorithms for TB diagnosis, treatment and prevention in PLHIV. Finally, the second chapter ends with a section addressing methods in economic evaluation. This section discusses methodological approaches for cost and cost-effectiveness, such as the ingredient approach, bottom-up and top-down, decision analysis modelling and uncertainty in cost-effectiveness analysis.

The third chapter of this thesis presents two literature reviews. The first is a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations [25] and registered at Prospero – International Prospective Register of Systematic Reviews. The review addressed the costs of TB diagnosis and treatment in PLHIV from the societal, provider and patient perspectives. The second, a comprehensive literature review, focused on modelling studies of TB diagnosis algorithms in PLHIV. The results from both reviews supported the methodological approaches used in this study.

The fourth chapter presents research paper 2 entitled "The economic burden of HIV and TB/HIV co-infection in a middle-income country: a costing analysis alongside a pragmatic clinical trial in Brazil." The paper discusses the cost of HIV/AIDS, TB/HIV and LTBI/HIV from the health system perspective for the patients' entire pathway of care. The paper also shows the cost incurred at outpatient, inpatient and emergency care during the pre-diagnosis and treatment periods. I adopted a mix of top-down and bottom-up approaches for cost estimates and performed a one-way sensitivity analysis to assess uncertainties related to the parameters used.

The fifth chapter presents research paper 3 entitled "The economic burden of tuberculosis and latent tuberculosis in People Living with HIV in Brazil: a cost study from the patient perspective". This paper discusses the costs incurred by PLHIV co-infected with TB during the

search for diagnosis and treatment, which was measured as the sum of direct medical and non-medical costs and indirect costs. This also assesses the impact of these expenditures on patients' income to evaluate the proportion of patients that incurred catastrophic expenditure during the course of diagnosis and treatment, as defined by the World Health Organization [26]. Costs were collected through a questionnaire applied at every patient appointment at a referral hospital during the course of TB/LTBI treatment.

The last research paper of this thesis is presented in chapter 6 and is entitled "Cost-effectiveness of a protocol for TB diagnosis in people living with HIV in Brazil: an interim analysis of a pragmatic clinical trial". As suggested by the title, I conducted an interim analysis for the first year of the pragmatic clinical trial to measure the cost/DALYs averted through a decision-analysis model. The modelling exercise also included a probabilistic sensitivity analysis to evaluate the joint uncertainty in costs and effects.

The final thesis chapter provides a broad discussion of the main findings, strengths and limitations of the research, discusses implications for public health in Brazil and worldwide, and suggests scope for further future research.

1.5 Contribution of the candidate to the thesis

I designed the cost and cost-effectiveness studies by planning all steps from the study design to be applied to the plan of analysis. I decided to develop a systematic literature review to support my design for the study. I designed, conducted and coordinated two years' field work, with primary data collection: adaptation and development of questionnaires and plans for the field work, supervision of initial interviews, correction of the questionnaires, data collection at the referral hospital and other health services in Recife Metropolitan Region, and exchange of information with the epidemiological team. I spent seven months (March to September 2014) in Recife to start-up the field work and two more months (February and March 2016) at the end of the field work activities. I developed and am first author of all the papers presented in this thesis. Three papers have been submitted to peer-reviewed journals that are relevant in the area of health economics and/or public health and HIV/AIDS, and they have been accepted for publication. The last paper, a modelling study, will be submitted after the preliminary analysis of the epidemiological data.

Research paper 1 is a systematic review conceived and developed by me with the support of Andreia Santos. I conducted the literature search of the databases; extracted, analysed and interpreted the data and produced the manuscript. Andreia Santos also conducted the literature search independently. Aracele Cavalcanti also extract the data and conflicts in this phase were discussed and solved by Andreia Santos. Andreia Santos also supported the planning of the data analysis and interpretation of results. Rosa Legood provided general guidance for interpreting the findings and reviewed the manuscript. All authors read and approved the final manuscript, which was submitted to *Value in Health* on 6th February 2017. The manuscript was under review by this journal at the time of submission of this thesis, and has been accepted for publication.

Research papers 2 and 3 are linked and were conceived and developed by me. I conducted all steps of the primary data collection, cost and statistical analysis, interpretation of results and wrote the manuscript. Andreia Santos and Maria de Fatima Militao supported me in the study design. Andreia Santos also supported the data analysis section and interpretation of results. Laura Rodrigues and Rosa Legood gave general guidance about the paper format for publication. All authors read and approved the final manuscript. Research paper 2 was submitted to the journal *Sexually Transmitted Infections* on 19th May 2017. Research paper 3 was submitted to the *Journal Public Health* on 22nd of May 2017. Both manuscripts were under review by the journals at the time of submission of this thesis, and both have been accepted for publication.

Research paper 4 was conceived and developed by me. I conducted the literature review to guide the development of the model, developed and ran the deterministic and probabilistic model and wrote the manuscript. Rosa Legood supported the development of the decision analysis model and probabilistic sensitivity analysis. Also, she gave guidance in the interpretation of results. Andreia Santos participated and gave suggestions in the discussion of the modelling methods and results. All authors participated in the development of the study design. The final manuscript was read and approved by all authors. The manuscript will be submitted to a scientific journal after obtaining the final results of the pragmatic clinical trial.

CHAPTER 2. BACKGROUND

2.1 HIV/AIDS, a global epidemic

The first rumours of the HIV/AIDS epidemic date from the early 20th century, between 1909 and 1930, when a combination of socio-economic and demographic features enabled the HIV-1 virus to spread from Kinshasa, Democratic Republic of Congo, to the rest of Africa and then to the entire world [27]. Currently, the UN Programme on HIV/AIDS (UNAIDS) report shows that the epidemic has reached 36.7 million people worldwide. According to the programme, there were 2.1 million new cases diagnosed and 1.1 million deaths reported in 2015 [28]. The distribution of the epidemic varies widely across the globe and the African continent remains the most affected region with more than 25 million PLHIV in 2015 [29].

Recently, the United Nations General Assembly established three action points aimed at ending the HIV/AIDS epidemic by 2030 as stated in SDG 3. The action points focus on a reduction in HIV infections, reduction in AIDS-related deaths and elimination of HIV-related stigma and discrimination. Several policies have been agreed to tackle these problems, such as scale-up of ART, prevention of mother-to-child transmission and pre-exposure prophylaxis (PrEP) [30]. Another important point to be considered in addressing AIDS-related deaths is TB/HIV co-infection. TB is the main opportunistic infection and leading cause of death in HIV patients. The great challenge is the improvement of TB diagnosis strategies because common diagnostic methods (e.g. SSM) are not sufficiently accurate in HIV patients [7].

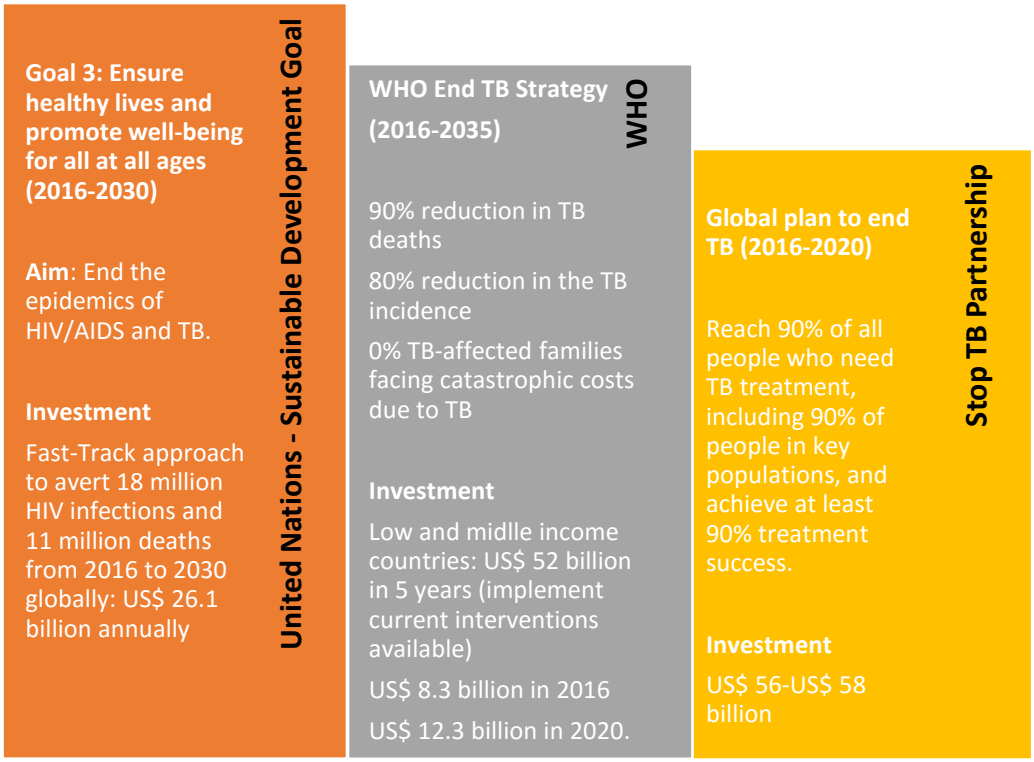
However, funding availability might affect the potential success of SDG 3. New estimates indicate that the necessary investment to achieve SDG 3 may increase to US$26.2 billion by 2020, about US$7 billion more than the funds available in 2015. At the same time, UNAIDS estimates that donor funding for the HIV global response decreased by 13% between 2014 and 2015 [31]. The United States President's Emergency Plan for AIDS Relief (PEPFAR) is the largest fund created by a country to fight the HIV/AIDS epidemic. PEPFAR has been contributing with the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and UNAIDS since 2003. For 2016, PEPFAR announced an investment of $100 million for prevention and treatment services. PEPFAR has also addressed HIV co-infections and co-morbidities by investing in supportive care such as screening for active TB and referral for treatment of those diagnosed with co-infection [32].

2.2 TB/HIV co-infection

TB is the main opportunistic and deadly disease in PLHIV. In 2014 there were 9.6 million new cases of TB worldwide, of which 1.2 million were among PLHIV. The number of TB deaths has fallen since 2014, but it is still high and reached 390,000 PLHIV in 2015. The African Region carries the highest burden of TB/HIV co-infection with 74% of all cases globally. WHO recommend the following strategies for TB control and prevention in PLHIV: three 'Is' (IPT, intensified case finding and infection control), earlier ART, use of Xpert and collaborative TB/HIV activities [2,15]. In addition, the UN, WHO and Stop TB partnership has established goals to deal with TB and, consequently TB/HIV co-infection. The goals share a common aim, i.e. to end the global TB epidemic (Figure 1) by 2030-35. [20–22].

IPT and intensified case finding were launched by WHO as part of the three 'Is' strategy in 2011. Both strategies were suggested to decrease the number of undiagnosed TB/HIV co-infection cases, interrupt disease transmission, reduce morbidity and delay mortality. The first step in the diagnosis cascade is intensified case finding, which is recommended through a clinical algorithm. Those patients without TB symptoms are unlikely to have active TB and should be offered IPT and ART [13]. To increase the utility of the screening, WHO also recommends the monitoring of the entire pathway of TB diagnosis for screening positive PLHIV. The monitoring should be performed through identification of TB in those who screened positive and documentation of the TB investigations that have been done. The number of PLHIV screened for TB reached 7 million in 2014 [2]. Only 12 high TB/HIV burden countries, Brazil is not included, reported data on the number of TB notified cases among newly HIV diagnosed patients. The average percentage of TB cases among PLHIV in these countries was 10% in 2015 (ranging from 5.5% to 23%) [15].The provision of IPT for PLHIV increased sharply from 2005 to 2014 and reached 933,000 people in 2014. A total of 49 countries, 13 of them high TB/HIV burden countries, have reported data on IPT in PLHIV. Most of the data comes from the African region, especially South Africa with 59% offered IPT in 2014 [2].

Figure 1. UN, WHO and Stop TB partnership plans to end TB epidemic globally.



References: [20–22]

Both IPT and screening strategies are included as activities to end the TB epidemic. The first target of the Global Plan to End TB 2016-2020 (developed by the Stop TB partnership in 2015) is that preventive therapy should reach 90% of the vulnerable population, such as PLHIV and those in contact with TB. The strategy is intended to reduce the spread of the disease and, consequently, its incidence. The Country Settings section of the document also recommends TB screening and IPT in PLHIV in Setting Two (Southern and central African countries where HIV and mining are key drivers of the epidemic) and Three (African countries with moderate to high HIV where mining is not a significant issue). Finally, in the section addressing PLHIV as a key population, the document highlights the importance of following all recommendations from WHO and UNAIDS for jointly addressing HIV and TB [22]. The End TB Strategy launched by WHO in 2015 also refers to IPT and screening in its first pillar by integrating patient centred TB care and prevention. The Strategy recommends systematic screening of contacts and high-risk groups and preventive treatment of persons at high risk [21].

Using gene Xpert as an initial TB test in adults and children suspected of having HIV associated TB has been a WHO recommendation since 2010 [33]. So far, 15 of 48 high TB, multidrug resistant TB and TB/HIV burden countries have implemented the test as initial diagnosis in all

patients with TB symptoms. Two other versions of the test, Xpert Ultra and Gene Xpert Omni, have been developed and are under evaluation by WHO, [15]. The first is a new generation of cartridge and has the potential to replace the current Xpert cartridge and culture as a primary diagnostic test. Initial tests have shown that the new cartridge is likely to be as sensitive as liquid TB culture. Also, the new cartridge can be used with the current Xpert instruments. The second is a new diagnostic platform and has been developed to be used as a point of care test using the current Xpert cartridges or the new Xpert Ultra cartridges. This new technology has the advantage of being less expensive, lighter, has lower power consumption and has an additional 12 hours of run time [15,34,35].

Molecular tests, which include Xpert technologies, have also been clearly recommended in the Stop TB partnership plans to end TB. The plan recommends the use of rapid molecular diagnostics in Setting One (Eastern European and central Asian countries that have a high proportion of drug-resistant TB and a hospital-based care delivery system), Three (African countries with moderate to high HIV where mining is not a significant issue), Five (settings with a high to moderate burden of TB with a large proportion in private sector care), Seven (India) and Eight (China) [22].

The introduction and scaling-up of intensified case finding, IPT, Xpert and other technologies are crucial to end the TB epidemic. However, they are not enough without addressing patients' costs. TB/HIV co-infected patients can face high, even, catastrophic costs during their TB diagnosis and treatment. In addition, these higher costs could lead to worse outcomes, such as treatment abandonment and death[36]. A systematic review conducted in low and middle-income countries shows that income loss represents 60% of total patient costs. Direct medical and non-medical costs each accounted for 20% of total costs [37]. WHO has been encouraging the development of local studies which address patient costs to support the goal of 0% of families facing catastrophic health expenditures[e] due to TB by 2020 [36]. The global plan to End TB recommends free or affordable health systems and access to social welfare systems as a way to eliminate catastrophic health expenditure [21].

Another important point is the necessary investment and funding available to end the TB epidemic, which implies a reduction in TB incidence and deaths. New estimates indicate that the necessary investments to reach the Fast-track goal of averting new HIV infections and AIDS-related deaths, including TB deaths, may increase to US$26.2 billion by 2020, about

[e] WHO defines catastrophic health expenditures as total costs that exceed 20% of annual household income.

US$ 7 billion more than the funds available in 2015 [31]. The funding available to deal with TB/HIV co-infection is also insufficient. Recent estimates indicate that US$8.3 billion is needed annually to combat TB in low and middle income countries. In 2015, US$6.6 billion was invested and only 6% of this fund was allocated to TB/HIV infection activities[2]. In the global context of resource constraints, ambitious goals and an increased need for funding, economic evaluation studies are an important tool to support the achievement of ending the TB epidemic in a sustainable way.

2.3 Brazilian scenario

Brazil is a Latin American, upper middle-income country, accounting for 36% of the population in the region. In 2015, 830,000 PLHIV and 15,000 AIDS-related deaths occurred in the country. The epidemic is classified as stable at the national level, but the country has 47% of PLHIV in Latin America and is one of 15 countries which account for nearly 75% of all PLHIV globally [38,39]. ART is offered free of charge through the Unified Health System (Sistema Único de Saúde, SUS) and covers 64% of patients. Brazil was the first developing country to adopt Treatment as Prevention (TasP), which allows the starting of ART regardless of the level of CD4 count. The country is a leader in the manufacture of antiretrovirals (ARV), but prices are still high for the second and third lines of ART [38,39].

Brazil is also among the 30 countries with the highest TB/HIV burden worldwide and the disease is responsible for about 12% of all deaths in PLHIV [15,40]. The mortality rate has followed the global declining trend. The current rate is 1.1 per 100,000 inhabitants and 1,773 AIDS-related deaths occurred in 2014. The incidence rate of TB/HIV co-infection has been stable since 1990 [41]. Currently, this rate varies from 0.6 per 100,000 inhabitants in Acre to 9.3 per 100,000 inhabitants in Amazonas, both states in the North region. Besides Amazonas, the highest incidences are concentrated in three more states across the country, Rio Grande do Sul (7.7), Rio de Janeiro (4.8) and Pernambuco (4.3). The coverage of Direct Observed Treatment Strategy (DOTS) in the country is about 43% and this strategy is not available in all referral services for PLHIV. When DOTS is not available, patients collect TB drugs from the health service monthly [42,43]. The proportion of TB patients with known HIV status has been increasing in recent years and in 2015 reached 78%. The coverage of ART in TB/HIV co-infected patients varies greatly across the country, reaching less than 1% in Amapa, North region, and 92% in Tocantins, Midwest region. TB/HIV positive cases have worse outcomes when compared with

TB/HIV negative; the proportion of cure is 50% and 81%, respectively. The proportion of abandonment and death is higher for the first group, 15% *vs* 8% and 5% *vs* 2%, respectively [42].

PLHIV outpatient treatment is decentralised in the country and patients are treated in Specialised Care Services (SAE, in Portuguese). Medical assistance is provided through a multidisciplinary team encompassing nurses, infection disease specialists, gynaecologists, psychologists, paediatricians and dentists. Other activities include HIV counselling and testing, control and distribution of ART, pharmaceutical guidance, offer of monitoring exams (CD4, viral load, hepatitis and others), educational activities for prevention and control of AIDS and other sexually transmitted diseases, and distribution of prevention products (i.e. condoms, leaflets) [44].

Currently, TB diagnosis in PLHIV is made mainly through sputum smear microscopy (SSM), chest X-ray (CXR) and sputum culture (SC) [43,45]. The gene Xpert test has been implemented in the country since 2012. Currently, 92 municipalities provide the test and the goal for 2017 is the distribution of 70 more machines across the country. Coverage of the test in the general population is quite low with only 32% of pulmonary TB cases being made through the test in 2015. Furthermore, the test is not available as a point of care for PLHIV in SAEs. Thus, the coverage of TB diagnostic testing in PLHIV is even lower [46,47]. The Ministry of Health (MoH) also recommends TB screening by a clinical algorithm in PLHIV at every appointment. However, the screening is not yet being adopted as routine at all SAEs[43,45]. The 2017 National Plan against Tuberculosis, entitled "Brazil free of TB", aims to change this scenario, by declaring the fight against TB as a governmental priority. The actions related to this priority include the expansion of TB diagnosis via the increasing of availability of gene Xpert and culture tests in every public health facility, including SAEs, and the assessment of potential new technologies, especially those aimed at diagnosis patients with resistance to drugs against TB (MDR/TB), strengthening policies for TB control in vulnerable populations (i.e. PLHIV, prisoners) and surveillance of TB deaths, LTBI and resistant TB [48].

Another recommendation from the Brazilian MoH is to offer tuberculin skin tests (TST) and IPT for PLHIV. IPT is indicated for those patients with a TST ≥5mm who are unlikely to have TB. The treatment is also indicated for patients who have contact with TB patients [45]. The country faced a shortfall of TST from 2014 to 2015, which caused some difficulties in the decision to start or not start IPT. The country is evaluating the possibility of producing the test

at national level, as it is currently imported. Another possibility is the production of Interferon Gama Release (IGRA) to increase the coverage of LTBI diagnosis [49].

In 2016, the estimated budget to deal with TB was US$60 million, but only 78% of the budget was funded - with 77% from domestic sources and less than 1% from international sources -, which means that some activities are not yet being conducted [41]. Brazil is committed to the goals stated by the UN, WHO and Stop TB partnership and aims to reduce TB incidence and mortality rates to less than 10 cases/100,000 inhabitants and less than one death/100,000 inhabitants, respectively, by 2035. Another goal is to reduce to zero the number of families facing catastrophic cost due to TB by 2020. The main actions to address TB/HIV co-infection are testing for HIV in all TB patients, TB screening in all PLHIV, early TB/HIV co-infection treatment, diagnosis and treatment of LTBI, promoting adherence to TB and HIV treatment and increasing collaborative TB/HIV activities [39,48]. However, the success of the National Plan against Tuberculosis depends not only on the expansion of better diagnosis and treatment technologies, and an infrastructure that supports the application of these technologies, but also on the understanding of the health and economic benefits generated by those, especially given the challenge of financial constraints. The study proposed by this thesis aimed at collaborating for the generation of evidence of such health and economic benefits to support the Brazilian efforts against tuberculosis.

2.4 Economic evaluation and modelling

The use of resources in the field of health increasingly needs to be rationalised due to the growth of expenditure and limited resources. The incorporation of new and costly technologies, the increase in life expectancy and the coverage expansion of health systems make health financing a challenge for policy-makers and managers. Furthermore, resources are scarce and insufficient to implement all the interventions required by the population. Consequently, health economic evaluations are important to produce information which will guide the decision-making process and contribute to improving efficiency in spending [50,51].

Economic evaluation is a comparative analysis which considers the costs and consequences of two or more interventions. The methodology is essential to identify effective alternatives by measuring, valuing and comparing their costs and consequences. Another concept that supports the method is the opportunity cost that reflects “the value of the benefit of the next best

alternative" [50,51]. All types of economic evaluation measure costs in monetary units and differ only in terms of the nature of consequences. The choice of method will depend on the policy question, availability of data and demand for information by the target audience [52,53]. Table 1 shows the characteristics of the principal types of economic evaluation.

In Brazil, the use of economic evaluations for the decision-making process is recent. In April 2011, the country introduced Law N. 12.401 creating the National Committee for Technology Incorporation (CONITEC, in Portuguese) [54]. The Committee advises the MoH regarding the introduction, exclusion and alteration of health technologies in the public health system. The decision to incorporate a new technology is based on the best available scientific evidence and considers the efficacy, accuracy, effectiveness and safety of the technology. The decision also considers the costs and benefits of the new technology compared with the existing one. CONITEC consists of Plenary and Executive Secretariat boards. The Plenary is responsible for issuing recommendations and the Executive Secretariat coordinates the activities of CONITEC and issues the final report on the technology. The final report addresses scientific evidence, economic evaluation and budget impact of the introduction of technology[55].

Table 1. Characteristics of the main economic evaluations approaches

Type of study	CBA	CEA[1]	CUA[1]
Outcome	Monetary units	Natural unit: cases averted, Life years gained; LYS	Utility: QALY, DALY
When to use	When the policy question intends to determine if the benefits of intervention are greater than the costs.	When comparing competing interventions	When the intervention has an impact on length of life and on health-related quality of life
Advantages	Capacity to compare interventions with different outcomes	Results are easily interpreted by decision-makers	Outcomes can be single or multiple; comparison between different disease areas
Disadvantages	Difficult to transform clinical benefits in monetary terms	Restricted to comparison of interventions with a common single unit of effect	Difficult to measure quality of life; measures not universally accepted
Indicators	NPV, BCR	ICER (cost per life years gained)	ICER (cost per QALY gained or cost per DALY averted)
Calculation	NPV = cost - benefits of an intervention BCR = benefits / cost of an intervention	ICER = total cost intervention A - total cost intervention B / total effects intervention A - total effects intervention B	ICER = total cost intervention A - total cost intervention B / total effects intervention A - total effects intervention B

References: [52,56]

[1] CEA and CBA are used interchangeably in the literature. CBA=cost-benefit analysis; CEA=cost-effectiveness analysis; CUA=cost-utility analysis; LYS=life-years saved DALY=disability adjusted life year; QALY=quality adjusted life year; NPV=net present value; BCR=benefit-cost ratio; CER=cost-effectiveness ratio; ICER=incremental cost-effectiveness ratio

2.4.1 Costs and consequences

Preparation of cost estimates is usually the first step in an economic evaluation and these can be assessed from the patient, provider and societal perspective. Costs are classified as direct medical and non-medical costs and indirect costs. Direct medical costs are those directly related to the health assistance (i.e. drugs, tests, staff salary). Direct non-medical costs are all non-medical expenses associated with the delivery of health care (i.e. transport, food, overheads). Indirect costs are the economic value of income and time loss, disability or premature death due to disease [57].

Several sources can be used to collect information on costs, such as clinical trials, meta-analysis, administrative databases, medical records, and questionnaires [52]. In this study, administrative databases (prices), medical records (quantities) and interviews with professionals were used to collect direct medical costs and overheads from the provider perspective. Questionnaires were applied to collect direct medical and indirect costs from the patient perspective.

The ingredient approach methodology is the more robust and transparent method to calculate direct medical costs and it was also adopted in this study [50]. Other approaches are top-down and bottom-up, which are related to the level of disaggregation at which a resource is valued. Pre-existing data are used to measure the average or total costs in the top-down approach. Thus, the cost of an input is not decomposed into their main elements. In the bottom-up approach each element of an input is measured and valued [58]. For instance, to calculate the cost of a SSM analysis, we considered the cost of reagents, labour, equipment calibration and maintenance. Then, the cost of each element is summed to obtain the total cost of the test. Both approaches were used in this study.

To calculate shared costs, such as overheads, two approaches were applied in this study to calculate costs of buildings and staff. The meter square rule was applied to calculate overheads. In this case, costs for utilities, maintenance and other hospital contracts were shared according to the percentage of floor used in each activity. To calculate staff costs, weights were assigned for each type of patient (i.e. HIV/AIDS emergency care, TB/HIV patient inpatient care) and the time dedicated to each type of patient was calculated.

Patients' direct costs can be collected from surveys using questionnaires or diaries. Indirect costs can be more challenging to measure, especially in countries where a high proportion of

the population works in the informal market. The human capital approach is commonly used to value the productivity loss due to illness. Productivity loss is calculated by multiplying the duration of the illness by the amount that person would be earning if they were not ill. Another method is the friction approach, which considers the need to replace workers who are absent due to illness[53]. Time loss can be calculated by attributing the value of an hourly minimum wage and income loss can be collected from patient surveys (questionnaires). For those patients who were on sickness benefit, income loss can be calculated as the difference between an employee's foregone wages and the sickness benefit received [59]. More details about these methodologies are given in Chapters 4 and 5.

In economic evaluation consequences can be measured in monetary units, natural units or utilities according to the type of economic evaluation (Table 1). The most common measurements are Quality Adjusted Life Years (QALYs) and Disability Adjusted Life Years (DALYs). QALYs combine quantity and quality of life and assume that each year of life is valued equally across people. The utility measure is based on primary data collection through the use of validated, reliable and sensitive questionnaires, such as EQ 5D [52]. DALYs was the unit adopted in the cost-effectiveness study presented in this thesis. Thus, the next paragraphs will conceptualise DALYs and present advantages and limitations of this outcome.

DALYs is a measurement of the burden of a disease that combines years of life lost (YLL) due to premature death and years of life with a disability (YLD). The sum of YLL and YLD results in the total number of DALYs due to a disease. The concept was developed by WHO and the World Bank, being first used in the World Development Report (1993) to analyse the burden of different conditions and states within and among countries [58,60]. DALYs is more predominant in low and middle-income countries. Its calculation takes into account the standard life expectancy in a country, the value of time lived at different ages, value of future time and value of avoiding disability. The disability weight included in DALYs calculation is a value varying from 0 (full health) to 1 (death) and is based on the description of a condition/disease. WHO provides the value of the disability weight for several conditions/diseases through the "Global Burden of Disease" report [61]. YLD is calculated by multiplying the incident cases by duration and disability weight for the condition. YLL is calculated by multiplying the average life expectancy of a given country (Japan, for instance, which has the highest life expectancy in the world), or in the country where the study is taking

place, by the number of deaths [52,58]. In this study, we used formulas provided by Fox-Rushby & Hanson [62] to calculate YLL and YLD as detailed in Chapter 5.

In a cost-effectiveness analysis, DALYS are presented as cost/DALYS averted. The cost-effectiveness threshold most commonly applied is the one established by the WHO Choosing Interventions that are Cost–Effective (WHO-CHOICE) project. The willingness to pay threshold is based on the Gross Domestic Product per capita (GDP per capita) and establishes that a cost-effectiveness ratio below three times the GDP per capita is considered cost-effective. Additionally, a cost-effectiveness ratio less than one times the national annual GDP per capita is considered highly cost–effective [63].

Like any other cost-effectiveness measurement, DALYs has advantages and limitations. The main advantages are: it measures both additional years of life gained and improved health; it is used by international agencies, such as WHO and the World Bank to support resource allocation; it is a more comprehensive measure of population health; it allows comparisons among a wide range of health interventions [52,64]. The main limitations are: different approaches have been used in DALYs calculation, which makes comparisons difficult; the burden of disease approach to decision-making has been criticised by different authors; it is less inclusive than other outcomes because it does not include the impact of side-effects, co-morbidities and involves evaluation from experts (disability weight calculation), rather the general public [52,62].

2.4.2 Modelling

The use of models has been widespread in economic evaluation for two main reasons. First, economic evaluations are based on data from different sources. Second, the uncertainty around these data generates uncertainty around the results. The model will reflect these uncertainties, giving more transparency to the decision-making process [58].

Models are a simplification of the "real world" and should represent the most important events caused by the disease and the effects of an intervention. A model includes inputs such as unit costs, resource use, clinical effects, health state evaluation and epidemiological data to give as an output the incremental cost-effectiveness ratio (ICER) of the intervention. Models should use the best data available, which are usually provided by meta-analysis or clinical trials. Additionally, the time frame should cover an appropriate period to capture all relevant costs and benefits of the intervention. The time frame will vary according to the intervention analysed and can cover the life of the cohort, life time, or shorter periods, such as one year.

Other important characteristics of a good model are reproducibility, transparency and high internal and external validity [52].

Infectious disease models can be classified as compartmental, individual-based or microsimulation, transmission dynamic, static or network. Compartmental models divide the individuals in the population in compartments to track the infection process collectively. Individual-based models tracks the infection process for every individual in the population. Transmission dynamic models incorporate transmission between individuals. The risk or force of infection is predetermined and does not consider the variation in the number of susceptible individuals in the population in static models. Network models consider the network of contacts between individuals [65].

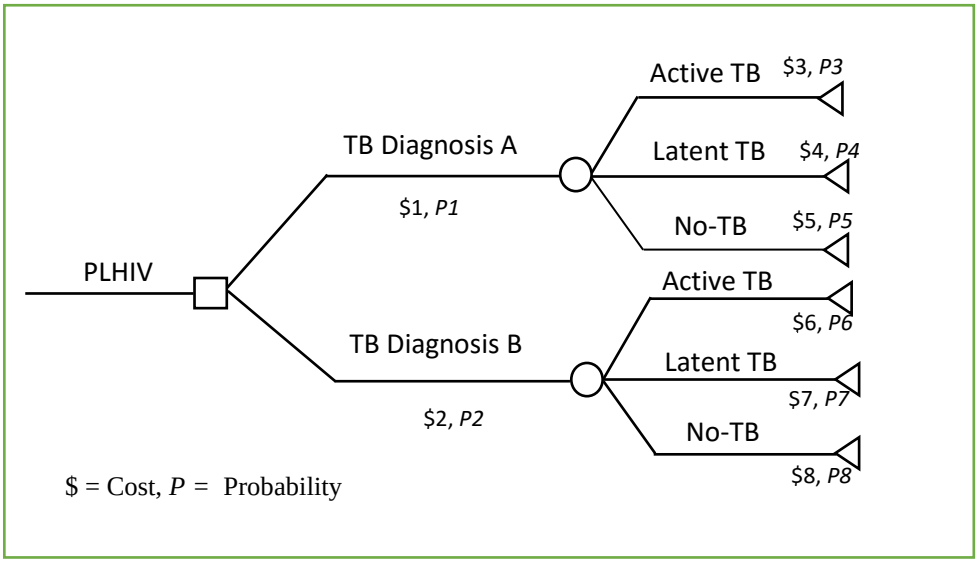
Another approach that can be used in both infectious and non-infectious diseases is decision analysis. Decision analysis uses mathematical relationships and theory of probability. In this approach, an intervention can generate a series of consequences, such as inpatient or outpatient care; cure of the disease or recurrence. These consequences are expressed in probabilities and they have costs and a final outcome that can be expressed in cost/DALYs or cost/QALYs. The cost ($) and outcome (DALYs or QALY) of an intervention will be the sum of all costs and consequences weighted by its probability. Decision analysis can be developed as a cohort or micro-simulation model. The cohort model characterises the experience of the average patient in a population. There are two main types of cohort models, Markov and decision tree model[66].

A decision tree model was developed in the cost-effectiveness study presented in this thesis. The decision tree model is a flow diagram showing the logical structure of an intervention with all the costs, consequences and final outcomes. A decision tree comprises a decision node (□), chance node (○) and terminal node (Δ). The decision node is the first point of the tree when the choice about one or another intervention is made (i.e. treatment A *vs* B; diagnosis A *vs* B *vs* C). After the decision node, chance nodes are added to represent the probability of each consequence of the intervention (i.e. side-effect *vs* non-side effect). The terminal node comes at the end of the tree to show the final cascade of events with the final outcome. The decision tree follows only one direction, usually left to right[52]. Figure 2 shows a simple representation of a decision tree.

Although the decision tree is a very simple tool in a cost-effectiveness analysis, there are some limitations to this approach. As the flow of the cascade of events only goes in one direction,

the model is not suitable for recurrent events. Another limitation is the lack of a temporal element, which means that all events happen at a single time. Thus, the model cannot be used to evaluate complex interventions, which could generate "busy" decision trees and less accuracy [52,66].

Figure 2. Example of a decision tree



2.4.3 Uncertainty

Models in economic evaluation can use several data sources and most of the data are estimates rather than absolute values. Thus, uncertainties can be generated around them. Consequently, it is important to carry out sensitivity analyses to examine the impact of changes in the model parameters and results [52]. In this thesis, two types of sensitivity analysis were used: one-way in the cost and cost-effectiveness studies, and probabilistic sensitivity analysis (PSA) in the cost-effectiveness study.

The one-way sensitivity analysis aims to demonstrate how sensitive the result is when one parameter of the model changes. Thus, in this type of analysis, the parameters of the model are varied one by one. To determine the range of variation, confidence intervals, values from previous studies or percentages, such as ± 50% can be applied. The result of the analysis is usually presented in a tornado diagram[58,67]. The limitation of this analysis is the underestimation of the uncertainty due to the variation of each parameter at a time [52].

In a PSA, all parameters are varied simultaneously which allows for the evaluation of the joint uncertainty of all parameters at the same time. The first step of this analysis is to assign

distributions to the parameters. Beta (α, β) distribution is suitable to represent uncertainty around the probabilities, which varies from 0 to 1. Alpha (α) represents the number of events(r), and beta (β) is the difference between the total sample (n) and r. For a cost that does not allow negative values and varies from zero to infinity, Gamma (α, β) distribution can be applied. In this case, alpha (α) is calculated by dividing the square of the mean (μ^2) by the square of the variance (S^2); while beta (β) is calculated by dividing the square of the variance by the mean. After assigning distributions, computer software can be used to run a thousand simulations and assign a distribution to all parameters. The analysis will calculate many different values for ICER, plotting the results in a scatter plane. A cost-effectiveness acceptability curve can also be calculated. This graph is useful to show the proportion of simulations where the intervention is cost-effective according to different willingness to pay thresholds [52,66,67].

CHAPTER 3. REVIEW OF THE LITERATURE

I am presenting two literature reviews in this thesis. The first one is a systematic literature review addressing the costs of TB diagnosis and treatment in PLHIV co-infection. The objective of this review was to summarise the costs of TB diagnosis and treatment in HIV infected patients and to assess the methodological quality of these studies. The second review is not systematic, but a comprehensive review aimed at addressing the cost-effectiveness of algorithms for TB diagnosis in PLHIV. Thus, we searched the papers only in four databases. The objectives of the latter were to identify previous studies that had evaluated similar policy question as in my thesis; give an overview of the study designs used, especially the modelling of economic data, parameters used and general findings and guide the methods design presented in this thesis for the cost-effectiveness study.

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SECTION A – Student Details

Student	NOEMIA TEIXEIRADE SIQUEIRA FILHA
Principal Supervisor	ANDREIA COSTA SANTOS
Thesis Title	COST-EFFECTIVENESS OF A PROTOCOL FOR TUBERCULOSIS DIAGNOSIS IN PEOPLE LIVING WITH HIV: AN ECONOMIC STUDY ALONGSIDE A PRAGMATIC CLINICAL TRIAL IN BRAZIL

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Value in Health		
When was the work published?	November/2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
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Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	NTSF and ACS planned the study. NTSF conducted the search, extracted, analysed and interpreted the data, and produced the manuscript. AC also extracted the data. ACS solved conflicts for the data extraction process, contributed to the interpretation of data and reviewed the manuscript. RL provided guidance and reviewed the manuscript. All authors read and approved the final manuscript. None of the authors have expressed any conflict of interest.

Student Signature: [redacted] **Date:** 03/04/2018

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3.1 Research paper 1: Cost of tuberculosis diagnosis and treatment in HIV patients: a systematic literature review

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Contributions: NTSF and ACS planned the study. NTSF conducted the search, extracted, analysed and interpreted the data, and produced the manuscript. AC also extracted the data. ACS solved conflicts for the data extraction process, contributed to the interpretation of data and reviewed the manuscript. RL provided guidance and reviewed the manuscript. All authors read and approved the final manuscript. None of the authors have expressed any conflict of interest.

3.1.1 Abstract

Objectives: To summarize the costs of tuberculosis(TB) diagnosis and treatment in human immunodeficiency virus(HIV)-infected patients and to assess the methodological quality of these studies. Methods: We included cost, cost-effectiveness, and cost-utility studies that reported primary costing data, conducted worldwide and published between 1990 and August 2016. We retrieved articles in PubMed, Embase, EconLit, CINAHLplus, and LILACS databases. The quality assessment was performed using two guidelines the Consolidated Health Economic Evaluation Reporting Standards and the Tool to Estimate Patient's Costs. TB diagnosis was reported as cost per positive result or per suspect case. TB treatment was reported as cost of TB drugs, TB/HIV hospitalization, and treatment. We analysed the data per level of TB/HIV endemicity and perspective of analysis. Results: We included34 articles, with 24 addressing TB/HIV treatment and 10 addressing TB diagnosis. Most of the studies were carried out in high TB/HIV burden countries (82%).The cost of TB diagnosis per suspect case varied from $0.5 for sputum smear microscopy to $175 for intensified case finding. The cost of TB/HIV hospitalization was higher in low/medium TB/HIV burden countries than in high TB/HIV burden countries ($75,406 vs. $2,474). TB/HIV co-infection presented higher costs than TB from the provider perspective ($814vs.$604vs.$454). Items such as "choice of discount rate," "patient interview procedures," and "methods used for valuing indirect costs" did not achieve a good score in the quality assessment. Conclusions: Our findings point to the need of generation of more standardized methods for cost data collection to generate more robust estimates and thus, support decision-making process.

Keywords: costs, diagnosis, TB/HIV co-infection, treatment.

3.1.2 Introduction

The World Health Organization (WHO) estimates that 1.1 people worldwide are living with tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection [15]. Among HIV patients the prevalence of co-infection can reach approximately 31% in African countries [68]. Although the number of deaths due to TB/HIV co-infection has been falling, TB is still the main cause of death for HIV patients [15]. Besides the epidemiological burden of the concurrent TB and HIV epidemic, TB diagnosis and treatment for the care of HIV can be costly to the health system, patients and their families. High costs of diagnosis and treatment can be a barrier for universal care of TB in HIV patients and an obstacle to achieve the end of both the epidemic by 2030 as advocated by the UN Sustainable Development Goals [69].

Within the context of TB diagnosis for HIV patients, interventions can include multiple interacting elements, with a combination of diagnosis algorithms. The treatment of TB can also present some level of complexity in HIV patients. Co-infected patients can present more side effects during chemotherapy and, have higher relapse rates [70,71]. Understanding the nature and dynamic of these costs is paramount for robust costs estimates. Also, an assessment on whether appropriate methods of economic evaluation are being undertaken is key for the scaling up interventions that can be cost-effective or cost-saving to the whole society.

Three previous reviews have explored the economics of TB/HIV co-infection and these focused mainly on African countries. These studies have a different focus from the current review such as, costs of expansion of interventions for TB/HIV patients and cost-effectiveness of delivering TB and HIV services [72–74]. So far, no studies have been published that either synthesise the different costs of TB/HIV co-infection or that assess the methodological quality of these studies. In addition, there has been no assessment to date on whether information on costs is widely available, especially for countries with high burden of TB/HIV co-infection. The aim of this article is therefore to undertake a systematic literature review to summarise the costs of diagnosis and treatment of TB/HIV by countries levels of endemicity, and to assess the methodological quality of these studies.

3.1.3 Methodology

This systematic review was designed and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations [25]. A protocol for this

review is registered at Prospero – International Prospective Register of Systematic Reviews - CRD42015020730.

Inclusion and exclusion criteria

All cost, cost-effectiveness and cost-utility studies that reported primary costing data on the diagnosis of TB in HIV patients, including case detection, and TB/HIV co-infection treatment were included in this review. Studies addressing costs of treatment and diagnosis of TB or HIV alone, but that included a sample of TB/HIV co-infected patients and presented the cost disaggregate were also selected and assessed. Only peer-reviewed papers, published between 1990 and August 2016, conducted worldwide and written in English, Spanish or Portuguese were included. Papers using only secondary data on costs and only including the cost of prevention with IPT were excluded. References reported in systematic reviews were screened to identify further studies not captured in the literature search.

Search strategy

We applied the MeSH (Medical Subject Headings) terms using the following key words "HIV OR HIV Infections" OR "Tuberculosis OR Mycobacterium tuberculosis" OR "coinfection" AND "costs and cost analysis OR cost allocation OR cost of illness OR health care costs OR health expenditures" to search the papers. We retrieved papers in PubMed, EMBASE, EconLit, CINAHL plus, and LILACS. Two reviewers (NTSF and ACS) independently selected the studies by title and abstract. A list of these independently selected studies was then compared. The reference list of retrieved studies was also reviewed to identify studies not captured by the search strategy. The literature search was undertaken on 11 August 2016.

Data extraction

Two reviewers (NTSF and AC) extracted independently the data in an Excel spreadsheet. A third reviewer (ACS) discussed discordances and decision was agreed by consensus. Mendeley software was used to manage all selected studies. We extracted: reference, country, endemicity of TB/HIV co-infection, geographical area, period of data collection, type of intervention, study design, level of treatment (inpatient, outpatient), period of cost analysis (pre-diagnosis, treatment), type of costs, source of costing data, perspective of analysis and costs results.

Quality assessment

The quality assessment of studies was based on two guidelines "Consolidated Health Economic Evaluation Reporting Standards (CHEERS)" and "The tool to Estimate Patient's Costs (TBCA)" [75,76]. The analysis was mainly focused on the methods through the assessment of the following criteria: target population; setting and location; study perspective; time horizon; discount rate; cost estimation methods; period of data collection, currency, price date, and conversions; methods used for valuing indirect costs; mean values of estimated costs; patient interview procedures, instrument and source of data collection. Studies were then assessed based on the proportion they reached pre-established criteria.

Data analysis

Costs were first inflated to 2015 prices using USD inflation rates [77]. Then, costs reported in local currency were converted to US Dollars using exchange rates as reported in the OANDA website[78]. Results were first presented as two main themes: (1) costs of TB diagnosis in HIV patients and (2) costs of treatment of TB/HIV co-infection. Sub-analyses were then presented reflecting the country burden of disease as defined by WHO TB report, 2015: high TB/HIV burden and low/medium TB/HIV burden country [2]. The analysis also took into account the perspective of cost (provider, patients and societal) and period of cost analysis (pre-diagnosis and treatment).

To analyse the cost of TB diagnosis in HIV patients, we first extracted the cost per positive result and/or cost per suspect case. We grouped the diagnostic algorithms in six categories: (1) Sputum culture; (2) Other cultures (i.e. pleura, bone marrow) (3) Intensified Case Finding (ICF) (4) Histology (i.e. pleura, bone marrow, liver) (5) Sputum smear microscopy and (6) Others smears (i.e. fluid, urine). We presented the results in box and whisker charts to show the range, the interquartile (IQR) distribution of the costs, mean and median.

To analyse the cost of TB/HIV co-infection treatment we extracted mean cost of the intervention analysed per cost perspective and period of cost analysis (pre-diagnosis and treatment). We extracted the following information, when available: cost of TB drugs for HIV patients, cost of TB/HIV hospitalisation and costs of TB/HIV treatment (inpatient plus outpatient treatment). We compared the cost of TB, TB/HIV and HIV categories, when possible.

3.1.4 Results

Selection, geographical distribution and scope of studies

We found 7,807 potentially relevant articles and selected 100 full text papers for assessment. We excluded thirty-three articles because the cost data were not disaggregated between HIV only and TB/HIV patients. A further thirty-three articles were excluded due to absence of information about the study sample or insufficient reporting of costs, or use of secondary data, or the study design was not a cost study, and one study addressed the cost of HIV screening in TB patients. We included 34 articles with 24 addressing costs to treat TB/HIV co-infection and 10 addressing TB diagnosis in HIV patients. Most of the studies were carried out in high TB/HIV burden countries, 28 in total (Figure 1). Figure 2 shows the distribution of the studies across the world based on the level of endemicity for TB/HIV co-infection. Although 41 countries were classified as high burden countries in the 2015 WHO list, information on costs was available only for 13 countries. Studies from high TB/HIV burden countries reported data mainly from African countries (n=20), especially South Africa, with nine studies, and Nigeria, with five studies. From the perspective of low/medium TB/HIV burden countries, the most frequent studies came from United States (n=3).

Studies estimated the costs of several interventions for TB/HIV treatment and the costs of different TB diagnostic algorithms from the provider and societal perspective. Studies also covered costs for patients and their families, addressing direct medical and non-medical costs, indirect costs and estimates for catastrophic and coping strategies costs. Table S1 in the Supplementary file summarises the characteristics of these studies and presents their main results adjusted by inflation.

Cost of TB diagnosis

Ten studies addressed the cost of TB diagnosis in HIV patients and all of them analysed the costs from the provider perspective. Only one of these studies was conducted in a low/medium TB/HIV burden country, this study analysed a TB screening among HIV infected patient in Laos. The mean cost per suspect case of a screening through sputum smear microscopy by bleach method, and through Acid Fast Staining was 2 USD and 0.5 USD, respectively [79].

Among those studies carried out in high burden countries [80–88], we found a variety of algorithms within the diagnostic groups. The ICF category was performed through chest x-ray screening [88]; symptom screening plus sputum smear (SS), culture (SC) and chest x-ray (CXR) [81];

symptom screening plus acid-fast bacilli (AFB) smear and PCR; symptom screening plus AFB smear and SC [86]; light-emitting diode microscopy (LED) screening; gene Xpert screening [84]; symptom screening plus CXR, AFB smear and SC[82]. The sputum culture category was performed using solid media and mycobacteria growth indicator tube (MGIT)[85]. Sputum smear category was performed through LED and Ziehl–Neelsen (ZN) light microscopy[87]. Finally, histology, other cultures and smear categories were performed in pleura, pleural fluid, bone marrow, urine and blood[80]. The diagnostic category "other cultures" presented the higher mean costs per positive result (348 USD), followed by ICF (294 USD), histology (252 USD) other smears (149 USD) and sputum culture (81 USD). For those studies, which reported the mean costs per suspect case, we only found the evaluation of two diagnostic categories, ICF (79 USD) and sputum smear (4 USD). Figures 3a and 3b show the mean, median and IQR interval of each diagnostic category.

Costs of TB/HIV treatment

Societal perspective:

Three articles analysed the costs of treatment for TB/HIV co-infection from the societal perspective in high burden countries, [89–91] but one of them provided data only about TB drug costs in HIV patients [90]. In Ethiopia, Mesfin et al (2010) analysed TB costs to seek care during the pre-diagnosis period and found similar cost for TB patients with or without HIV co-infection, 262 USD and 296 USD, respectively [89]. Koening et al (2008) analysed the cost of ART provision in Haiti. The authors found that higher cost was associated with TB treatment, hospitalisation and change in ART regimen. Also, TB/HIV patients required more physician and nursing time. The mean total treatment cost of TB/HIV patient was 4,059 USD [91]. Only one study was carried out in a low/medium TB/HIV burden country, USA, and the mean cost to treat TB/HIV co-infection was 10,300 USD [92].

Provider perspective:

Thirteen studies reported cost from the provider perspective disaggregated by TB/HIV status [89–91,93–102]. Another study carried out in Haiti found the cost to treat TB/HIV patient as 22 USD, however it is not clear which cost components was included in the analysis [94]. One study carried out in Ethiopia analysed the costs during the pre-diagnosis period and found a cost 11.6 times higher for TB/HIV patients when compared with TB patients (348USD vs 33 USD) [89]. During the treatment period, one study carried out in Sudan provided the mean cost of TB and

TB/HIV hospitalisation, and found higher costs for the last category (1,152 USD vs 1,558 USD). The same study also found higher costs of TB/HIV treatment (inpatient plus outpatient) when compared with TB patients (858 USD vs 604 USD) [98]. Another study carried out in South Africa reported the mean cost only for TB/HIV outpatients (2,831 USD) [102].

Overall, the mean cost of TB drugs for HIV patient was 91 USD and the mean treatment (inpatient plus outpatient), and hospitalisation cost of TB/ HIV patient were 814 USD and 2,474 USD, respectively. When compared with TB patients, TB/HIV patient presented higher mean costs for hospitalisation (2,474 USD vs 1,152 USD) and treatment (814 USD vs 604 USD). Finally, the mean cost of TB/HIV hospitalisation in low/medium burden countries (USA and Portugal) was 30 times higher than the mean cost of hospitalisation in high burden countries (Table 1).

Four studies analysed the cost from provider perspective in low/medium TB/HIV burden countries [103–106]. One study carried out in Peru analysed a program for integrated care of TB/HIV patients and found a cost of 817 USD/patient/year [105]. Three other studies analysed the costs based on charges, the mean cost of TB/HIV hospitalisation was 75,407 USD[103,104,106]. Gomes et al (2003) also compared the hospitalisation cost for TB and TB/HIV in Portugal and found higher cost for the last category (11,560 vs 18,327) [104]. One study carried out in USA, analysed TB/HIV outpatient cost, which was 1,186 USD [106]. We could not find studies providing information about TB drug costs in HIV patients in low/medium burden countries.

Patient/family perspective:

Seven studies presented the results disaggregated by TB/HIV co-infection. All studies were carried out in high burden countries and four of them in Nigeria. [99,107–112]. During the pre-diagnosis period three studies reported cost for TB and TB/HIV co-infection. The mean direct cost for TB and TB/HIV was 273 USD and 313 USD and the mean indirect cost was 76 USD and 147 USD, respectively. One of these studies carried out in Ethiopia also compared the cost for TB, TB/HIV and HIV categories. The mean direct cost was 639 USD, 783 USD and 1,417 USD for TB, TB/HIV and HIV, respectively. The mean indirect cost was 53 USD, 117 USD and 107 USD for TB, TB/HIV and HIV, respectively [108]. During the treatment period six studies reported costs for TB and TB/HIV categories. The mean direct cost was 227 USD and 278 USD for TB and TB/HIV, respectively. The mean indirect cost was 247 USD and 314 USD for TB and TB/HIV, respectively. One of these studies carried out in Nigeria also compared TB, TB/HIV and HIV mean direct cost, which was 508 USD, 780 USD and 489

USD, respectively [107]. Overall, comparing TB/HIV and TB patients, we found similar direct costs during the pre-diagnosis and treatment period. However, TB/HIV patients experience higher indirect costs during the pre-diagnosis period. Comparing TB/HIV and HIV patients, we found higher mean direct costs for the last category during both pre-diagnosis and treatment period (Table 2).

Quality assessment

Consolidated Health Economic Evaluation Reporting Standards (CHEERS)

We assessed 10 quality indicators using CHEERS recommendations. "Study perspective", "period for resources estimation, quantities and unit costs", "target population" "time horizon" and "cost estimation methods" achieved scores higher than 90%. The provider perspective was the most frequently adopted point of view for analyses, with 68% of the studies assessing the costs from this perspective. Two studies did not report the perspective of analysis; although their results suggest the costs were collected from a provider perspective. The "cost estimation methods" was clearly reported in 94% of papers and the ingredient approach was most common applied method - 78% of all studies. Other methods included expenditure approach (costs based on tariff fees, refund claim, charges), and extrapolation approach (when the cost of an intervention is extrapolated to the current analysed intervention). "Time horizon" covering the treatment period was stated in 62% of the papers, and 17% stated for both the pre-diagnosis and treatment period. The definition of TB treatment period varied among studies, with some covering different phases of the treatments.

Another methodological requirement for cost analysis presented relatively high score in the quality assessment, "sources used for resource quantities and unity costs", with 82% of studies reporting it. Less frequently reported methodological aspects include "values for main categories of estimated costs", with 76% of studies reporting this aspect; "setting and location", with 74%, and "methods for adjusting unit costs and currency conversion", with 69%. (Table 3).

The tool to Estimate Patient's Costs (TBCA):

We applied the TBCA protocol to analyse 10 studies which included costs for patients and their families in the cost analysis. A clear description of patient interview procedures was given in 67% of the studies.

Questionnaires were applied to collect data on direct out-of-pocket expenditures, including fees, charges for tests and medicines, transport, food and accommodation, and indirect costs, defined as time and/or productivity lost due the disease. Two studies did not provide explanations either on the procedures to collect data on indirect costs [91,107] or have stated they have applied a questionnaire to collect direct and indirect costs, but have not explained the process of interviewing the patient (e.g. information contained in the questionnaire; adaptation of the questionnaire to local circumstance; training interview) [110]. Indirect costs covering losses in time and/or productivity for visiting or caring for patients, travelling to the medical service, waiting for consultation or due to hospitalisation and disability), were assessed in 9 papers (80%), and 67% of them described the methods used to value these costs. Ways to estimate and present indirect costs varied from studies. Umar et al (2012) estimated the income loss from the difference in patient's self-reported monthly income and household income for the periods before and during the illness [109]. Other methods applied local labour cost, minimum wage or average wage rate per day/hour reported by patients to calculate indirect costs [89–92,112] (Table 3). Tables S2 and S3 in the Supplementary file give the detailed quality assessment of the articles.

3.1.5 Discussion

In our review, the cost of diagnostic tests per suspect case were estimated as cheaper as 0.5 USD for SSM, in Laos, and as expensive as 175 USD for the ICF algorithm through screening with gene Xpert test, in Malawi [79,84]. We also found substantial variation within the same diagnostic groups/tests such as ICF, sputum culture and other cultures categories. Apart from differences in healthcare settings and systems, this variation in estimated costs might be also explained by the adoption of different aspects of costs components into the analysis. For example, some studies included training and overheads costs into their calculations while others did not. Furthermore, there are different costs and medical system within the countries. Thus, it may not be possible to simply compare cost analysis results across different countries.

The costs of TB/HIV hospitalisation were considerably higher in low/medium burden countries when compared to high burden countries, 75,406 USD vs 2,474 USD, respectively. HIV prevalence, as well as these being high resource settings where all costs would be higher can explain differences in costs between low/middle and high burden countries. While this difference in estimates certainly reflect characteristics of health systems settings and type of treatment received, the methods for calculating costs may also be an important factor. In USA

and Portugal, the estimates included charges as a proxy for costs; this approach clearly overestimates the cost figures for hospitalisation in that setting.

We also found higher costs of TB/HIV co-infected patients when compared with TB patients from the provider perspective. The higher costs are highlighted in the hospitalisation care when the cost of TB/HIV was the double of TB patients. Considering inpatient plus outpatient care, the cost to treat TB/HIV patients was also the double to treat HIV other opportunistic infections. The higher cost for TB/HIV patients is possibly associated with higher relapse rates, more side effects due to the combination of ART and chemotherapy and, consequently, more frequent hospitalisations during the course of TB/HIV treatment.

A considerable number of studies were excluded from this review (N = 33) because they presented their findings without separating TB outcomes for diagnosis and treatment for the population of HIV patients. While we understand studies have different objectives and they not necessarily should aim for the presentation of diseases outcomes in a separated manner, the results of this review clearly point for the gap in information about disaggregated data on the co-infection TB/HIV for both, diagnosis and treatment. A notable piece of information when efforts are being made in order to scale-up and promote access to cost-effective alternatives for the diagnosis and treatment of TB in HIV patients for the elimination of both diseases [15,69].

We also found a huge variation in costs among the studies addressing the patient perspective. Variation in costs can be explained by the use of different approaches to capture these costs, for example the human capital approach estimates time lost from employment by using the current salary wages, or caregiver time that can be valued using average hourly wages as a proxy. Although comparisons of indirect costs can become a difficult objective to be reached due to different methodologies applied, all these approaches allow for relatively straightforward data collection and easy adaptability of tools by countries, even though they are not free of limitations [59].

Besides the expected variation in costs estimates, our review also found some important discrepancy in the methodological aspects of the reviewed studies. In spite of the fact that there is no universal checklist for costing analysis, a recent systematic review addressing TB costs used the same type of assessment [113]. Our findings showed key economic principles are not being covered by all studies, with some items being covered by less than 90% of studies, such as, “methods for adjusting unit costs and currency conversion” and “choice of discount rate”, with the latter covering only 62% of the studies. The adjustment of costs by inflation and

currency conversion, as obscure figures can result in costs estimates that are not robust enough to be taken into consideration in an economic analysis.

Another important finding relates to the geographical distribution of the studies. Our results showed that more than 80% of studies were conducted in high TB/HIV burden countries. Nevertheless, 29 out of 41 high burden countries do not have any published cost data addressing TB/HIV costs, for either diagnosis or treatment. The purpose of the WHO list dividing countries by the burden of TB/HIV was to encourage global action on the co-infection and scale-up of collaborative activities addressing both diseases, including supporting discussions on costs [114]. Our review shows that there are still important limitations on the generation of costing data to give support to the assessment of scaling up of interventions. Also, there is still a gap in terms of standardisation of methods used to capture a full cost evaluation.

3.1.6 Conclusion

This review highlighted important conclusions on cost evaluations within the context of the co-infection TB/HIV. However, as our searches were limited to English, Portuguese and Spanish languages, we cannot be completely confident our review was comprehensive. Besides, the quality assessment showed that studies varied in terms of methodological rigour and so, generalisation of estimates should be taken with caution.

Our review findings clearly point to the need of generation of data on costs estimates for diagnosis and treatment, in a disaggregated manner, especially for countries with a high burden of TB/HIV. We also call for the attention on more standardised economic methods to the collection and estimation of costs that can generate transparent, comprehensive, reliable, valid, and therefore more robust cost estimates, to support decision-making upon the introduction of new technologies or scale-up of the existing ones.

Acknowledges

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Figure 1. Literature review flow chart.

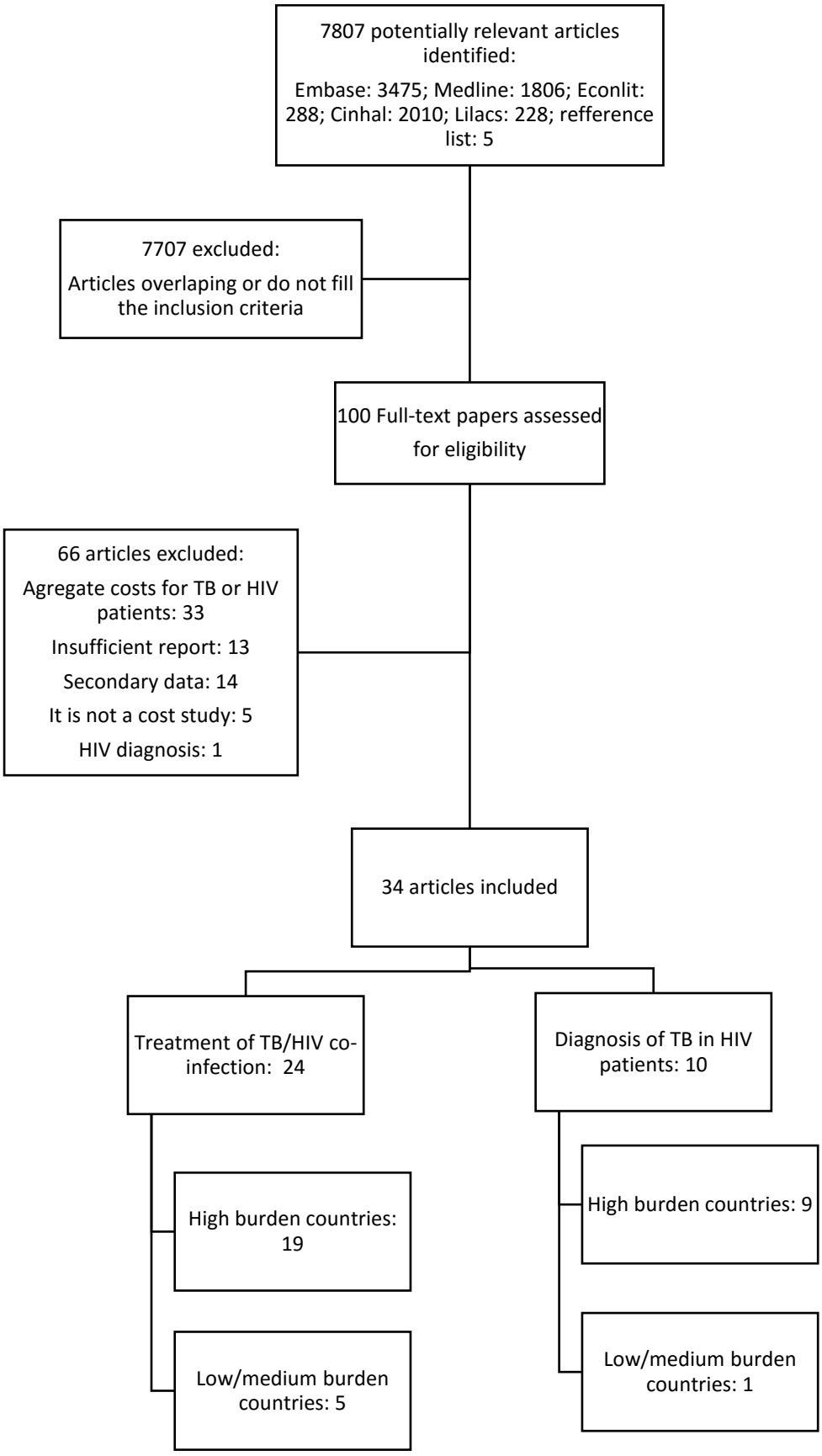

Figure 2. Reported cost studies distributed through countries according to the burden of TB/HIV co-infection.

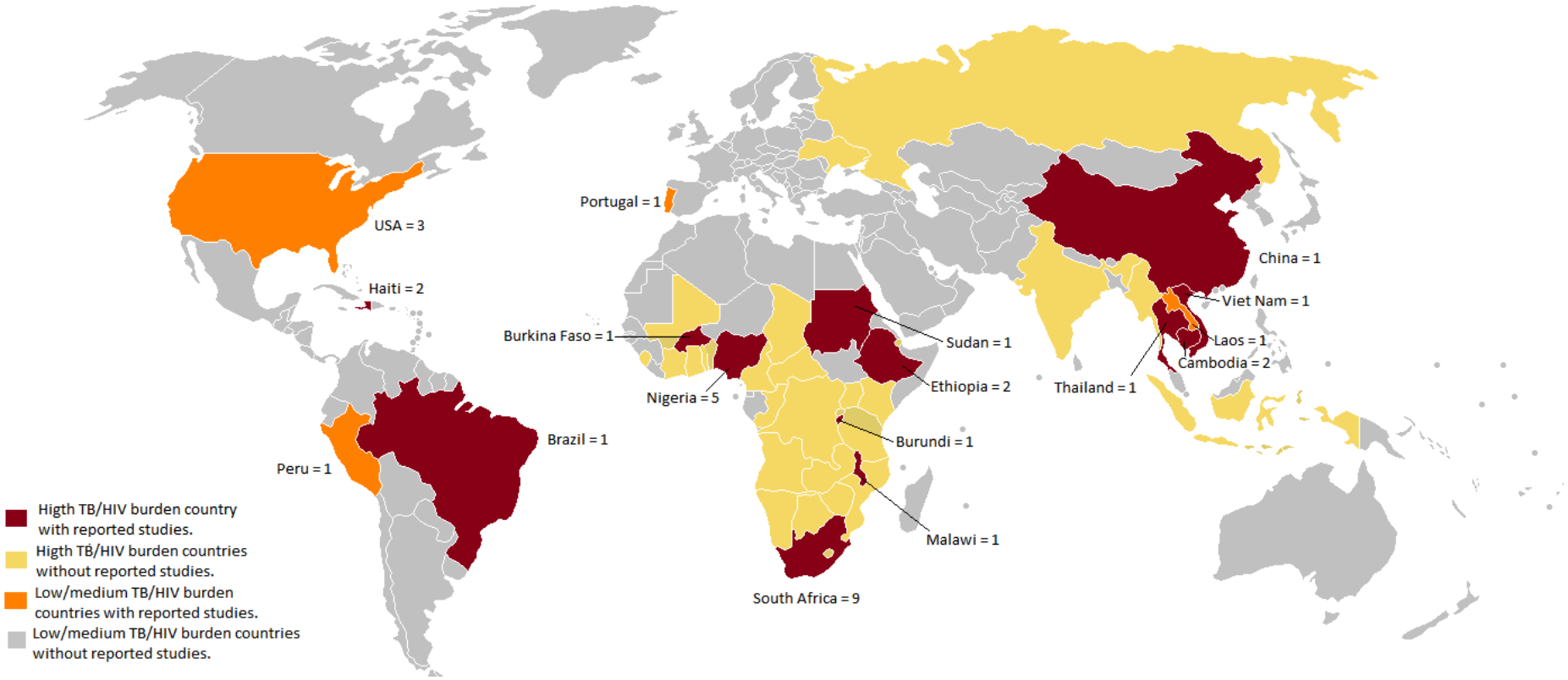

Figure 3a. Median and mean costs of TB diagnosis, by type of diagnosis, in HIV patients, per positive result: provider perspective, high TB/HIV burden country

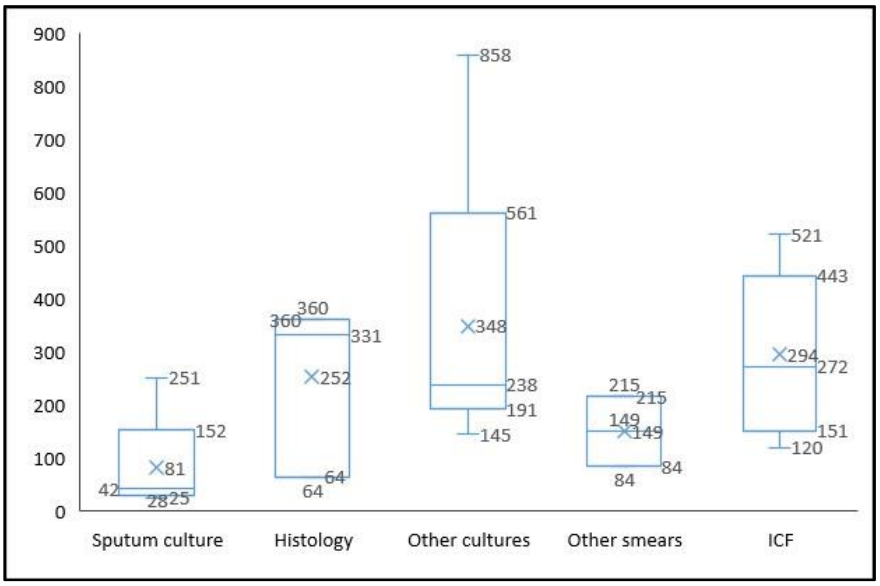

Figure 3b. Median and mean costs of TB diagnosis, by type of diagnosis, in HIV patients, per suspect case: provider perspective, high burden TB/HIV country

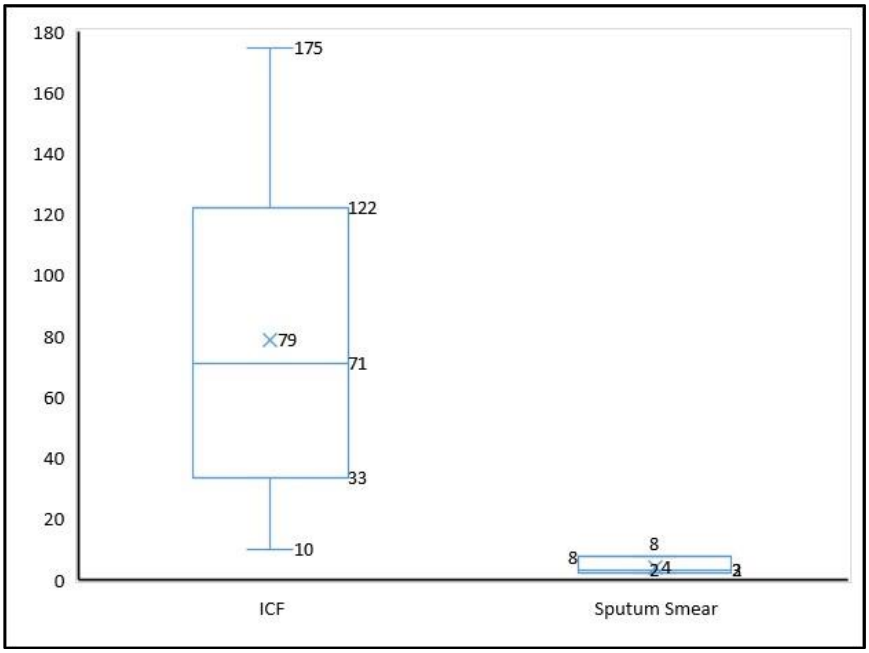

Table 1. Mean and median TB drugs, treatment and hospitalisation cost (US$) for TB/HIV co-infected patient from the provider perspective

High burden countries	Mean	SD	Median	IQR
TB drugs (N = 11)	91	71	92	18-142
Hospitalisation				
TB/HIV (N = 9)	2,474	958	2,288	1,875 - 3,136
TB (N = 1)	1,152	NA	NA	NA
HIV others OI's (N = 27)	2,571	1,455	2,261	1,644 - 2,901
Treatment (in and outpatient)				
TB/HIV (N = 3)	814	463	858	330 - 1,253
TB (N = 1)	604	NA	NA	NA
HIV others OI's (N = 6)	454	599	179	105 - 818
Treatment TB/HIV - outpatient (N=1)	2,831	NA	NA	NA
Low/medium burden countries				
Hospitalisation TB/HIV based on charges (N = 5)	75,407	68135	42,458	18,126 - 149,162
Treatment TB/HIV (in and outpatient) (N = 2)	1,165	1,165	NA	NA

N = number of observations, data from 7 studies for TB drugs, 13 studies for hospitalisation and 12 studies for treatment; NA = not applicable

Table 2. Mean and median direct and indirect TB/HIV co-infection cost (US$) according to period of analysis from patient perspective

Pre-diagnosis	Mean	SD	Median	IQR
Direct cost TB/HIV (N = 3)	313	410	121	34 - 783
Direct cost TB (N = 3)	273	317	95	84 - 638
Direct cost HIV (N = 1)	1,417	NA	NA	NA
Indirect cost TB/HIV (N = 2)	147	42	NA	NA
Indirect cost TB (N = 2)	76	33	NA	NA
Indirect cost HIV (N = 1)	107	NA	NA	NA
Treatment				
Direct cost TB/HIV (N = 6)	278	269	163	105 - 479
Direct cost TB (N = 6)	227	177	154	99 - 410
Direct cost HIV (N = 1)	489	NA	NA	NA
Indirect cost TB/HIV (N = 3)	314	181	253	171 - 517
Indirect cost TB (N = 3)	247	161	173	137 - 432

N = number of observations, data from 18 studies for the pre-diagnosis period and 25 for the treatment period.
NA = not applicable

Table 3. Percentage of papers with clear description of the quality assessment items

CHEERS										TBCA	
Cost estimation methods	Target population	Setting and location	Study perspective	Sources used for resource quantities and unit costs	Period for resources estimation; quantities and unit costs	Methods for adjusting unit costs to the reporting year and performing currency conversion	Values for main categories of estimated costs	Choice of discount rate(s) used for costs and outcomes and why[1]	Time horizon over which costs and consequences are being evaluated and why	Patient interview procedures	Methods used for valuing indirect costs
Diagnosis (N = 10)											
90	80	60	100	60	100	60	70	50	100	NA	NA
Treatment (N = 24)											
90	100	79	92	92	96	73	79	67	96	67	67
Overall (N = 34)											
94	94	74	94	82	97	69	76	62	97	67	67

[1] Only studies with time horizon above 1 year are expected to discount rates to adjust costs estimates. CHEERS: Consolidated Health Economic Evaluation Reporting Standards; TBCA: Tool to Estimate Patient's Costs

3.1.7 Supplementary file

This file will provide a summary of the main characteristics of the retrieved studies (Table S1) and also the complete quality appraisal of the studies (Table S2). In table S1, the term hospitalisation is used interchangeable with hospital admission. In some articles, we have calculated costs that were not explicitly indicated. The details of these calculations is given below. Furthermore, we have made some observations about the costs included and results.

In Pichenda et al (2012), the costs for the health service perspective is unclear. In Rosenblum et al (1999), the total cost of hospital charges adjusted by inflation was divided by 5 years and 16,200 hospitalisations due to TB/HIV co-infection to obtain the mean hospitalisation cost per TB/HIV patients. In the same paper, the inclusion of charges in the cost analysis can probably overestimate the costs. In Gomes et al (2003) the mean hospitalisation cost per TB/HIV patient is the sum of medications, other costs and complementary ways of diagnosis and therapeutic.

Table S1. Details of the studies included in the review

Treatment

High TB/HIV burden countries

Reference	Country	Intervention	Data cost collected	Perspective	Main findings
1. Kamolratanakul et al, 2002	Thailand	Management of TB in zonal TB centres	Direct cost: labour, material and capital cost	Provider	Mean TB drugs cost/TB/HIV patient: $142
2. Jack et al, 2004	South Africa	Integrating ART into an existing TB/DOT program	ART, personnel, medications, chest radiography, and laboratory tests	Provider	Mean treatment cost outpatient: $2,831
3. El-Sony, 2006	Sudan	Management of TB/HIV co-infection care	Direct medical costs (drugs, tests)	Health service	Mean treatment cost: $858; mean hospitalisation cost patient: $1,558; mean TB drug cost/HIV patient: $62-$208
4. Cleary et al, 2006	South Africa	ART	Direct health care costs and costs of non-governmental organisations: patient-specific, clinical staff, overhead and capital components, TB treatment	Provider	Mean treatment cost: $1,253
5. Sadoh & Oviawe, 2007	Nigeria	Subsidised HIV treatment program	Direct medical and non-medical costs	Family	Mean direct cost treatment period: $780 (monthly cost multiplied by 6 months of follow-up)
6. Thomas et al, 2007	South Africa	Management of HIV hospitalised patients	Direct cost: pharmaceutics, intravenous fluids, laboratory and radiological investigations, other investigative or therapeutic procedures, hotel and labour costs relating to the length of stay, personnel; indirect costs	Hospital	Mean hospitalisation cost Adult: $2,288 - $4,145; Child: $2,156 - $3,918
7. Cleary et al, 2008	South Africa	Management of HIV care	Direct healthcare costs: medicines, labs, imaging, clinical personnel; economic cost; patient-specific, clinical staff, overhead and capital components	Public health system	Mean cost: $22
8. Koenig et al, 2008	Haiti	ART	Direct medial and non-medical and indirect costs (time spent)	Societal	Mean TB drug costs: $18; mean treatment cost: $4,059
9. Renaud et al, 2009	Burundi	Integrated care for people living with HIV including ART in a primary health care centre	Capital, recurrent and overhead costs: out-patient visit, pharmacy, laboratory, VCT for HIV, adherence counselling, psychological and social support, food support	Provider	Mean TB drug costs: $28
10. Mesfin et al, 2010	Ethiopia	Management of TB care	Patients and escorts (indirect – income lost; direct – transport, lodging, drugs, consultation, investigation, hospital admission); health system (drugs, investigation, hospital admission, consultations)	Societal	Mean treatment cost pre-diagnosis period - societal: $262; Mean treatment cost pre-diagnosis period - provider: $348
11. Vassall et al, 2010	Ethiopia	Collaborative TB, HIV services	Direct (transport and non-transport), indirect and carer costs	Patients	Mean direct cost pre-diagnosis: $783; mean indirect cost pre-diagnosis: $117

Reference	Country	Intervention	Data cost collected	Perspective	Main findings
12. Koenig et al, 2011	Haiti	Early *vs* standard ART	ART, TB medications, laboratory, radiograph, labour, overhead, hospital and procedures	Societal	Mean TB drug cost: $7
13. Zhou et al, 2011	China	Management of HIV care	Medications, laboratory testing and ancillary examinations and medical service charges	Provider	Median treatment cost: $330, mean TB drug cost: $172
14. Pichenda et al, 2012	Cambodia	Diagnosis and treatment of TB and different DOT programmes	Direct household costs of seeking diagnosis and treatment (consultations, drugs, transportation, foods and other); indirect household costs (working days lost); direct medical spending by health care providers (medicines, laboratory examinations, salaries, equipment, administration, vehicles and building facilities)	Household and health service	Mean direct and indirect treatment cost for TB/HIV households before diagnosis to completion of treatment: $864
15. Umar et al, 2012 (A)	Nigeria	Management of TB care	Direct costs	Patients	Mean direct treatment cost for hospitalised patients: $379; mean direct treatment cost for non-hospitalised patients: $189
16. Umar et al, 2012 (B)	Nigeria	Management of TB care	Indirect costs (time spent, productivity loss)	Patients	Mean indirect treatment cost for hospitalised patients: $253; mean indirect treatment cost for non-hospitalised patients: $171
17. Ukwaja et al, 2012	Nigeria	Management of TB care	Direct and indirect costs (income loss), coping costs, guardian costs, household cost	Patients	Mean direct cost pre-diagnosis: $121, Mean direct cost treatment: $62
18. Laokri et al, 2013	Burkina Faso	Management of TB care	Out of pocket expenses: medical and non-medical	Patients	Median direct treatment cost: $129
19. Long et all, 2016	South Africa	Management of HIV hospitalised patients	Direct costs: drugs, tests, staff, overheads	Provider	Mean hospitalisation cost: 2,255

Low/Medium TB/HIV burden countries

Reference	Country	Intervention	Data cost collected	Perspective	Main findings
20. Rosenblum et al, 1999	USA	Management of HIV and TB hospitalised patients	Direct costs of inpatient care, data on hospital daily charges (including facility fees)	NR - Provider	Mean hospitalisation cost/TB/HIV patients: $153,740
21. Wurtz & White, 1999	USA	Management of TB care	Charges and costs for: attending physician, inpatient consultation, daily room, isolation room, outpatient clinic visit, antibiotics, TB treatment	NR - Provider	Mean charges/patients Initial hospitalisation: $42,458; Long term care: $144,584; Re-admission: $17,925; Outpatients: $1,186
22. Gomes et al, 2003	Portugal	Management of TB hospitalised patients	Direct and indirect laboratory and ancillary services, medication	Provider	Mean hospitalisation cost/patient: 18,327
23. Miller et all, 2009	USA	Management of TB care	Infrastructure: depreciation, maintenance, janitorial services, power, water, administrative costs. Patients: time loss, disability, death.	Societal	Mean cost of TB/HIV patients: $10,300

Reference	Country	Intervention	Data cost collected	Perspective	Main findings
			Transmission: costs for each additional TB case		
24. Cerda et al, 2011	Peru	Community -Based Accompaniment with Supervised ART (CASA) for TB/HIV co-infected patients	Out-patient visit and hospital day	Health system	CASA - mean hospitalisation cost/patient/year: $299; mean treatment cost/patient/year: $817; Control - mean hospitalisation cost/patient/year: $814; mean treatment cost/patient/year t: $1,512

Diagnosis

High TB/HIV burden countries

Reference	Country	Intervention	Data cost collected	Perspective	Main findings
25. Hudson et al, 2000	South Africa	TB diagnosis in HIV patients	Laboratory costs - reagents, staff and other costs	Health system	Cost/positive result From $16 (Lymph node aspiration) to $858 (blood culture)
26. Hausler et al, 2006	South Africa	ProTEST package: community health centre *vs* primary health care clinics	ICF component: capital and recurrent costs, economic and financial costs	Provider	Cost/positive result - ICF community health centre: $365; ICF primary health care: $178 Cost/suspect case - ICF community health centre: $26; ICF primary health care: $15
27. Shah et al, 2008	Vietnam	Population-based CXR screening for PTB in HIV patients	Supplies, equipment and services	Public health program	Cost/positive result: $120 Cost/suspect case: $10
28. Dowdy et al, 2008	Brazil	TB diagnosis in HIV patients through SC in solid media *vs* SC using MGIT	Costs for initiation and maintenance of TB culture (transportation of specimens and results, laboratory supplies and equipment)	Public sector	Cost/positive result SSM+TB culture in solid media: $42 - $54; SSM+TB culture MGIT: $54 - $32
29. Sutton et al, 2009	Cambodia	Intensified case finding	Financial and economic costs, training costs and continuing education activities	Provider	Cost/positive result: $162
30. Basset et al, 2010	South Africa	Intensive TB screening for HIV-Patients	Program costs: personnel, materials, and cultures	Provider	Cost/positive result - cough + other symptoms + SSM + SC: $251; patients with cough (SSM + SC): $417; Cost/suspect case - cough + other symptoms + SSM + SC: $99; patients with cough (SSM + SC): $105
31. Whitelaw et al, 2011	South Africa	LED Microscopy in HIV/TB patients	Economic costs - laboratory costs (equipment, space, overhead)	Health service	Mean cost/slide read LED: $2; ZN stain: $3
32. Aliyu et al, 2014	Nigeria	SSM + Point-of-care digital CXR in HIV patients	Recurrent costs of the smear and chest-x-ray diagnosis test for TB. Economic costs of key capital investments	Health service	Cost/suspect case SSM: $7, CXR: $4
33. Zwerling et al, 2015	Malawi	Xpert x LED	Labour, material and overhead	Health service	Cost/suspect case LED: $8 ~ $78; Xpert: $48 ~ 315

Low/medium TB/HIV burden countries

Reference	Country	Intervention	Data cost collected	Perspective	Main findings
34. Thammavong et al, 2011	Laos	SSM by bleach vs direct method for TB diagnosis in HIV patients	material, reagents, staff salaries and investments	Provider	Cost/suspect case SC bleach: $2; direct method: $0,5

DOT: directly observed treatment; ART: antiretroviral therapy; PTB: pulmonary tuberculosis; EPTB: extra pulmonary tuberculosis; PCR: Polymerase chain reaction; ZH: Ziehl-Neelsen; CXR: chest x-ray; SC: sputum culture; AFB: Acid fast bacilli smear microscopy by Ziehl-Neelsen staining; MGIT: Mycobacteria Growth Indicator Tube; LED: light-emitting diode; TLA: thin-layer agar; LJ: Lowenstein Jensen; SSM: sputum smear microscopy; LPA: Line probe assay.

Table S2. Quality appraisal of the retrieved studies: Consolidated Health Economic Evaluation Reporting Standards - CHEERS

References	Ingredient approach	Cost estimation methods	Target population	Setting and location	Study perspective	Sources used for resource quantities and costs	Resources estimation; quantities and unit costs	Methods for adjusting unit and currency conversion	Main categories of costs	Discount rate	Time horizon
Kamolratanakul et al, 2002	Y	Y	Y	Y	Y	N	Y	Y	Y	NA	Y
Jack et al, 2004	N	N	Y	Y	Y	N	N	N	Y	N	Y
El-Sony, 2006	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	N
Cleary et al, 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sadoh & Oviawe, 2007	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y
Thomas et al, 2007	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y
Cleary et al, 2008	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y
Koenig et al, 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
Renaud et al, 2009	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Mesfin et al, 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
Vassall et al, 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
Koenig et al, 2011	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	Y
Zhou et al, 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Pichenda et al, 2012	N	Y	Y	Y	Y	Y	Y	Y	N	NA	Y
Umar et al, 2012 (A)	NA	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y
Umar et al, 2012 (B)	NA	Y	Y	Y	Y	Y	Y	N	Y	NA	Y
Ukwaja et al, 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y

Continued

Laokri et al, 2013	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y
Rosenblum et al, 1999	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y
Wurtz & White, 1999	N	Y	Y	N	N	Y	Y	N	Y	N	Y
Gomes et al, 2003	N	Y	Y	N	Y	Y	Y	NA	Y	NA	Y
Miller et all, 2009	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y
Cerda et al, 2011	N	Y	Y	N	Y	Y	Y	Y	N	N	Y
Long et all, 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hudson et al, 2000	Y	Y	Y	Y	Y	Y	Y	N	Y	NA	Y
Hausler et al, 2006	Y	Y	N	Y	Y	Y	Y	Y	Y	NA	Y
Shah et al, 2008	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y
Dowdy et al, 2008	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y
Sutton et al, 2009	Y	Y	N	N	Y	N	Y	N	N	N	Y
Basset et al, 2010	N	N	Y	Y	Y	N	Y	Y	N	NA	Y
Whitelaw et al, 2011	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	Y
Aliyu et al, 2014	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	Y
Thammavong et al, 2011	Y	Y	Y	Y	Y	N	Y	N	Y	N	Y
Zwerling et al, 2015	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y

Y = yes; N = No; NA = Not applicable

Table S3. Quality appraisal of the retrieved studies: Tool to Estimate Patient's Costs - TBCTA

References	Patient interview procedures	Methods used for valuing indirect costs
Sadoh & Oviawe, 2007	N	N
Koenig et al, 2008	N	Y
Mesfin et al, 2010	Y	Y
Vassall et al, 2010	Y	N
Koenig et al, 2011	NA	Y
Pichenda et al, 2012	Y	N
Umar et al, 2012 (A)	Y	NA
Umar et al, 2012 (B)	N	Y
Ukwaja et al, 2013 (A)	Y	Y
Laokri et al, 2013	Y	NA
Miller et all, 2009	NA	Y

Y = yes; N = No; NA = Not applicable

3.2 Cost-effectiveness of algorithms for TB diagnosis in PLHIV: literature review

3.2.1 Methods

Inclusion and exclusion criteria

The literature review included published peer-reviewed articles conducted worldwide and written in English, Spanish or Portuguese. Only modelling studies (cost-effectiveness analysis; incremental cost-effectiveness analysis; cost-utility analysis; cost-benefit analysis) published in the last ten years were included. Articles about HIV screening in TB patients, those focused on specific populations (e.g. drug users, prisoners) and those addressing TB/HIV co-infection treatment were excluded. Endnote software was used to manage all the selected studies.

Search strategy

The PICOS (Population, Intervention, Comparison, Outcome, Study design) criteria was used to formulate two research questions. These were (1) What is the cost-effectiveness of TB diagnosis algorithms in PLHIV; (2) Which modelling approaches are applied in cost-effectiveness studies addressing TB diagnosis in PLHIV? Studies were searched in the following databases: PubMed, EMBASE, LILACS (Latin America and Caribbean Literature), and EconLit. Several combinations of key words and MeSH (Medical Subject Headings**)** terms were used to find articles (complete search strategy shown in the appendix). The reference lists of retrieved studies were reviewed to identify further studies that met the eligibility criteria. The studies were reviewed by title and abstract.

Data extraction and analysis

The following data were extracted from the articles: country, population of study and type of TB, algorithm for TB diagnosis, main outcome, perspective of analysis, type of cost included, time horizon, type of model, sensitivity analysis and cost-effectiveness result. Costs were first inflated to 2015 prices using USD inflation rates [77]. Then, costs reported in local currency were converted to US Dollars using exchange rates as reported on the OANDA website [78]. If papers did not provide the year of cost data, we used the year prior to the publication date.

3.2.2 Results

Study selection

The inital search identified 370 potentially relevant papers, 210 from Medline, 132 from Embase, 20 from Econlit and 8 from LILACS. Seventy four of them were duplicates and 272 records were excluded based on their titles and abstracts. Twenty seven full text papers were selected for assessment, including 3 additional papers identified from the reference list of retrieved studies. From those 27, a further 11 articles were excluded: 10 because their study designs were not a cost-effectiveness or modelling study, and one because it assessed the cost-effectiveness of different interventions comparing TB diagnosis and treatment, such as expansion of access to TB care *vs* Xpert. In total, 16 papers were included in this review (Figure 4).

Study settings

Of 16 papers retrieved, 12 included Sub-Saharan African countries in the analysis, especially South Africa (eight studies). Other study countries outside Africa included Brazil (four studies), India (one study) and Vietnam (one study). All countries are included in the WHO list of TB/HIV high burden countries, except Vietnam which has been excluded from the more recent (2016-2020) list. Namibia and Lesotho are included in this list due to the severity of their TB burden; in other words, countries with a high TB incidence per 100,000 population. Brazil, India, South Africa, Botswana, Swaziland, Tanzania, Uganda and Kenya are included in the WHO list on the basis of high absolute number of incident cases per year [114]. Figure 5 shows the incidence case of TB/HIV co-infection in all countries included in this review.

Description of the studies

<u>Algorithms for TB screening and diagnosis in PLHIV</u>

The retrieved studies assessed several algorithms for TB screening and diagnosis in PLHIV. The diagnostic tests were evaluated alone or in combination with one or more tests, such as sputum smear microscopy (SSM, bleach or direct method), sputum culture (SC, solid and liquid media), chest x-ray (CXR), Xpert, lateral-flow immune-chromatographic assay (LF-LAM) and a hypothetical point of care. Symptom screening algorithms were evaluated in five studies using the following rules: fever or cough of any duration or weight loss or AIDS-defining illness [115]; chronic cough; any symptoms; two or more symptoms[116]; cough of any duration or

fever or night sweats or weight loss [84,117]; prolonged cough for more than two weeks or haemoptysis[118]. Other screening methods included Xpert alone or combined with symptom screening [119], CXR and SSM alone or combined with symptom screening [116].

Dowdy (2008), Samandari (2010), Maheswaran (2012) evaluated pulmonary TB (PTB) diagnosis in PLHIV [85,115,116]; Abimbola (2012) and Andrews (2012) evaluated PTB diagnosis in PLHIV initiating ART [119,120]; Sun (2013) evaluated only hospitalised PLHIV and Zwerling (2015) evaluated newly diagnosed PLHIV[84,121]. Shah (2013) was the only study that included the evaluation of PTB, extra pulmonary TB and disseminated TB in PLHIV[117]. All other studies evaluated screening or diagnostic methods in PTB suspect patients, but included PLHIV in the sample.

Modelling methods

Most of the studies (14) adopted a static model and 11 of them used a decision analytic model to evaluate the cost-effectiveness of TB screening/diagnosis. Dowdy et al (2008) developed a decision analytic model using a hypothetical cohort of PLHIV with symptoms of PTB. The model assumed a constant proportion of annual deaths and that sputum culture offered benefits only for sputum smear negative patients. The model included costs to treat false-positive diagnosis and decrement in quality of life during TB treatment. The main outcome was DALYs averted and parameters were based on the literature and study data [85]. Another study developed in South Africa, Brazil and Kenya developed a decision analytic model classifying patients according to TB and HIV status (positive or negative), access to ART (yes or no) and degree of TB infectivity (highly infectious and less infectious). Parameters were estimated based on literature and WHO field estimates[122]. The decision analytic model developed by Scherer (2009), included cost from the patient and health system perspective and assumed the possibility of secondary transmission from false negative TB patients. The main outcome was cost per correctly diagnosed TB case[123]. Samandari (2011) developed a model to evaluate the cost-effectiveness of TB screening in a cohort of 10,000 PLWH. The analytic horizon adopted was three years and it was based on the duration of potential benefits of IPT. The authors performed a scenario analysis considering base-case, worst and best scenarios. Parameters were based on the "Botswana IPT Trial" and literature. The main outcome was deaths averted [115]. Bonnet (2010) constructed four analytical decision tree models. The first model evaluated potential combinations of SSM by direct or bleach method (10 in total); the second evaluated only two interventions and the third and fourth were similar to the first and second with the

addition of patient transport costs [124]. Vassal (2011) developed a decision analytic model to evaluate the cost-effectiveness of Xpert for TB diagnosis in India, South Africa and Uganda. The model followed a cohort of 10,000 TB suspects through the diagnosis and treatment pathway and the main outcome was DALYs averted. The model used parameters based on WHO data, assumptions and primary data collection at the study sites[125]. Abimbola (2012) also developed a decision analytic model to evaluate the impact of TB diagnostic strategies on the mortality of PLHIV. The main outcome was deaths averted and the six-month' time horizon was based on the high risk of death of TB/HIV co-infected patients in this period. The model parameters were based on South African studies [120]. Shah (2013), Sun (2013) and Zwerling (2015) also analysed the cost-effectiveness of TB diagnosis in PLHIV using a decision analytic model. The first two studies stratified the model according to CD4 cell count and studies applied one-year or the period of TB treatment time horizon for costs and the life expectancy of the cohort for immediate effects using DALYs as the main outcome. The latter study applied a time horizon based on the life expectancy of 59.2 years for HIV-infected individuals on ART [84,117,121]. Pinto (2016) developed a decision-tree model following a cohort of 10,000 TB suspects stratified by HIV status. The model parameters came from the literature and micro-costing analysis conducted in Brazil [126].

Other static models developed were deterministic[118], Monte Carlo simulation and individual sampling plus Markov model. Maheswaran (2012) developed a model where PLHIV were classified as TB screening positive/false positive; TB screening positive/true positive; TB screening negative/false negative and TB screening negative/true negative. Subsequently, a Markov model was built for each group including adverse consequences of TB treatment [116]. The Monte Carlo simulation developed by Andrews (2012) did not include transmission in the analysis because the benefits of Xpert MTB/RIF relate only to SSN patients who have lower probability of TB transmission when compared with sputum smear positive patients [119].

Only two studies developed a dynamic model, Menzies (2012) developed a dynamic compartmental model including demographic and epidemiological data, TB transmission dynamic, TB programme coverage, and treatment outcomes. The model simulated the TB incidence three decades after the introduction of Xpert and used data from earlier TB models, UN and published reporting data[127]. Langley (2014) developed a model to integrate operational (discrete simulation approach) and transmission components (based on previous epidemic compartmental models). The models were calibrated using data from Tanzania and validated using results from the 2010 National TB and Leprosy Programme [128].

Cost-effectiveness results

Ten studies evaluated the Xpert test for TB diagnosis and the test was likely to be cost-effective when used in place of: (1) SSM + clinical diagnosis of sputum smear negative TB in India, South Africa, Uganda; (2) SSM + CXR in South Africa and (3) SSM + SC + drug sensitivity analysis in Botswana, Lesotho, Namibia, South Africa, and Swaziland. A study carried out in Tanzania compared Xpert and SSM and found that Xpert in all presumptive PTB cases would prevent 17,000 cases of incident TB; 39,700 TB deaths over 10 years and avert 346,000 DALYs [128]. In Sub-Saharan Africa, the cost-effectives of a TB screening by clinical algorithm in PLHIV in addition to Xpert for those with at least one symptom was determined by prevalence of TB among PLHIV and volume of testing. In this case, the test would be more cost-effective than LED microscopy[84]. In Brazil, the use of Xpert combined with CXR and SC in PLHIV would add US$1.2 million per year to confirm 3,344 more TB patients to the TB National Program. The cost per additional TB diagnosis was US$1,078; and the cost per additional TB diagnosis with bacteriological confirmation was US$407. In Uganda, the combination of TB screening by clinical algorithm plus Xpert and LF-LAM was highly cost-effective for TB diagnosis (all forms) in PLHIV (US$82/DALY averted)[117]. Another study carried out in Uganda and South Africa evaluated the same intervention in hospitalised PLHIV. Again, the findings pointed to a high probability of the intervention being cost-effective, 84% in Uganda and 96% in South Africa[121]. Also in South Africa, the use of screening with Xpert in all PLHIV, independent of TB symptoms, before starting ART would increase life expectancy in TB/HIV co-infected patients by 6.6 months [119].

Three studies analysed SSM alone or in combination with SC. In Brazil, SSM + SC in solid media would avert 37 DALYs per 1,000 TB suspects and prevent 49% of all TB deaths at a cost of $1,584 per DALY averted[85]. In South Africa, Brazil and Kenya, SSM would be more cost-effective when compared with a hypothetical new point of care with 70% of sensitivity and 95% of specificity[122]. Also in Brazil, the combination of SSM + PCR was cost-effective when compared with SSM + SC [123]. Three more studies analysed SSM for TB screening in PLHIV. In South Africa the screening by SSM was very cost-effective when compared with no screening [13]. In Botswana a policy with screening by clinical algorithm followed by IPT would prevent more TB and TB-related deaths, and use fewer resources, than a policy that uses SSM and CXR in addition to symptom screening[115]. In the Sub-Saharan Africa study, screening by clinical algorithm was the most cost-effective strategy when compared with screening by SSM alone[116]. Another study carried out in Vietnam in PTB suspects found screening by

clinical algorithm plus SSM to be cost-effective when compared with other screening strategies (SCA + SSM +CXR; screening by CXR; prevalence surveys; prevalence surveys + Xpert; SCA + screening by CXR + Xpert)[118]. Table 4 summarises the main characteristics of the retrieved studies and the cost-effectiveness result.

3.2.3 Conclusions and contribution of the review to the thesis

Most of the papers did not stratify the analysis according to HIV status, showing a lack of evidence of TB diagnosis in this specific population. Three studies conducted in Brazil included PLHIV in the analysis, but the result was not stratified per disease category (i.e. TB, TB/HIV). Only one study conducted in Brazil assessed TB diagnosis in PLHIV. This study evaluated the cost-effectiveness of different methods of SC for TB diagnosis and did not include screening by clinical algorithm or Xpert in the analysis [85].

Only one study included both PTB and extra-pulmonary TB. This led us to include both types of TB in the current study. Although most PLHIV present PTB, the proportion of extra pulmonary TB in this population is higher when we compare it with TB without HIV co-infection [45]. For this reason, diagnosis algorithms based only on sputum samples may have decreased effectiveness in PLHIV. In addition, Xpert tests require a minimum of 2 ml of sputum and some patients are unable to produce this amount[129]. Thus, for PLHIV, it is important to add CXR or other tests, such as LF-LAM, which use urine analysis for TB diagnosis. We were not able to add LF-LAM to our diagnostic algorithm because the test is not available in the public health system in Brazil. Thus, we decided to create an algorithm based on symptom screening plus Xpert for those patients with ≥2ml of sputum or SSM and SC for patients with ≤2ml of sputum or/and CXR and lymph node aspiration. A specialist doctor could also use clinical judgment for TB diagnosis to conduct empirical treatment.

Most papers developed a decision analytic model and ran a one-way and probabilistic sensitivity analysis. Few papers included secondary transmission in the model. TB/HIV patients produced less bacillus due to their immunosuppression. Consequently, for TB/HIV co-infected patients, the probability of transmitting secondary TB infections is lower when compared with TB patients without HIV co-infection [127]. We therefore decided not to include this parameter in the model. We developed a decision analysis model with a one-year time horizon. The model is a representation of real life and uses mathematical relationships to calculate probabilities and costs of each outcome in each intervention analysed [66]. The choice for the one-year time horizon took into account the length of TB treatment in PLHIV in Brazil,

which varies from six to nine months. We also decided to run a one-way and probabilistic sensitivity analysis to evaluate the robustness of the model and to explore the joint uncertainty in costs and effects. Finally, the more common primary outcome was DALYs, which we also decided to adopt based on WHO recommendations and for purpose the of comparisons [130].

Figure 4. Literature review flow chart: cost-effectiveness of algorithms for TB diagnosis in PLHIV.

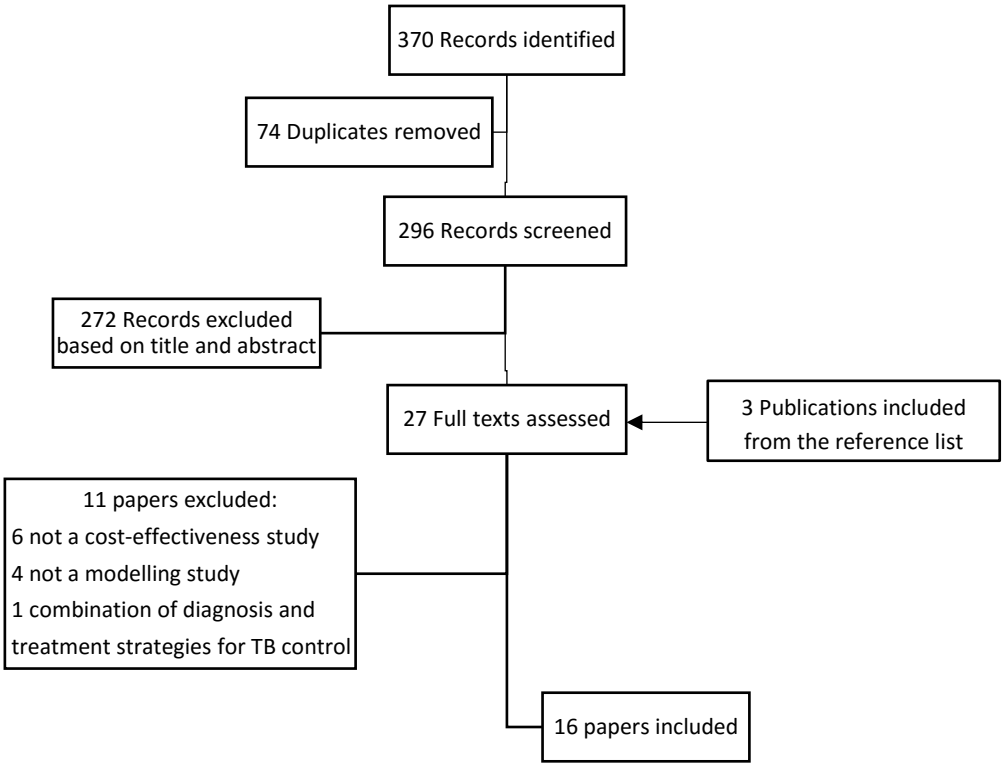

Figure 5. TB/HIV co-infection rate per 100,000 inhabitants. WHO, 2015.

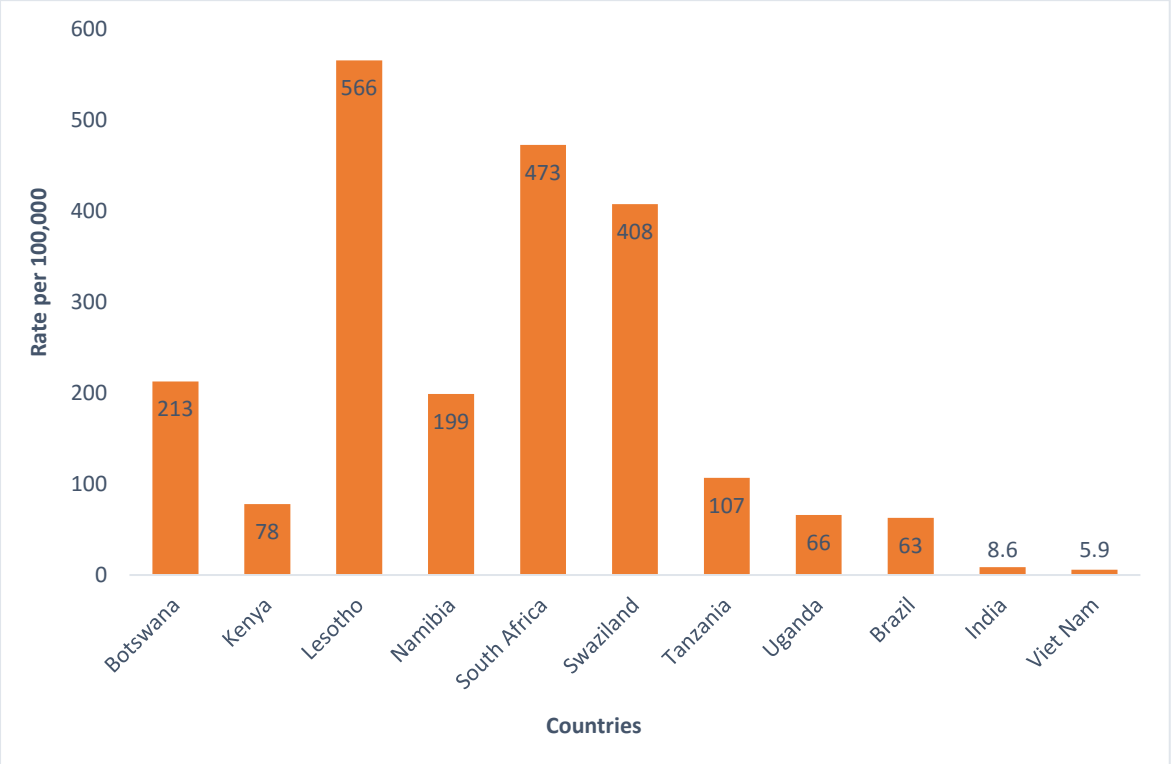

Table 4. Extract and synthesise data: how cost-effective are algorithms to diagnose TB in PLHIV

Reference	Country	Population	Algorithm	Principal outcome	Perspective of study	Cost elements	Time horizon	Type of model	Sensitivity analysis	Result
1. **Dowdy et al, 2008**[85]	Brazil	PLHIV PTB suspects	(1) SSM; (2) SSM + SC/solid media (L-J) (3) SSM + SC/liquid media (MGIT)	DALYs averted	Health system	Initiation and maintenance of TB culture programme	Life of the cohort	Decision analytic	One way (±25%) and multivariate sensitivity analysis (beta and gamma distribution)	*Throughput 8 patients/ week:* (1) base case; (2) $1,584 (3) Dominated; *Throughput 24 patients/ week:* (2) $682; (3) Dominated
2. **Dowdy et al, 2008**[122]	South Africa, Brazil, Kenya	PTB suspects	(1) SSM (reference); (2) Hypothetical new point of care; (3) SSM + SC; (4) SSM+ new test	DALYs averted	Ministry of Health	TB diagnosis and drug	1 year	Decision analytic	One-way and three-way sensitivity analysis (variation by 75%-125% or based on literature)	(3) South Africa $ 596; Brazil $ 670 Kenya $ 291; (3) South Africa $ 757; Brazil $ 1,029 Kenya $ 356
3. **Scherer et al, 2009** [123]	Brazil	PTB suspects	(1) SSM + SC; (2) SSM + PCR	TB case correctly diagnosed and treated	Health system and patients	Patient, laboratory costs, drugs, consumables, equipment. Treatment: inpatients and outpatients	1 year	Decision analytic	One-way	(1) $ 113,806; (2) $ 30,818
4. **Samandari et al, 2010**[115]	Botswana	PLHIV	(1) SCA; (2) SCA + CXR + SSM; (3) SCA + CXR + SSM + tracking	Deaths averted	Health system	Labour and drugs	3 years	Decision analytic	One-way (75 to 125% variation; tornado diagram)	(1) Baseline; (2) dominated; (3) $ 3,290,310
5. **Bonnet et al 2010**[124]	Kenya	PTB suspects	(1) Two direct smears if 1st (-), (2) One bleach smear (reference case), (3) Two bleach smears if 1st (-), (4) One direct smear plus one bleach on it if (-), (5) One bleach smear plus one direct smear, (6) One direct plus one bleach if (-), (7) One direct plus one bleach and direct if 1st (-), (8) One direct plus one direct and bleach if 1st and 2nd (-), (9) One direct plus one bleach if (-) plus one bleach if 2nd (-), (10) One bleach plus one direct plus one bleach if previous (-)	TB positive cases detected	Health system and patient (transport)	Human resources (laboratory technicians), consumables and reagents	NR	Decision analytic	One-way	Base case: (2) (3) = $122 Others = dominated
6. **Vassall et al, 2011**[125]	India, South	PTB suspect	(1) SSM + CXR + antibiotic trial (base case); (2) SMM + Xpert; (3) Xpert	DALYs averted	Health system	Diagnostic: building, overhead, staff,	NR	Decision analytic	One and two-way (outer limits of their confidence	(1) Base case India: (2) $ 107; (3) $132

Reference	Country	Population	Algorithm	Principal outcome	Perspective of study	Cost elements	Time horizon	Type of model	Sensitivity analysis	Result
	Africa, Uganda					equipment, consumables, quality control, maintenance, calibration. Treatment: drugs, outpatient and inpatient			intervals); probabilistic sensitivity analysis (Monte Carlo simulation)	South Africa (2) $ 58; (3) $ 74 Uganda: (2) $ 189; (3) $ 237
7. **Abimbola et al, 2012**[120]	South Africa	PLHIV initiating ART; PTB	(1) SSM + CXR; (2) SSM + CXR + SC; (3) Xpert	TB deaths averted	Health system	TB diagnosis and treatment, ART (in and outpatient), health care utilisation	6 months	Decision analytic	One-way (tornado diagram, confidence intervals), threshold analysis and probabilistic sensitivity analysis – Monte Carlo simulation (confidence intervals or variation by 50%-200%)	(1) *vs* (3) Dominated; (2) vs (3) $ 86,122
8. **Andrews et al, 2012**[119]	South Africa	PLHIV initiating ART	No active screening and diagnostic strategies in any or only TB symptomatic patients: (1) two samples; (2) SSM + SC; (3) one sample Xpert; (4) two samples Xpert	LYS	Health system	Costs of care for both HIV and TB: unit costs for inpatient, outpatient visits, laboratory monitoring and pharmaceutical costs, ART and TB drug toxicities, TB diagnosis	Life time	Monte Carlo microsimulation	One way (tornado diagram) and two-way sensitivity analysis (willingness to pay threshold)	(1) TB symptoms - $ 3,705; (1) all patients - $ 3,990 (2) TB symptoms - dominated; (2) all patients - $ 7,268; (3) TB symptoms - dominated; (3) all patients - dominated (4) TB symptoms - dominated; (4) all patients - $ 7,268
9. **Menzies et al, 2012**[127]	Botswana, Lesotho, Namibia, South Africa, and Swaziland	TB suspects	(1) SSM + SC +DST; (2) Xpert	LY saved and DALYs averted	Health system	TB diagnosis and treatment, ART	10 years	Dynamic compartmental model	One-way (±1 standard deviation) and Bayesian uncertainty analysis; probabilistic sensitivity analysis (cost-effectiveness acceptability curves.)	Cost/DALYs averted - Regional 10 years: $ 959 20 years: $ 784

Reference	Country	Population	Algorithm	Principal outcome	Perspective of study	Cost elements	Time horizon	Type of model	Sensitivity analysis	Result
10. **Maheswaran & Barton, 2012** [116]	Sub-Saharan Africa	PLHIV	ICF: (1) chronic cough; (2) any symptom; (3) two or more symptom; (4) CXR; (5) SSM; (6) any symptom + CXR; (7) any symptom + SSM; (8) any symptom + SSM + CXR; (9) any symptom + CXR + SSM	QALY gained	Health system	Screening: clinic visit (long-run capital costs and labour costs); TB / IPT treatment; managing adverse effects of treatment; investigation costs: overhead, equipment, consumables and labour	2 years	Individual sampling model and Markov	Probabilistic sensitivity analysis (Monte Carlo Simulation), beta and gamma distribution; value of information as an alternative to one univariate sensitivity analysis	(5) base case (3); (7); (4); (6) extended dominance; (1) dominated; (8) $ 7,775; (9) $ 13,552; (2) $ 24,376
11. **Shah et al, 2013**[117]	Uganda	PLHIV PTB/EPTB and disseminated forms of TB	SCA + (1) SSM; (2) SSM + LF-LAM; (3) Xpert; (4) Xpert + LF-LAM	DALYs averted	Health system	Staff time, consumable supplies, and equipment utilised for each test, overhead, TB treatment	1 year for costs and life expectancy of the cohort for immediate effects	Decision analytic	Probabilistic sensitivity analysis (Monte Carlo Simulation)	(1) Reference case; (2) $ 48; (3) $ 84; (4) $ 82; (5) $ 75
12. **Sun et al, 2013**[121]	Uganda, South Africa	PLHIV with clinical suspicion of TB and hospitalised	(1) Clinical judgment + SSM (base case); (2) Clinical judgment + SSM + LAM; (3) Clinical judgment + Xpert + LAM	DALYs averted	Health system	Tests, TB treatment	Lifetime of the cohort	Decision analytic	One-way (literature or ±15%); three-way; probabilistic sensitivity analysis (beta and gamma distribution; standard deviation equal to 12.5%; acceptability curve)	(2) South Africa = $ 503; Uganda = $ 148; (3) South Africa = $ 1,042; Uganda: $ 358
13. **Nishikiori & Weezenbeek, 2013**[118]	Vietnam	PTB suspects	(1) SCA + SSM; (2) SCA + SSM +CXR; (3) screening by CXR; (4) prevalence surveys; (5) prevalence surveys + Xpert; (6) SCA + screening by CXR + Xpert	Cost/TB case detected	Health system	Direct diagnostic cost	NR	Deterministic	One-way (varying the proportion of symptomatic patients between 30% and 50% and the proportion of smear-positive patients between 50% and 70%)	(1) $ 100; (2) $ 147; (3) $ 541; (4) $ 713; (5) $ 742; (6) $ 232
14. **Langley et al, 2014**[128]	Tanzania	PTB suspects	(1) ZN microscopy (base case); (2) LED fluorescence microscopy; (3) LED fluorescence microscopy and	DALYs averted	Health system	Running costs (consumables, TB and MDR-TB	10 and 20 years	Discrete event simulation	Uncertainty analysis and one-way sensitivity	(2) $43; (3) $ 66; (4) $ 250; (5) dominated; (6)

Reference	Country	Population	Algorithm	Principal outcome	Perspective of study	Cost elements	Time horizon	Type of model	Sensitivity analysis	Result
			two sputum samples provided on the same day; (4) Xpert for all presumptive TB cases (5) LED fluorescence microscopy and Xpert for known HIV (+) status; (6) HIV test and LED fluorescence microscopy and Xpert for known HIV(+) status; (7) LED fluorescence microscopy and Xpert for smear (-) patients with known HIV(+) status; (8)) HIV test and LED fluorescence microscopy Xpert for smear (-) individuals with known HIV (+) status			drugs, radiographs, equipment maintenance, and laboratory personnel) and the investment costs (microscopes and the equipment related to Xpert implementation)		integrates operational and transmission components	analysis using 1000 posterior simulations	dominated; (7) dominated; (8) dominated
15. **Zwerling et al, 2015** [84]	Sub-Saharan Africa	Newly diagnosed PLHIV	SCA + (1) SSM (reference case); (2) Xpert; (3) LED microscopy	DALYs averted	Health system	Diagnosis and treatment included labour costs, material costs, and overhead costs. Start-up costs: recruitment and advertising costs for project and field managers, microscopy or Xpert training, petty cash, and postage costs	Life expectancy of 59.2 years for HIV-infected individuals on ART	Decision analytic	One and two-way sensitivity analysis; probabilistic sensitivity analysis (Monte Carlo simulations; beta distribution and uniform alpha parameter of 4)	Scenario analysis by test volume per year (1) 50 tests = $ 3,658; 100 tests = $ 2,460; 1000 tests = $ 1,414 (2) 50 tests = $ 5,6833; 100 tests = $ 3,267; 1000 tests = $ 1,141
16. **Pinto et al, 2016**[126]	Brazil	TB suspects	(1) CXR plus SSM plus HIV test and SC for HIV (+), (2) Xpert plus CXR plus SC for HIV (+)	Additional cost per detected TB case and per bacteriologically confirmed TB case	Health system	Tests and treatment costs	NR	Decision analytic	One and two-way (50% to 200%) and Monte Carlo probabilistic sensitivity analysis	Cost/ additional TB diagnosis $1,078; Cost/ additional TB diagnosis with bacteriological confirmation $ 407

SSM = sputum smear microscopy; SC = sputum culture; PCR = polymerase chain reaction; SCA = screening by clinical algorithm; CXR = chest radiography; Xpert = gene Xpert MTB/RIF; ICF = intensive case finding; NS = no screening; DST = drug sensitivity test; LF-LAM = lateral-flow immune-chromatographic assay; ZN = Ziehl-Neelsen; LED = light-emitting diode; PTB = pulmonary TB; DALY = disability adjusted life year; LYS= life-years saved; QALY = quality adjusted life year; NR = not reported.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	NOEMIA TEIXEIRADE SIQUEIRA FILHA
Principal Supervisor	ANDREIA COSTA SANTOS
Thesis Title	COST-EFFECTIVENESS OF A PROTOCOL FOR TUBERCULOSIS DIAGNOSIS IN PEOPLE LIVING WITH HIV: AN ECONOMIC STUDY ALONGSIDE A PRAGMATIC CLINICAL TRIAL IN BRAZIL

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Sexually Transmitted Infections		
When was the work published?	February/2018		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The study was designed by NTSF, MFPMA and ACS. NTSF was responsible for data collection, analysis and writing the manuscript. ACS, LR, RL and MFPMA reviewed the manuscript.

Student Signature: [redacted] **Date:** 03/04/2018

Supervisor Signature: [redacted] **Date:** 03/04/2018

CHAPTER 4. RESEARCH PAPER 2: THE ECONOMIC BURDEN OF HIV AND TB/HIV CO-INFECTION IN A MIDDLE-INCOME COUNTRY: A COSTING ANALYSIS ALONGSIDE A PRAGMATIC CLINICAL TRIAL IN BRAZIL.

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Contributions: The study was designed by NTSF, MFPMA and ACS. NTSF was responsible for data collection, analysis and writing the manuscript. ACS, LR, RL and MFPMA reviewed the manuscript.

4.1 Abstract

Objective: The objective of this study is to measure the costs of people living with HIV (PLHIV) as well as active tuberculosis (TB/HIV), latent tuberculosis infection (LTBI/HIV) or without TB (HIV/AIDS).

Methods: We analysed the costs through the entire pathway of care during the pre-diagnosis and treatment periods from the Brazilian Public Health System perspective. We applied a combination of *bottom-up* and *top-down* approaches to capture and estimate direct medical and non-medical costs. We measured mean cost per patient per type of care (inpatient, outpatient and emergency care) and disease category, HIV/AIDS, HIV/AIDS death, TB/HIV, TB/HIV death and LTBI/HIV.

Results: Between March 2014 and March 2016 we recruited 239 PLHIV. During the follow-up 26 patients were diagnosed and treated for TB and five received chemoprophylaxis for LTBI. During the pre-diagnosis and treatment period, the mean total costs for HIV or AIDS and AIDS death categories were US$1,558 and US$2,828, respectively. The mean total costs for TB/HIV and TB/HIV death categories were US$5,289.0 and US$8,281, respectively. The mean total cost for the LTBI/HIV category was US$882.

Conclusions: TB/HIV patients impose a higher economic burden on the health system than HIV/AIDS and LTBI/HIV. Patients with LTBI/HIV were the lowest cost group among all disease categories, indicating that preventive TB treatment can avoid the further costs treating active TB.

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Clinical trial registration number: RBR-22t943

4.2 Key messages

- TB/HIV patients can cost 3.4 more than those with HIV/AIDS alone. TB/HIV death can cost almost three times more than an AIDS death.
- Patients with LTBI/HIV had lower costs than all the other disease categories.
- Results can support policy planning and direct resource allocation for the Brazilian response to the HIV epidemic
- The study could be a reference for economic evaluation for countries with similar socio-economic and epidemiological characteristics.

4.3 Introduction

The AIDS epidemic has affected 37 million people worldwide and caused 1.1 million deaths in 2015. Among these deaths, one in three was due to HIV associated tuberculosis (TB). Additionally, one-third of people living with HIV (PLHIV) presented latent tuberculosis infection (LTBI)[30]. The lack of, or delays in, diagnosis and treatment of active TB can explain the high mortality rate among co-infected patients[4,5]. The reduction of AIDS-related deaths is a milestone established by the United Nations through Sustainable Development Goal 3 (SDG 3)[20,30] and tackling TB co-infection is a key vehicle for reducing AIDS-related deaths. The treatment of LTBI is also crucial for the reduction of TB incidence in PLHIV. Mathematical models have predicted that the scaling-up of LTBI treatment, together with the diagnosis and prompt treatment of active TB, can sharply reduce TB incidence[21,131].

However, the funding available to address AIDS/HIV and TB/HIV co-infection is insufficient and might affect the potential success of SDG 3. Recent estimates indicate that US$8.3 billion is needed annually to combat TB in low and middle-income countries. In 2015, US$6.6 billion was invested and only 6% of this fund was allocated in TB/HIV co-infection actions[2]. Therefore, costing analyses can play a key role in supporting the achievement of the SDGs in a sustainable way, especially with the reduction in the amount of funding available to combat both epidemics in recent years. In addition, the majority of high TB/HIV burden countries face both financial and human resource constraints. Thus, cost analyses are essential to inform better allocation of resources and to support economic evaluations and budget impact studies for decision making.

The objective of this study is to estimate the costs of PLHIV with or without active or latent TB, from the symptomatic phase until the first year of treatment from the perspective of the Brazilian public health system. We thus aim to contribute to the literature on costs of interventions for the control of TB and HIV/AIDS.

4.4 Methods

Study location

The study was conducted in the city of Recife, capital of the state of Pernambuco. We conducted the data collection in the Correia Picanco Hospital (CPH). The hospital provides care for approximately 60% of all individuals with HIV/AIDS in the state, carrying out almost 3,000 outpatient appointments a month, including emergency and inpatient care[132].

Study population, inclusion and exclusion criteria

The cost study was conducted alongside a pragmatic clinical trial designed to evaluate the cost-effectiveness of a protocol for TB diagnosis in PLHIV. The costing study followed the trial criteria: we included newly-diagnosed HIV infected patients, aged 18 years or over. Participants who were being treated for TB at the time of enrolment or had been treated for TB in the previous 3 months were excluded, as the trial aimed to test a protocol for diagnosis. We also excluded patients who were treated in the private sector and only visited the hospital to collect medicines. Further details of the clinical trial can be found in the Supplement.

Procedures

The cost study was conducted from the health system perspective, during the first two years of the trial (March/2014 to March/2016). We applied a mix of bottom-up and top-down approaches to capture and estimate the direct costs[51,75,133]. We obtained drug prices from the Brazilian Ministry of Health (MoH) database[134] and test costs from health system records[135]. Staff wages, hospital productivity and values of contracts and utility bills were collected from the CPH administrative division. Further details on data collection and cost estimates are given in the Supplement and Tables S1 and S2. Costs were calculated in local currency (Real, 2015 prices) and converted to US dollars using an average exchange rate for the period of study as calculated by OANDA (R$1= US$0.34765)[78].

Interviews with patients were conducted by trained technical nurses during pre-admission at CPH. The interviews were intended to collect data on the use of medical resources at emergency and outpatient care during the HIV pre-diagnosis period, from the onset of the disease until diagnosis. Interviewers also collected data on demographic, socio-economic characteristics and lifestyle habits of individuals. For those who were diagnosed with TB or LTBI during the two-year data collection period, we considered the TB/HIV pre-diagnosis period as the time between TB first symptoms and its diagnosis. As LTBI/HIV patients do not present TB symptoms, we considered pre-diagnosis the period between the first HIV symptoms and LTBI diagnosis.

Subsequent interviews were conducted at every patient appointment at CPH. Besides checking for TB or LTBI diagnosis, the interviewer also collected data on the use of medical resources at outpatient and emergency care and on hospitalisations at CPH and other health services sought by the patients during the treatment period. To assess the use of resources at inpatient

care in both the pre-diagnosis and treatment period, we reviewed patients' medical notes at CPH and other health services. Details of the drug scheme for TB and LTBI treatment can be found in the Supplement.

Data cleaning and analysis

Questionnaires were double entered in an Excel spreadsheet. The cost estimates were produced in Excel and statistical analyses in Stata/IC 14. The main outcomes were the cost per type of care (emergency, outpatient and inpatient care) and total costs (pre-diagnosis + treatment period) per patient per category of disease (HIV or AIDS, AIDS death, TB/HIV, TB/HIV death, LTBI/HIV). The mean was reported for all cost estimates as measures of central tendency, as well as the associated standard deviation (SD). To test difference in proportions, we used the Chi square test for categorical variables or Fisher's exact test when one or more cells had a frequency of five or less observations. For continuous variables with non-parametric distribution, we used the Wilcoxon-Mann-Whitney test. Differences in cost per category of patient were analysed using a Dunn's test with Benjamini-Hochberg adjustment for multiple comparisons. All *p*-values below 0.05 were considered statistically significant. We used the mean imputation approach to handle costing missing data; this assigns the mean cost of each item, at each level of care, to the missing value[136]. In order to compare our results with studies conducted in other countries, we also presented our results in International Dollars ($) applying purchase power parity (2015 prices) (Table S5 and S6)[137]. Costs of the studies presented in the discussion section were updated to 2015 using USD inflation rate, estimated by the International Monetary Fund[77] and converted to international dollars applying World Bank indices [137].

Sensitivity analysis

A one-way sensitivity analysis was performed to assess uncertainties related to the parameters used. We varied the mean costs of TB/HIV, HIV/AIDS and LTBI/HIV per type of care by ± 50%, as we did not have information regarding the highest and lowest value for each cost item. We varied the following direct medical cost parameters at emergency, outpatient and inpatient care: drugs, tests, medical appointment, bed days, ART and TB drugs. Results are presented in tornado diagrams to demonstrate the impact of each parameter change in the total cost.

Ethics

The study was approved by the Fundacao Oswaldo Cruz (No 279.324) and the London School of Hygiene and Tropical Medicine (Ref: 7371) ethics committees. All patients signed a consent form. The clinical trial was registered at Brazilian Registries for Clinical Trials (RBR-22t943). We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials.

4.5 Results

In a two-year study period, 315 PLHIV were recruited, 15 patients were excluded at the randomisation stage, 25 were transferred to another health service and 37 were considered lost to follow-up. The final sample for this study was 239 PLHIV, with 79 patients in the control arm (72 HIV or AIDS, 7 TB/HIV, none LTBI/HIV) and 160 in the intervention arm (136 HIV or AIDS, 19 TB/HIV and 5 LTBI/HIV). In total, during the follow-up period, 208 patients were treated for HIV or AIDS, 26 were diagnosed and treated for active TB/HIV co-infection and five were diagnosed and treated for LTBI/HIV (Figure S1). Tables 1, S3 and S4 show the baseline characteristics of the patients included in our analysis. In the HIV or AIDS and TB/HIV categories, most patients were male whilst most of the LTBI/HIV patients were female (P = 0·007). For all disease categories, most patients were in the 18-39 years age group and most patients were literate with a minimum of four years of study (90% of the total sample). When compared with HIV or AIDS and LTBI/HIV, patients in the TB/HIV category presented higher rates of alcohol dependence (P = 0·009) and use of illicit drugs, crack (P = 0.002) and glue (P = 0·009).

Treatment characteristics

Patients in the TB/HIV category were seen more frequently at emergency care in both pre-diagnosis and treatment period, but frequency of use only differed from that of the HIV/AIDS category in the pre-diagnosis period (p<0·001). The average length of hospitalisation during the treatment period was twice as high as that during pre-diagnosis period for both disease categories. Patients in the TB/HIV category presented lower CD4 counts (<200 cells/mm^3) at first appointment than the other categories (P = 0·009). Although the proportion of Hepatitis B and C co-infection seemed higher in TB/HIV compared to LTBI/HIV patients, the difference between the two groups was not statistically significant. LTBI/HIV and TB/HIV co-infected patients started ART later than HIV/AIDS patients (P = 0·003). Also, the proportion of deaths

was higher among TB/HIV patients than HIV/AIDS patients (31% *vs* 6%; *P* = 0·001) (Table 2).

Cost per site of care

During the pre-diagnosis period, the TB/HIV category had the highest costs at emergency, outpatient and inpatient care. The difference in the mean total costs was higher between the TB/HIV and HIV/AIDS categories: emergency care – US$419 vs US$109; outpatient care - US$269 vs US$64. There was no hospitalisation among LTBI/HIV patients during the pre-diagnosis period and the mean total cost was higher for the TB/HIV patients than the HIV/AIDS patients, US$2,532 and US$1,710, respectively.

During the treatment period, the LTBI/HIV category patients did not have emergency care and only one patient was hospitalised (US$549). At outpatient care, all patients presented similar costs, with the HIV/AIDS patients presenting a slightly higher mean total cost: HIV or AIDS – US$777; TB/HIV - US$687; LTBI/HIV – US$609. At inpatient care, the mean total cost for TB/HIV was almost double that of the HIV/AIDS patients, US$4,372 vs US$2,850 (Table 3).

Costs per patient category

The category TB/HIV death presented the highest mean costs (pre-diagnosis, treatment and total) when compared with other categories. The mean total direct cost (pre-diagnosis + treatment period) of TB/HIV death was almost three times that of the mean cost of HIV or AIDS death: US$8,281 vs US$2,828. When compared with the LTBI/HIV category, the mean direct cost of the TB/HIV category was more than five times higher; US$5,289 vs US$882 (Table 4). Statistical significance in the total costs (pre-diagnosis plus treatment period) was found for HIV or AIDS *vs* TB/HIV (p <0·0001), TB/HIV *vs* LTBI/HIV (*P* = 0·0015) and AIDS death *vs* TB/HIV death (pre-diagnosis period only) (*P* = 0.0016). Table S7 shows the complete statistical analysis for the pre-diagnosis, treatment period and total cost.

Sensitivity analysis

During the pre-diagnosis period, the cost item ‘medical appointment’ had the highest impact on the total cost for all types of care and disease categories. During the treatment period, the cost item ‘ART’ had highest impact on outpatient care for HIV or AIDS and TB/HIV categories. Medical appointment also had the highest impact on all other types of care. Tornado diagrams are presented in Figure S2.

4.6 Discussion

TB/HIV patients cost 3.4 times more than those with HIV/AIDS and those who died due to TB/HIV co-infection cost almost three times more than those who died due to AIDS. In the meantime, patients with LTBI/HIV presented the lowest cost among all disease categories, indicating the treatment of patients at the latent phase can be cheaper than the active phase. The highest cost for TB/HIV was mainly due to inpatient care. Our findings reinforce the hypothesis that TB/HIV patients have more complications during treatment and, therefore, are hospitalised more frequently and treated with more expensive drugs[138]. Indeed, in our study, the cost of drugs and tests at inpatient care was higher for TB/HIV than HIV or AIDS. Another study carried out in Sudan found greater costs of hospitalisation among TB/HIV co-infection than TB/HIV negative patients. Nevertheless, the updated costs of hospitalisation in international dollars (2015) found in the Sudanese study were lower than the costs found in our study: $2,847 vs $6,801. The mean treatment cost of TB/HIV category was also lower compared with our study: $1,568 vs $6,341[98].

Other studies carried out in low- and middle-income countries reported similar or lower costs compared with our study. In Burundi, the mean annual cost to treat HIV/AIDS patients was $3,223 vs $2,032 in Brazil[97]. In Thailand the mean costs to treat TB/HIV patients was $1,535 vs $6,341 in Brazil[93]. In China, TB was the most expensive opportunistic infection in PLHIV after Cytomegalovirus infection, $647 and $3,189, respectively[139]. In South Africa, the cost of hospitalised TB/HIV patients was $3,925. In the same study, the treatment of other common diseases in PLHIV presented higher costs, such as endocrine and metabolic disease ($5,260) and gastrointestinal disease ($4,889)[100]. Another South African study reported hospitalisation costs of TB/HIV patients varying from $2,541 to $4,885 according to type of TB, ART status and ward (adult and paediatric)[95].

In contrast to ART, the cost of TB drugs was lower at outpatient care. Furthermore, in Brazil, TB drug costs in HIV patients were lower than in other low and middle-income countries: $36 vs $50 in Burundi; $338 in China and $397 in Thailand[93,97,139]. In Sudan, the cost of TB drugs in PLHIV varied from $113 to $380 according to TB outcome and TB drug scheme[98].

The higher cost of TB/HIV can be explained by the higher proportion of patients presenting with CD4 counts below 200 cells/m^3, which indicates that co-infected patients are arriving at the health service at a more advanced stage of HIV infection for the first appointment. Another hypothesis is the delay in TB diagnosis and treatment, which can cause a deterioration in the

patient's health and, consequently, increase treatment costs. Also, analysing the lifestyle of TB/HIV patients, we perceive higher rates of lifestyle vulnerability, such as drug and alcohol dependency. All these aspects can be linked to rising costs and worse outcomes, such as higher mortality and hospitalisation rates, within TB/HIV patients. UNAIDS states that the achievement of the Fast-Track Target prevention and treatment tools could decrease the number of HIV-related deaths, including TB deaths in HIV patients, by 81% up to 2030[140].

In our study, only five out of 213 HIV/AIDS patients received IPT to prevent TB. During the study period, the hospital faced a shortfall in the provision of TST reagent and IPT was based only on the history of contact with TB patients and a medical practitioner's decision as to whether treatment was offered. Our estimates showed that the mean cost to treat LTBI/HIV was much cheaper than the treatment of TB/HIV (US$882 vs US$5,289). The treatment is strongly recommended by WHO to prevent TB in PLHIV and should be provided to those who are unlikely to have TB, regardless of TST readings[13,18]. Thus, the scaling-up of IPT for all PLHIV should be adopted to prevent deaths and save costs related to treatment of TB/HIV co-infection.

The trial design raises some limitations to our study, in spite of advantages that it also brings, such as reduction in potential bias due to the randomisation, practicality of the data collection, and collection of costing data and outcomes at patient-level[141]. In our study, the gene Xpert test, which is not routinely implemented in the hospital, was used in patients from the intervention arm. However, it was applied at outpatient care and only nine TB suspect patients were able to perform the test due to lack of sputum. Thus, this cost does not seem to influence the final cost of the disease in outpatient care. The lack of sputum for culture and gene Xpert testing might have also increased the probability of misdiagnosing MDR/TB. Although the costs of these tests do not seem to influence the final cost of the disease in outpatient care, undiagnosed MDR/TB patients can generate very higher costs for treatment, especially with more expensive drugs and at inpatient care[140,141]. Furthermore, we cannot generalise our results to countries where costs are likely to be different; thus, our results have a low external validity. The artificial environment created by a trial (patient tracing, for instance) is also another issue to be considered when extrapolating our data, although the pragmatic design is likely to reduce the limitations created by this artificial environment[141]. Another limitation relates to the price of laboratory tests collected from the Brazilian MoH database. These values represent amounts paid to providers to partially cover their laboratory costs, and do not represent the full costs of the tests. In our sensitivity analysis, these costs did not present an important impact on the cost

estimates by disease categories. The small sample size, especially for TB/HIV and LTBI/HIV patients could also be a limitation for the generalisability of our results.

Successful experience of TB/HIV control in another Latin American country, Peru, was evaluated. The Community-Based Accompaniment with Supervised Antiretroviral (CASA) was a cost-saving intervention and decreased the rate of death from 30% to 9%[105]. In Brazil, the strengthening of collaborative TB/HIV activities, early and accurate TB diagnosis, IPT and other policies addressing vulnerable populations can save further costs for the public health system and can contribute to the achievement of SDG and UNAIDS Fast-Track goals in a sustainable and consolidated way.

In conclusion, TB/HIV patients impose a higher economic burden on the public health system than HIV or AIDS and LTBI/HIV patients in all pathways of care. Further studies should address the costs of scaling-up of IPT. It is important that other studies addressing the budget impact of social protection programmes for TB/HIV patients and costs of intensive TB case finding algorithms and more accurate TB diagnosis among HIV patients are carried out in the Brazilian context.

Contributors

The study was designed by NTSF, MFPMA and ACS. NTSF was responsible for data collection, analysis and writing the manuscript. ACS, LR, RL and MFPMA reviewed the manuscript.

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Table 1. Socio-economic, demographic and life style characteristics of the study population.

Variable	Total (N=239)		HIV or AIDS (N=208)		TB/HIV (N=26)		LTBI/HIV (N=5)		*P*-value[1]
	N	%	N	%	N	%	N	%	
Socio-economic									
Gender									
Female	64	27	57	27	3	12	4	80	0·007
Male	175	73	151	73	23	88	1	20	
Age									
18-28	81	34	72	35	8	31	1	20	0·906
29-39	75	31	63	30	10	38	2	40	
40-50	60	25	53	25	6	23	1	20	
≥51	23	10	20	10	2	8	1	20	
Literate [2]									
Yes	216	90	190	91	21	81	5	100	0·212
No	23	10	18	9	6	19	0	0	
Income [3]									
No income	38	16	35	17	3	12	0	0	0·265
< Minimum wage	81	34	65	31	13	50	3	60	
≥ Minimum wage	120	50	108	52	10	38	2	40	
Life style habits									
Smoking									
Current	58	24	52	25	6	23	0	0	0·034
Never	137	57	122	59	10	38	5	100	
Former	44	18	34	16	10	38	0	0	
Alcohol [4]									
Low risk	146	61	134	64	9	35	3	60	0·009
Hazardous drinking	48	20	41	20	5	19	2	40	
Harmful drinking	18	7	14	7	4	15	0	0	
Alcohol dependence	27	11	19	9	8	31	0	0	
Illicit drug use – last year									
Cannabis									
Yes	20	8	16	8	3	11	1	20	0·458
No	217	91	190	91	23	88	4	80	
Cocaine									
Yes	10	4	6	3	3	12	1	20	0·074
No	228	95	201	97	23	88	4	80	
Glue									
Yes	2	1	0	0	2	8	0	0	0·025
No	236	99	207	99	24	92	5	100	
Crack									
Yes	8	3	4	2	4	15	0	0	0·039
No	228	95	201	97	22	85	5	100	

[1] Fisher's exact. After exclusion of LTBI/HIV patients from the analysis, only the variables smoking (P = 0·028), alcohol (P = 0·002), glue (P = 0·012) and crack (P = 0·009) remain statistically significant.

[2] Minimum of four years of study (mec.gov.br)

[3] Brazilian minimum wage, 2015 = US$ 251.7 per month

[4] As defined by the WHO: The Alcohol Use Disorders Identification Test (AUDIT), 2011

Table 2. Characteristics of treatment and health outcomes for patients treated at the Correia Picanco Hospital, Recife/Brazil.

Variables	**HIV or Aids (N =208)**		**TB/HIV (N = 26)**		**LTBI/HIV (N = 5)**		
Emergency care	**N**	**%**	**N**	**%**	**N**	**%**	**P- value**[3]
Pre-diagnosis period[1]							
Yes	86	41	21	81	-	-	<0·001
No	122	59	5	19	-	-	
Treatment period[2]	**N**	**%**	**N**	**%**	**N**	**%**	**P- value**[4]
Yes	112	59	19	73	-	-	0·060
No	96	41	7	27	-	-	
Hospitalisation	**N**	**%**	**N**	**%**	**N**	**%**	**P- value**[4]
Pre-diagnosis period							
Yes	19	8	11	42	-	-	<0·001
No	189	92	15	58	-	-	
Treatment period							**P- value**[3]
Yes	39	19	20	77	1	20	<0·001
No	169	81	6	33	4	80	
Length of hospitalisation	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-Value**[5]
Pre-diagnosis period							
Days	12.4	12.2	18.3	14.2	-	-	0·140
Treatment period							
Days	18.8	17.0	28.0	22.4	-	-	0·240
CD4 count (1st appointment)	**N**	**%**	**N**	**%**	**N**	**%**	**P-Value**[3]
>500	53	25	2	8	2	40	0·009
200-499	55	26	5	19	1	20	
<200	85	41	16	62	0	0	
Not informed	15	7	3	12	2	40	
Hepatitis B co-infection[6]							
Yes	3	2	2	8	0	0	0.165
No	181	98	22	92	3	100	
Hepatitis C co-infection[7]							
Yes	2	1	2	9	0	0	0.129
No	165	99	21	91	3	100	
First ART schemes (1st year)							
TDF+3TC+EFZ	128	61	13	50	2	40	0·010
AZT+3TC+EFZ	18	9	8	31	1	20	
Others	40	19	2	8	0	0	
Did not start ART	22	11	3	11	2	40	
Average days of ART - 1st year	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-Value**[5]
	249	87.0	181	102.8	160	56.6	0·003
Outcome	**N**	**%**	**N**	**%**	**N**	**%**	**P-Value**[3]
Cure or end of follow-up	195	94	18	69	5	100	0·001
Death	13	6	8	31	0	0	

[1] Pre-diagnosis period: on-set of TB or HIV symptoms until TB, LTBI or HIV/AIDS diagnosis
[2] Treatment period: one year of treatment or death before one year for HIV or AIDS, complete TB (six to nine months) or LTBI (six months) treatment or death before end of treatment
[3] Fisher's exact
[4] Chi square
[5] Two-sample Wilcoxon rank-sum (Mann-Whitney) test
[6] Eighteen HIV/AIDS patients had an inconclusive result and six did not perform the test; two TB/HIV patients had an inconclusive result and one LTBI/HIV patient had an inconclusive result and one did not perform the test
[7] Twenty-eight HIV/AIDS patients had an inconclusive result and thirteen did not perform the test; three TB/HIV patients had an inconclusive result and one LTBI/HIV patient had an inconclusive result and one did not perform the test.

Table 3. Mean direct medical costs (US$) per cost category for pre-diagnosis and treatment from the public health system perspective, Correia Picanco Hospital, Recife/Brazil.

Cost item	*HIV or AIDS*				*TB/HIV*				LTBI/HIV			
	N	Pre-diagnosis Mean (SD)	N	Treatment Mean (SD)	N	Pre-diagnosis Mean (SD)	N	Treatment Mean (SD)	N	Pre-diagnosis Mean (SD)	N	Treatment Mean (SD)
Emergency care	*86*		*112*		*21*		*19*					
Drugs		1.2 (4.0)		2.0 (4.3)		45.3 (193.1)		78.9 (234.8)		-		-
Tests		5.7 (15.0)		8.2 (14.1)		22.4 (30.1)		8.2 (11.6)		-		-
Medical appointment		87.6 (47.5)		110.4 (89.8)		299.6 (355.8)		489.9 (1,114.7)		-		-
Total direct medical		*94·5 (53.3)*		*120·6 (95.0)*		*367.4 (540·6)*		*574.1 (1,334.0)*		-		-
Overhead		15.0 (8.2)		18.8 (15.4)		51.4 (59.6)		83.4 (185.8)		-		-
Total direct medical and non-medical		*109.5 (61.2)*		*139.4 (109.8)*		*418.8 (586.9)*		*657.4 (1,439.9)*		-		-
Outpatient care	*150*				*26*		26		*5*		*5*	
Drugs		0.1 (0.5)		15.4 (52.8)		1.7 (3.1)		45.3 (50.3)		2.3 (4.8)		7.9 (5.0)
ART		-		467.7 (276.4)		70.9 (142.0)		261.6 (205.4)		7.4 (16.5)		140.9 (185.5)
TB drugs		-		-		-		23.0 (17.0)		-		4.9 (0.0)
Tests		7.8 (12.3)		61.9 (38.2)		65.0 (83.7)		45.2 (53.8)		65.5 (23.6)		65.7 (56·3)
Medical appointment		47.0 (32.8)		195.1 (119.1)		110.8 (71.3)		262.7 (155.0)		73.7 (55.0)		328.1 (207.0)
Total direct medical		*54·8 (38.8)*		*740.2 (357.5)*		*248.5 (218.4)*		*637.9 (389.0)*		*148.8 (48.2)*		*547.5 (394.0)*
Overhead		8.8 (6.2)		36.7 (22.4)		20.8 (13.2)		49.4 (28.6)		*13.9 (9.3)*		61.7 (34.8)
Total direct medical and non-medical		*63.7 (44.7)*		*776.9 (369.9)*		*269.3 (220.4)*		*687.3 (406.3)*		*162.7 (49.9)*		*609.3 (383.4)*
Inpatient care	*19*		38		*11*		20		*0*		*1*	
Drugs		111.4 (161.6)		407.9 (549.2)		172.0 (172.5)		754.7 (874.7)		-		15.3
ART		-		18.6 (37.9)		12.7 (23.7)		29.1 (36.9)		-		0.0
TB drugs		-		-		-		3.9 (4.1)		-		0.0
Tests		119.7 (109.9)		177.0 (184.9)		170.3 (165.1)		237.7 (201.7)		-		175.6
Bed day		479.9 (446.9)		733.2 (617.2)		706.5 (576.1)		1,092.4 (990·8)		-		117.0
Total direct medical		*710·9 (633.4)*		*1,336.8 (1,265·3)*		*1,061.5 (870.1)*		*2,117.7 (1,795·1)*		-		*307.9*
Overhead		999.1 (930.0)		1,513.0 (1,367.0)		1,471.0 (1,143.7)		2,254.0 (1,926.6)		-		241.5
Total direct medical and non-medical		*1,710.1 (1,547.2)*		*2,849.8 (2,562.6)*		*2,532.5 (1,971.3)*		*4,371.7 (3,652.7)*		-		*549.5*

Table 4. Total mean cost (US$) for pre-diagnosis and treatment periods from the health system perspective, Correia Picanco Hospital, Recife/Brazil.

Status	N	Pre-diagnosis	Treatment	Total
		Mean (SD)	Mean (SD)	Mean (SD)
HIV or AIDS				
Drugs		11.3 (60.3)	76.3 (277.3)	87.6 (286.0)
Tests		19.3 (50.6)	91.9 (104.4)	11.3 (118.1)
ART		-	492.0 (266.7)	492.0 (266.7)
Medical appointment/bed	195	114.4 (200.7)	373.5 (422.1)	487.9 (471.1)
day		107.3 (413.3)	273.3 (800.8)	379.5 (899.4)
Overhead		252.4 (697.3)	1,306.0 (1,549·5)	1,558.4 (1,713.7)
Total				
AIDS death				
Drugs		1.5 (3.5)	344.2 (339.4)	345.8 (340.2)
Tests		12.8 (33.4)	215.2 (133.1)	228.0 (143.7)
ART		-	159.3 (236.7)	159.3 (236.7)
Medical appointment/bed	13	106.6 (106.9)	730.4 (465.9)	837.0 (526.3)
day		52.8 (125.4)	1,205.5 (857.7)	1,258.3 (963.1)
Overhead		173.8 (231.0)	2,654.7(1,648.6)	2,828.4 (1,833.9)
Total				
TB/HIV				
Drugs		84.0 (238.2)	478.8 (625.5)	562.8 (834.2)
Tests		131.7 (137.9)	209.7 (182.8)	341.4 (243.0)
ART		81.3 (163.0)	354.7 (171.5)	436.0 (209.8)
TB drugs	18	-	33.0 (12.7)	33.0 (12.7)
Medical appointment/bed		531.6 (488.2)	1,478.0 (1,398.2)	2,009.6 (1,767.9)
day		384.6 (555.4)	1,521.7 (1,733.5)	1,906.3 (1,864.0)
Overhead		1,213·2 (1,189.0)	4,075·8 (3,558.2)	5,289·0 (4,190.2)
Total				
TB/HIV death				
Drugs		172.1 (202.9)	1,442.2 (1,123.3)	1,316.4 (1,049.5)
Tests		208.1 (183.5)	289.0 (244.0)	497.1 (203.7)
ART		65.1 (61.4)	125.1 (177.4)	190.2 (205.6)
TB drugs	8	-	10.1 (11.8)	10.1 (11.8)
Medical appointment/bed		921.7 (727.0)	1,415.8 (1,144.0)	2,337.5 (821.7)
day		1,359.9 (1,466.7)	2,569.9 (2,297.2)	3,929.8 (1,693.8)
Overhead		2,727.0 (2,523.8)	5,554.1 (4,591.2)	8,281.0 (3,466.9)
Total				
LTBI/HIV				
Drugs		2.3 (4.3)	10.9 (10.5)	13.2 (10.1)
Tests		65.5 (21.1)	100.8 (117.2)	166.4 (108.7)
ART		7.4 (14.8)	140.9 (165.9)	148.3 (168.5)
TB drugs	5	-	4.9 (-)	4.9 (-)
Medical appointment/bed		73.7 (49.2)	351.6 (207.5)	425.2 (233.3)
day		13.9 (9.3)	110.0 (114.5)	123.9 (122.7)
Overhead		162.7 (49.9)	719.2 (565.7)	881.9 (613.1)
Total				

4.7 Supplementary file

Pragmatic clinical trial

The cost study was conducted alongside a three-years pragmatic clinical trial with individual randomisation led by epidemiologists from the Oswald Cruz Foundation (FIOCRUZ) and the London School of Hygiene and Tropical Medicine. The trial started in March 2014 and patients were recruited until October/2016. The trial was designed to evaluate the effectiveness, cost and cost-effectiveness of a new protocol for TB diagnosis in HIV patients. The clinical trial was registered at Brazilian Registries for Clinical Trials (RBR-22t943). The two arms trial compares the hospital routine for TB diagnosis which follows the Brazilian Ministry of Health (MoH) protocol and advocates TB diagnosis through sputum smear microscopy (SSM), chest X-ray (CXR) and sputum culture (SC), with a new protocol comprising a screening by clinical algorithm in every appointment to examine the presence of cough, weight loss, fever and night sweets plus confirmatory tests (SSM, SC, CXR, gene Xpert MTB/RIF and liquor aspiration for extra pulmonary TB) in those patients with any one of the symptoms.

The sample size for the epidemiological study was calculated based on the estimated proportion of deaths between the exposed (new protocol) and unexposed group (hospital routine). Using an annual mortality rate of 20% [23], study power of 80% and an alpha error of 5%, a sample size of 483 patients was estimated for the whole trial, including 20% losses in the follow up. Figure S1 shows the flow chart of the study population.

Country Background

Brazil is an upper middle-income country and accounts for 36% of the Latin American population. In 2015, there were 830,000 PLHIV and 15,000 HIV/AIDS-related deaths. The country is classified as a high burden country for HIV/AIDS and TB/HIV co-infection [38,39,142]. Both antiretroviral therapy (ART) and TB treatment are offered free of charge through the Brazilian Unified Health System (SUS). However, the coverage of ART in TB patients was below 50% in 2015[142]. Brazil was the first developing country to adopt the Treatment as Prevention strategy, whereby all PLHIV start ART regardless the CD4 count. Currently, ART covers 64% of all diagnosed PLHIV. The country is a leader in the manufacturing of antiretroviral (ARV), but prices are still high for the second and third lines of ART[38,39]. Brazil, as well as other low- and middle-income countries, faces limited resources and challenges for a timely delivery of treatment following diagnosis of HIV/AIDS and/or co-infection TB/HIV.

TB and LTBI treatment

IPT (6 months of isoniazid, 100mg) was provided for LTBI/HIV patients when the tuberculin skin test (TST) was higher than 5 mm or for those who had contact with TB patients. However, some doctors decided not to offer IPT for HIV/AIDS patients meeting the LTBI treatment criteria and those patients continued the treatment only for HIV/AIDS. Patients diagnosed with TB performed treatment with two months of rifampicin (150 mg) + isoniazid (75 mg) + pyrazinamide (400 mg) + ethambutol (275 mg) *plus* four to seven months of rifampicin (150 mg) + isoniazid (75 mg). TB treatment was self-administered and patients collected the drugs monthly at CPH pharmacy to proceed with the treatment at home.

Procedures for the economic/epidemiological study

After admission to the CPH with known HIV positive status, patients had a first appointment with a nurse when initial tests were required (CD4 count, viral load, hepatitis and blood tests). Patients were then approached and received an explanation about the purpose of the study and those who agreed to take part in it signed an informed consent form. Randomisation was performed after the first interview with a nurse, who was also responsible for the allocation of patients to specific study's arms.

We followed up the entire patients' pathway of care (emergency, outpatient and inpatient care), from the pre-diagnosis to treatment period. Pre-diagnosis was the period between the onset of HIV or TB symptoms until HIV or TB diagnosis. Treatment period for HIV/AIDS patients was the period from the beginning of treatment with prophylactic drugs and/or ART until one year after starting this treatment or death before or at one year of follow-up. For those patients who were diagnosed with TB or performed isoniazid preventive treatment (IPT) during the study period, treatment period was the time from the beginning of TB or TBL treatment until cure, death or treatment abandonment. We considered as loss of follow-up those patients who did not attend outpatient appointments at CPH for six months after starting the treatment.

To estimate the cost of medical staff we first calculated the gross annual wage of all medical staff by type of care (inpatient, outpatient and emergency care). For those medical staff working on two types of care (i.e. inpatient and outpatient), we split the annual wage equally. After that, we calculate the costs per type of care:

- Outpatient care: covers solely HIV/AIDS patients. We divided the annual medical staff wages by the annual number of appointments to obtain the cost of medical staff per appointment.
- Emergency care: comprises two sub-wards - urgency (rapid appointment) and bed day (patients can stay up to 24 h). The urgency ward covers HIV/AIDS and meningitis patients, sexual exposure and occupational accident care, whilst the bed day sector covers solely HIV/AIDS patients. To calculate the percentage of appointments dedicated for HIV/AIDS patients in the urgency ward, we applied weights for each type of patient according to the staff time dedicated for them as follow: HIV/AIDS urgency = 1.5; HIV/AIDS bed day = 3; meningitis = 2; occupational accident = 0.5; sexual exposure = 0.5. The information regarding time dedicated for each type of patient was collected through medical interview. We then multiplied the annual wages of emergency medical staff by the percentage of HIV/AIDS appointments and divided the result by the adjusted annual number of HIV/AIDS appointment to obtain the costs of medical staff per appointment.
- Inpatient care: we first calculated the average annual occupancy rate of the hospitals' bed to obtain the annual bed day. We then divided the annual staff wages by the annual bed day to obtain the cost per bed day.

We also included overheads costs: collection of hospital waste, water, electricity, administrative, cleaning and security personnel, laundry. We allocated the total amount paid by the hospital according to the building space of each type of care, then the value was divided by the number of appointments or bed day to obtain overhead cost per patient.

Table S1. Cost calculations

Item	Method	Formulae	Source
Drugs, tests	Ingredient approach	Quantity of medical resource x price of medical resource	Medical record and patient interview, Department of Sexually Transmitted Diseases, AIDS and Viral Hepatitis, Banco de Precos em saude and Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS
Medical staff	Allocation rule by type of care	Emergency: % annual wages allocated for HIV/AIDS patients [1]/ adjusted number of HIV/AIDS appointments = US$ 69.9/appointment	Medical interview and CPH administrative division
		Outpatient: Annual wages/annual number of appointments = US$ 33.5/appointment	
		Inpatient: Annual wages * % bed for HIV patients[2] / (annual bed day[3] * average annual occupancy rate[4]) = US$ 38.7/bed day	
Overhead	Allocation rule by meter square	Emergency Area: 338.16 m^2 Emergency: Total US$ overhead * 6% /total number of appointments a year = US$ 12.0	CPH administrative division
		Ambulatory Area: 378.98 m^2 Outpatient: Total US$ overhead * 7% / total number of appointments a year = US$ 6.3	
		Hospital Area: 4,727.08 m^2 Inpatient: Total US$ overhead * 87% / annual bed day = US$ 80.5	

[1] Percentage of annual wages allocated for HIV/AIDS patients = 63%
[2] Percentage of beds for HIV patients = 71%
[3] Annual bed days = 11,195· 28 (total beds (36) * 365 days * occupancy rate (85%))
[4] Average annual occupancy rate of HIV beds = 85%

Table S2. Unit and treatment costs (US$) of the main components of the medical resource

Drugs	Unit cost (US$)	Treatment cost (US$)
TB LTBI drugs		
Rifampicin (150 mg) + isoniazid (75 mg) + pyrazinamide (400 mg) + ethambutol (275 mg), four in one	0.05	2 months treatment with 4 daily tablets: US$ 12
Rifampicin (150 mg) + isoniazid (75 mg), two in one	0.03	Average 7 months treatment with 4 daily tablets: US$ 25.2
Total cost TB treatment[1]		US$: 37.2
Isoniazid (75 mg), tablet	0.009	6 months treatment with 3 daily tablets: US$ 4.86
Antiretroviral (ARV) drugs		
AZT (300 mg) + 3TC (150 mg) two in one	0.4	Monthly cost, 1 daily tablet: US$ 12.0
EFZ (600 mg)	0.5	Monthly cost, 1 daily tablet: US$ 14.1
3TC (150 mg)	0.2	Monthly cost, 1 daily tablet: US$ 5.7
TDF (300 mg)	1.3	Monthly cost, 1 daily tablet: US$ 37.8
TDF (300 mg) + 3TC (150 mg) + EFZ (600 mg) three in one	1.7	Monthly cost, 1 daily tablet: US$ 51.4
Monthly cost (AZT+3TC) + EFZ		1 daily tablet of each ARV: US$ 24.1
Monthly cost TDF +3TC + EFZ		1 daily tablet of each ARV: US$ 57.6
Tests[2]		Unit cost (US$)
Gene Xpert		54.9
Culture		2.0
Sputum smear microscopy		1.5
Chest X-ray		3.3
CD4 count		5.2
Viral load		0.7
Other drugs		Range of unit cost (US$)[3]
Analgesics (e.g. dipyrone, paracetamol)		0.02 – 0.2
Opioid analgesic (e.g. morphine, tramadol)		0.05 – 10.7
Anaesthetic (e.g. Propofol, lidocaine)		0.4 – 9.4
Antiallergic/antihistamine (e.g. Dexchlorpheniramine, loratadine)		0.01 – 4.0
Antacid (e.g. omeprazole, ranitidine)		0.02 – 1.3
Antibiotic (e.g. gentamicin, amoxicillin, sulfamethoxazole + trimethoprim)		0.02 – 89.3
Anticoagulant (e.g. heparin, enoxaparin)		0.04 – 9.2
Psychotropic (e.g. fluoxetine, amitriptyline)		0.01 – 1.2
Antiviral (e.g. acyclovir, ganciclovir)		0.03 – 21.8
Corticoid (e.g. hydrocortisone, prednisone)		0.02 – 5.0
Anti-inflammatory (e.g. diclofenac, tenoxicam)		0.01 – 1.4
Antifungal (e.g. amphotericin, ketoconazole)		0.04 – 379.0
Anti-emetic (e.g. bromopride, ondansetron)		0.02 – 2.1
Antiparasitic (e.g. albendazole, ivermectin)		0.1 – 1.0
Sedative (e.g. dexmedetomidine hydrochloride, midazolam)		4.2 – 45.9
Antiepileptic/anticonvulsant (e.g. carbamazepine, phenytoin)		0.02 – 2.1
Anti-hypertensive (e.g. captopril, hydrochlorothiazide)		0.01 – 1.2
Vitamin (e.g. ascorbic acid)		0.08 – 0.8
Antispasmodic/anti gases (e.g. hyoscine butylbromide, simethicone)		0.02 – 0.9
Saline solution (e.g. sodium chloride, saline)		0.5 – 6.5
Diuretic (e.g. furosemide, spironolactone)		0.01 – 0.3
Others (drugs to treat leukopenia, bronchodilator, antidiarrheal)		0.01 – 44.5
Other tests[2]		
Biochemistry (e.g. polymerase chain reaction, cholesterol, bilirubin)		0.5 – 34.8
Haematology (e.g. coagulation, hemogram)		0.5 – 5.2
Image examination (e.g. ultrasound, magnetic resonance imaging)		1.3 – 142.0
Immunology (e.g. hepatitis, herpes)		0.3 – 32.0
Microbiology (e.g. anaerobic and bacteria culture)		1.0 – 12.5
Parasitological (e.g. parasitological stool)		2.1 – 5.3
Medical procedures (e.g. haemodialysis, blood transfusion)		2.8 – 92.3
Others (e.g. invasive examinations, neoplasia)		1.2 – 41.1

[1] TB treatment costs can vary according to the number of months in treatment and numbers of daily tablets
[2] Values paid by the Brazilian Ministry of Health
[3] Unit costs vary according to the active ingredient, pharmaceutical form (tablet, capsule, ampule, drop) and dosage.

Table S3. Socio-economic, demographic and life style characteristics of the include and excluded study population, Correia Picanco Hospital, Recife/Brazil.

Variable	Total (N=315)		Included (N=239)		Excluded (N=76)		*P*- value
	N	%	N	%	N	%	
Socio-economic							
Gender							
Female	84	27	64	27	20	26	0·937[1]
Male	231	73	175	73	56	74	
Age							
18-28	107	34	81	34	26	34	0·556[2]
29-39	104	33	75	31	29	38	
40-50	77	24	60	25	17	22	
≥51	27	9	23	10	4	5	
Literate							
Yes	278	88	216	90	62	82	0·038[1]
No	37	12	23	10	14	18	
Income							
No income	53	17	38	16	15	20	0·692[1]
< Minimum wage	104	33	81	34	23	30	
≥ Minimum wage	158	50	120	20	38	50	
Life style habits							
Smoking							
Current	88	28	58	24	30	39	0·020[1]
Never	168	53	137	57	31	41	
Former	59	19	44	18	15	20	
Alcohol[3]							
Low risk	193	61	146	61	47	62	0·446[2]
Hazardous drink	60	19	48	20	12	16	
Harmful	23	7	18	6	5	7	
Alcohol dependence	38	12	27	11	11	14	
Missing	1	0	0	0	1	1	
Illicit drug use – last year							
Cannabis							
Yes	34	11	20	8	14	18	0·033[2]
No	278	88	217	91	61	80	
Missing	3	1	2	1	1	1	
Cocaine							
Yes	15	5	10	5	5	7	0·522[2]
No	299	95	228	95	71	93	
Missing	1	0	1	0	0	0	
Glue							
Yes	4	1	2	1	2	3	0·429[2]
No	310	98	236	99	74	97	
Missing	1	0	1	0	0	0	
Crack							
Yes	14	4	8	3	6	8	0·208[2]
No	298	95	228	95	70	92	
Missing	3	1	3	1	0	0	

[1] Chi-square
[2] Fisher's exact
[3] WHO AUDIT, 2011

Table S4. Socio-economic, demographic and life style characteristics of the HIV or AIDS and TB/HIV study population, Correia Picanco Hospital, Recife/Brazil.

Variable	Total (N=234)		HIV or AIDS (N=208)		TB/HIV (N=26)		*P*- value[1]
	N	%	N	%	N	%	
Socio-economic							
Gender							
Female	60	26	57	27	3	12	0·097
Male	174	74	151	73	23	88	
Age							
18-28	80	34	72	35	8	31	0·899
29-39	73	31	63	30	10	38	
40-50	59	25	53	25	6	23	
≥51	22	10	20	10	2	8	
Literate							
Yes	211	90	190	91	21	81	0·093
No	23	10	18	9	6	19	
Income							
No income	38	16	35	17	3	12	0·189
< Minimum wage	78	34	65	31	13	50	
≥ Minimum wage	118	50	108	52	10	38	
Life style habits							
Smoking							
Current	58	25	52	25	6	23	0·028
Never	132	56	122	59	10	38	
Former	44	19	34	16	10	38	
Alcohol[2]							
Low risk	143	61	134	64	9	35	0·002
Hazardous drink	46	20	41	20	5	19	
Harmful	18	7	14	7	4	15	
Alcohol dependence	27	11	19	9	8	31	
Illicit drug use – last year							
Cannabis							
Yes	19	8	16	8	3	11	0·570
No	213	91	190	91	23	88	
Missing	3	1	2	1	0	0	
Cocaine							
Yes	9	4	6	3	3	11	0·170
No	224	95	201	97	23	88	
Missing	1	1	1		0	0	
Glue							
Yes	2	1	0	0	2	8	0·012
No	231	99	207	99	24	92	
Missing	1		1	0	0	0	
Crack							
Yes	8	3	4	2	4	15	0·009
No	223	95	201	97	22	85	
Missing	3	1	3	1	0	0	

[1] Fisher's exact
[2] WHO AUDIT, 2011

Table S5. Mean direct medical costs ($) per cost category for pre-diagnosis and treatment from the public health system perspective, Correia Picanco Hospital, Recife/Brazil.

Cost item	*HIV or AIDS*				*TB/HIV*				LTBI/HIV			
	N	Pre-diagnosis Median (IQR)	N	Treatment Median (IQR)	N	Pre-diagnosis Median (IQR)	N	Treatment Median (IQR)	N	Pre-diagnosis Median (IQR)	N	Treatment Median (IQR)
Emergency care	86		112		21		19		0		0	
Drugs		1.9		3.1		70.5		122.7		-		-
Tests		8.9		12.8		34.8		12.8		-		-
Medical appointment		136.3		171.7		466.1		762.1		-		-
Total direct medical		147.0		187.6		571.6		893.1		-		-
Overhead		23.3		29.2		80.0		129.7		-		-
Total direct medical and non-medical		170.3		216.9		651.5		1,022.7		-		-
Outpatient care	150				26		26		5		5	
Drugs		0.2		24.0		2.6		70.5		3.6		12.3
ART				727.6		110.3		407.0		11.5		219.2
TB drugs								35.8				7.6
Tests		12.1		96.3		101.1		70.3		101.9		102.2
Medical appointment		73.1		303.5		172.4		408.7		114.7		510.4
Total direct medical		85.3		1,151.5		386.6		992.4		231.5		851.7
Overhead		13.7		57.1		32.4		76.9		21.6		96.0
Total direct medical and non-medical		99.1		1,208.6		418.9		1,069.2		253.1		947.9
Inpatient care	19		38		11		20		0		1	
Drugs		173.3		634.6		267.6		1,174.1		-		23.8
ART		-		28.9		19.8		45.3		-		-
TB drugs		-		-		-		6.1		-		-
Tests		186.2		-		-		369.8		-		273.2
Bed day		746.6		1,140.6		1,099.1		1,699.4		-		182.0
Total direct medical		1,105.9		2,079.6		1,651.4		3,294.5		-		479.0
Overhead		1,554.3		2,353.7		2,288.4		3,506.5		-		375.7
Total direct medical and non-medical		2,660.4		4,433.4		3,939.8		6,801.0		-		854.8

Table S6. Total mean cost ($) for pre-diagnosis and treatment periods from the health system perspective, Correia Picanco Hospital, Recife/Brazil.

Status	N	Pre-diagnosis	Treatment	Total
		Mean (SD)	Mean (SD)	Mean (SD)
HIV or AIDS				
Drugs	195	17.6	118.7	136.3
Tests		30.0	143.0	17.6
ART		-	765.4	765.4
Medical appointment/bed day		178.0	581.0	759.0
Overhead		166.9	425.2	590.4
Total		392.7	2,031.7	2,424.4
AIDS death				
Drugs	13	2.3	535.5	538.0
Tests		19.9	334.8	354.7
ART		-	247.8	247.8
Medical appointment/bed day		165.8	1,136.3	1,302.1
Overhead		82.1	1,875.4	1,957.5
Total		270.4	4,129.9	4,400.1
TB/HIV				
Drugs	18	130.7	744.9	875.5
Tests		204.9	326.2	531.1
ART		126.5	551.8	678.3
TB drugs		-	51.3	51.3
Medical appointment/bed day		827.0	2,299.3	3,126.3
Overhead		598.3	2,367.3	2,965.6
Total		1,887.4	6,340.6	8,228.0
TB/HIV death				
Drugs	8	267.7	2,243.6	2,047.9
Tests		323.7	449.6	773.3
ART		101.3	194.6	295.9
TB drugs		-	15.7	15.7
Medical appointment/bed day		1,433.9	2,202.5	3,636.4
Overhead		2,115.6	3,997.9	6,113.5
Total		4,242.3	8,640.4	12,882.6
LTB/HIV				
Drugs	5	3.6	17.0	20.5
Tests		101.9	156.8	258.9
ART		11.5	219.2	230.7
TB drugs		-	7.6	7.6
Medical appointment/bed day		114.7	547.0	661.5
Overhead		21.6	171.1	192.7
Total		253.1	1,118.8	1,372.0

Table S7. Result of Dunn's test for pot-estimation analysis with Benjamini-Hochberg adjustment.

Pre-diagnosis

	HIV or AIDS	AIDS Death	TB/HIV	TB/HIV Death
AIDS Death	0·83			
TB/HIV	<0·0001	<0·0001		
TB/HIV Death	<0·0001	0·0016	0·43	
LTBI/HIV	0·17	0·32	0·32	0·26

Treatment

	HIV or AIDS	AIDS Death	TB/HIV	TB/HIV Death
AIDS Death	0·005			
TB/HIV	0·0001	1.00		
TB/HIV Death	0·03	0·49	0·76	
LTBI/HIV	0·37	0·01	0·005	0·02

Total

	HIV or AIDS	AIDS Death	TB/HIV	TB/HIV Death
AIDS Death	0·01			
TB/HIV	<0·0001	0·35		
TB/HIV Death	<0·0001	0·13	0·18	
LTBI/HIV	0·26	0·02	0·0015	0·0006

Figure S1. Flow chart of the study population.

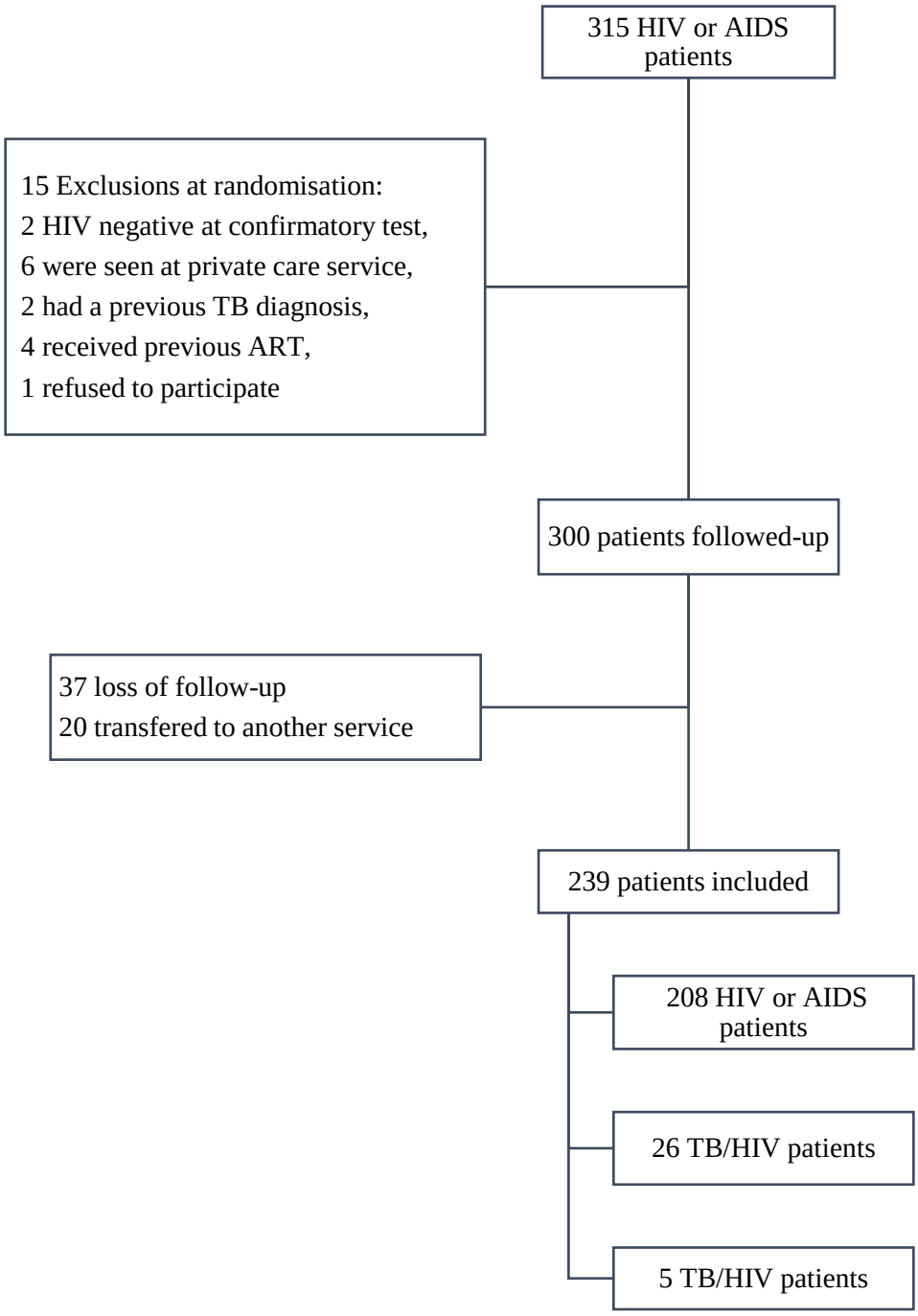
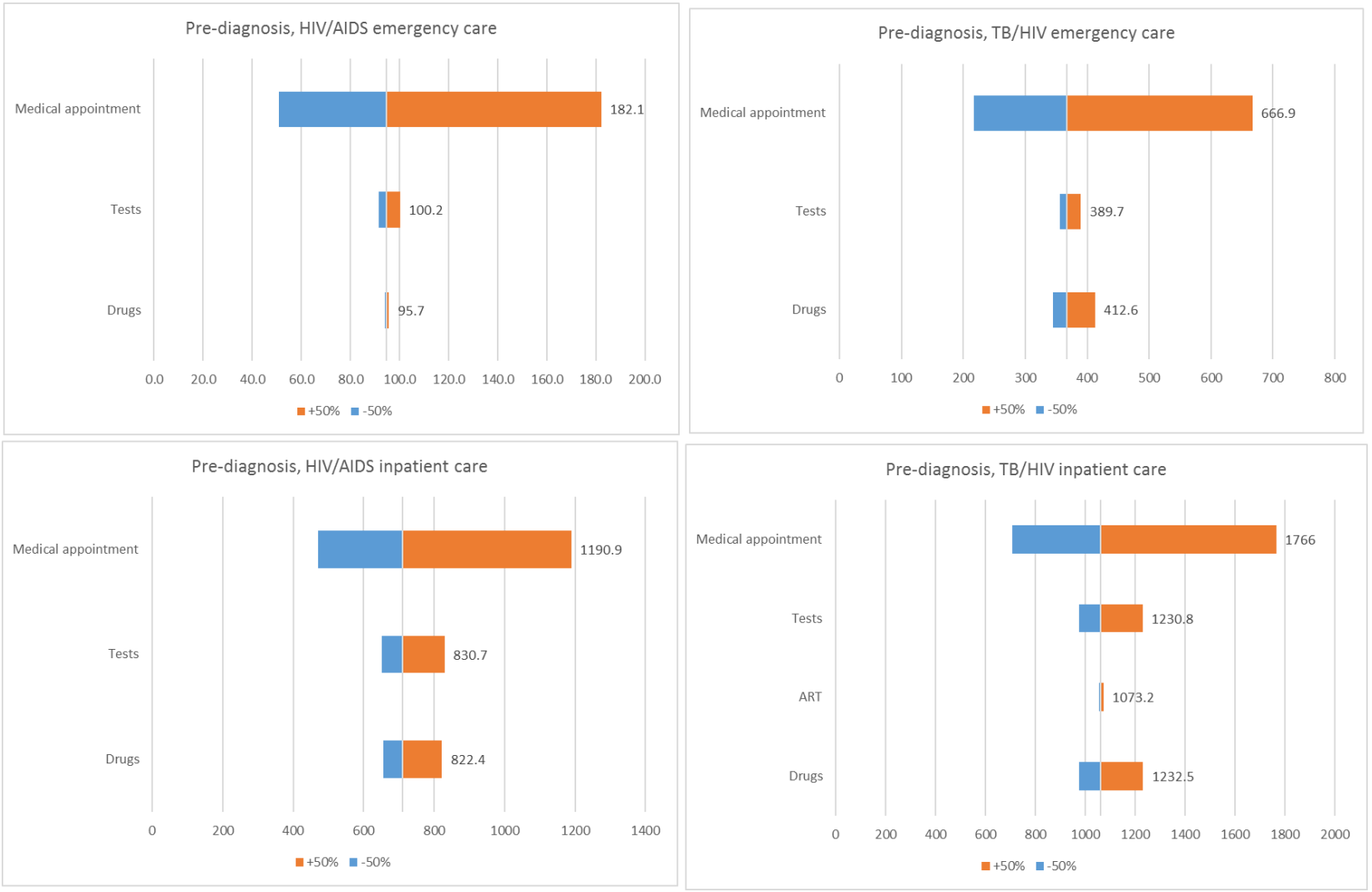
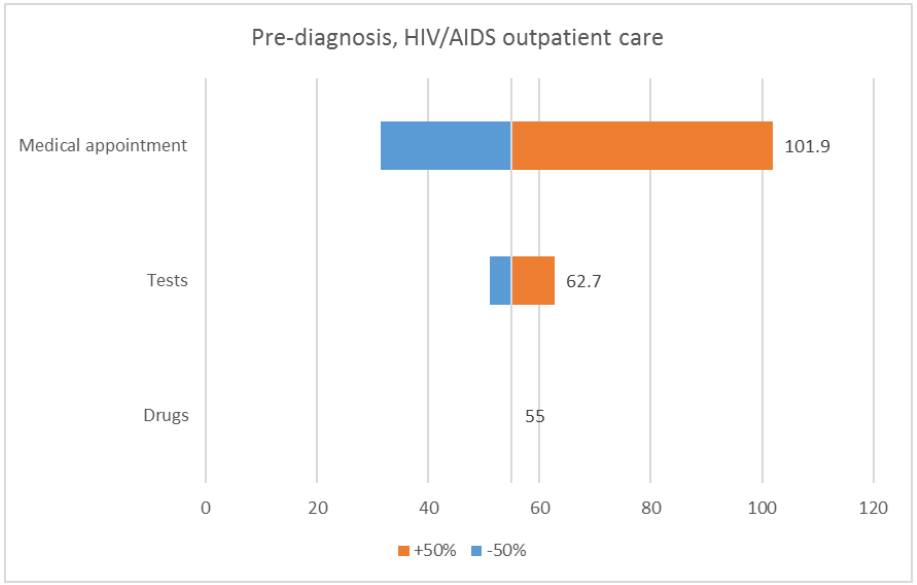
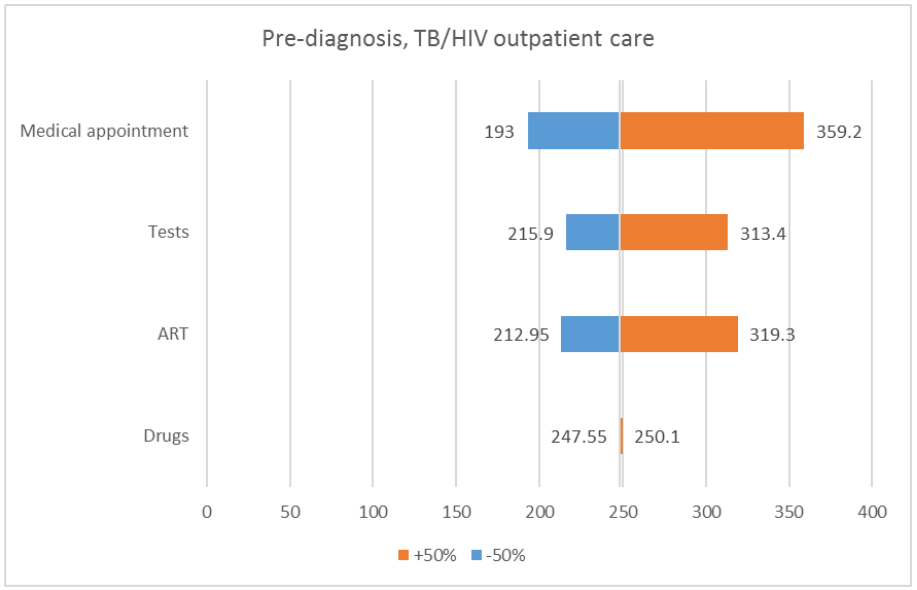
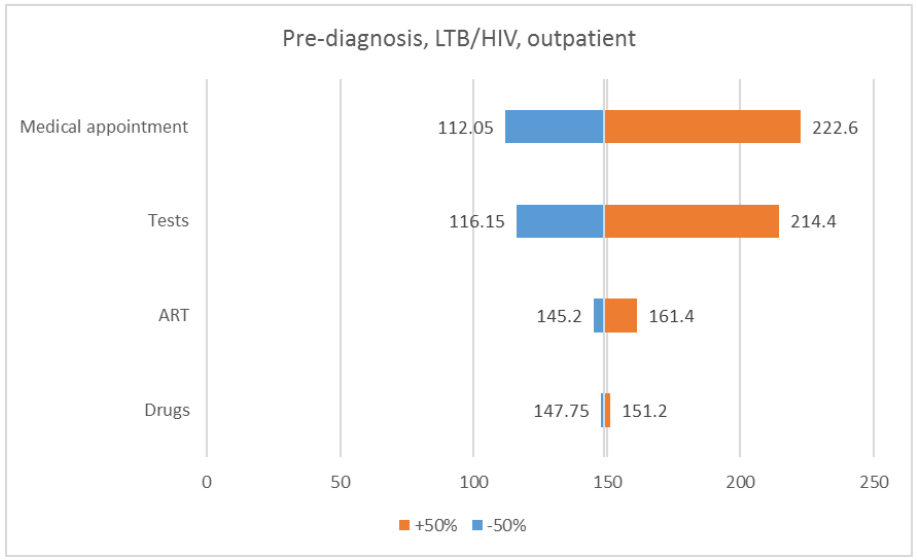


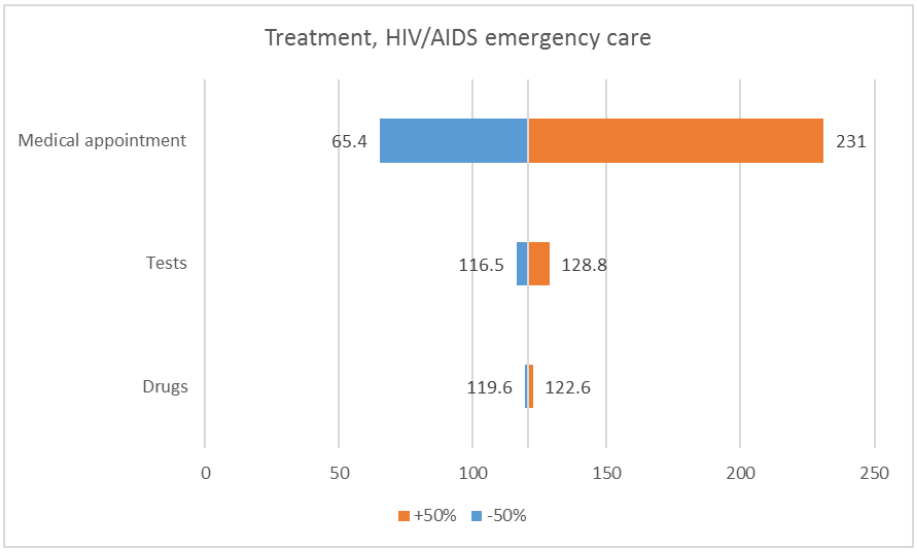
Figure S2. Sensitivity analysis: Tornado diagrams.




Pre-diagnosis, HIV/AIDS outpatient care
Medical appointment
Tests
Drugs
101.9
62.7
55
0
20
40
60
80
100
120
+50%
-50%


Pre-diagnosis, TB/HIV outpatient care
Medical appointment
Tests
ART
Drugs
193
359.2
215.9
313.4
212.95
319.3
247.55
250.1
0
50
100
150
200
250
300
350
400
+50%
-50%


Pre-diagnosis, LTB/HIV, outpatient
Medical appointment
Tests
ART
Drugs
112.05
222.6
116.15
214.4
145.2
161.4
147.75
151.2
0
50
100
150
200
250
+50%
-50%


Treatment, HIV/AIDS emergency care
Medical appointment
Tests
Drugs
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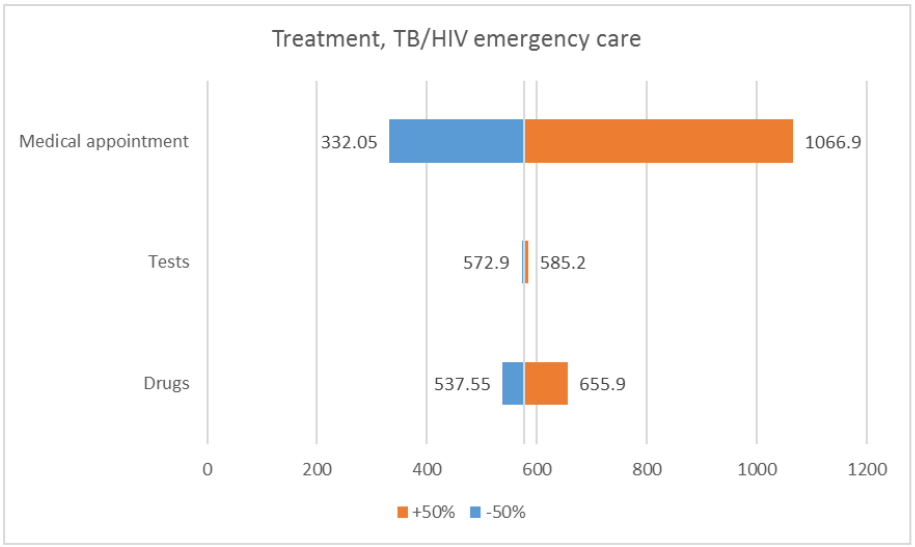
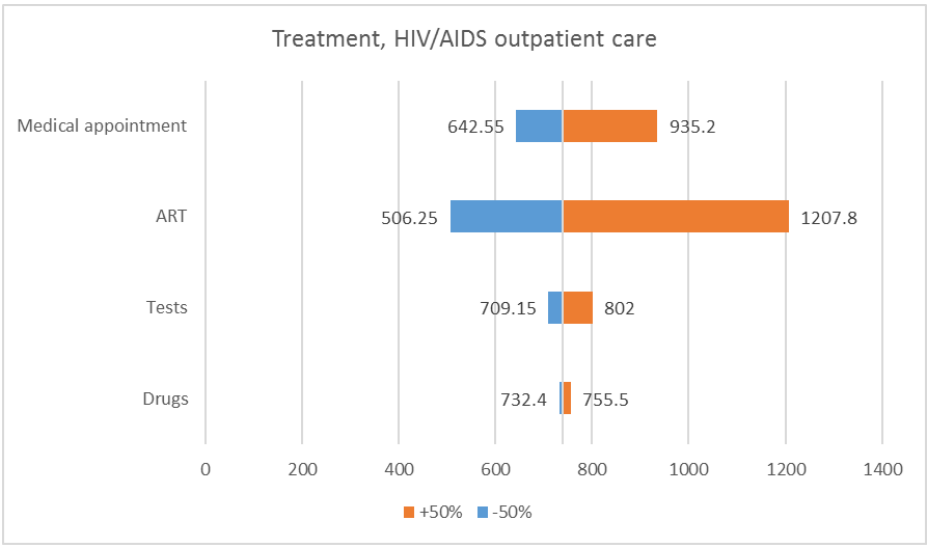
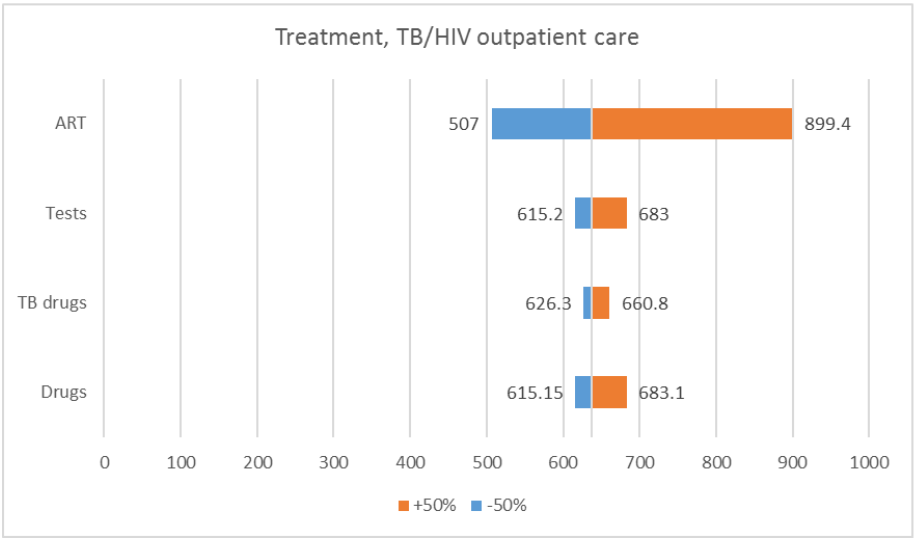
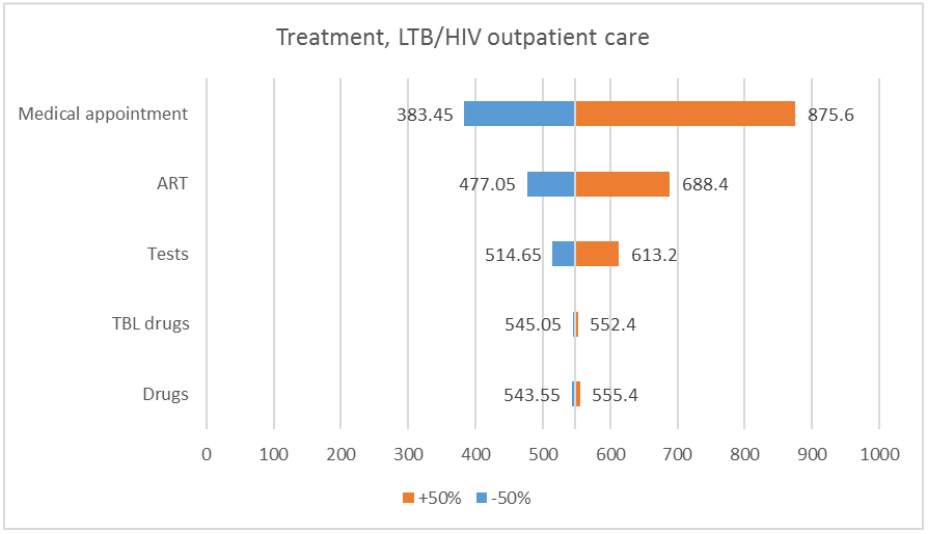
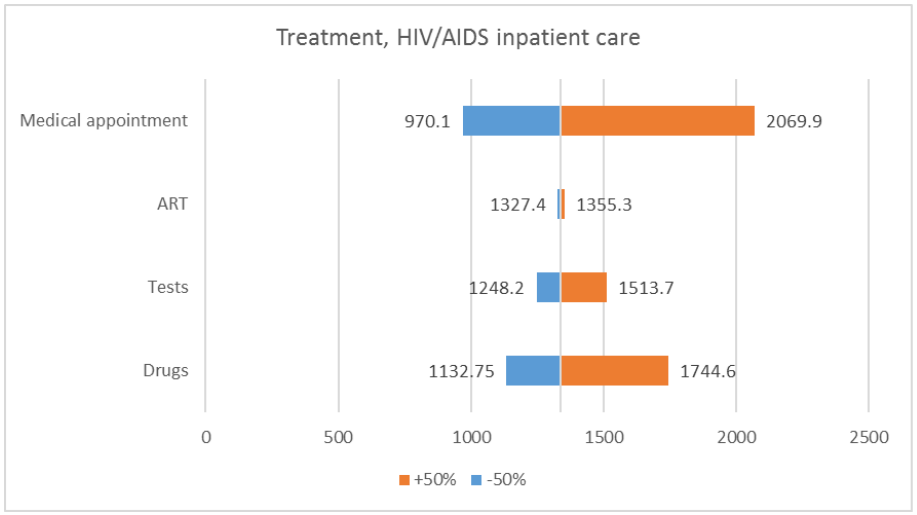
116.5
128.8
119.6
122.6
0
50
100
150
200
250
+50%
-50%


Treatment, TB/HIV emergency care
Medical appointment
Tests
Drugs
332.05
1066.9
572.9
585.2
537.55
655.9
0
200
400
600
800
1000
1200
+50%
-50%


Treatment, HIV/AIDS outpatient care
Medical appointment
ART
Tests
Drugs
642.55
935.2
506.25
1207.8
709.15
802
732.4
755.5
0
200
400
600
800
1000
1200
1400
+50%
-50%


Treatment, TB/HIV outpatient care
ART
Tests
TB drugs
Drugs
507
899.4
615.2
683
626.3
660.8
615.15
683.1
0
100
200
300
400
500
600
700
800
900
1000
+50%
-50%


Treatment, LTB/HIV outpatient care
Medical appointment
ART
Tests
TBL drugs
Drugs
383.45
875.6
477.05
688.4
514.65
613.2
545.05
552.4
543.55
555.4
0
100
200
300
400
500
600
700
800
900
1000
+50%
-50%


Treatment, HIV/AIDS inpatient care
Medical appointment
ART
Tests
Drugs
970.1
2069.9
1327.4
1355.3
1248.2
1513.7
1132.75
1744.6
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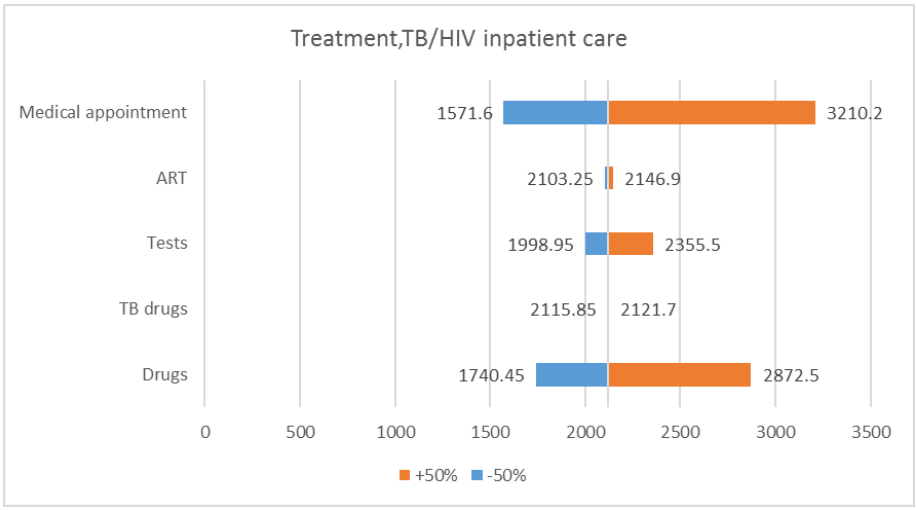
500
1000
1500
2000
2500
+50%
-50%


Treatment,TB/HIV inpatient care
Medical appointment
ART
Tests
TB drugs
Drugs
1571.6
3210.2
2103.25
2146.9
1998.95
2355.5
2115.85
2121.7
1740.45
2872.5
0
500
1000
1500
2000
2500
3000
3500
+50%
-50%

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	NOEMIA TEIXEIRADE SIQUEIRA FILHA
Principal Supervisor	ANDREIA COSTA SANTOS
Thesis Title	COST-EFFECTIVENESS OF A PROTOCOL FOR TUBERCULOSIS DIAGNOSIS IN PEOPLE LIVING WITH HIV: AN ECONOMIC STUDY ALONGSIDE A PRAGMATIC CLINICAL TRIAL IN BRAZIL

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Public Health		
When was the work published?	December/2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The study was designed by NTSF, MFPMA and ACS. NTSF was responsible for data collection, analysis and writing the manuscript. ACS, LR, RL and MFPMA reviewed the manuscript.

Student Signature: [redacted] **Date:** 03/04/2018

Supervisor Signature: **Date:** 03/04/2018

CHAPTER 5. RESEARCH PAPER 3: THE ECONOMIC BURDEN OF TUBERCULOSIS AND LATENT TUBERCULOSIS IN PEOPLE LIVING WITH HIV IN BRAZIL: A COST STUDY FROM THE PATIENT PERSPECTIVE

[1] Noemia Teixeira de Siqueira Filha MsC, [2]Maria de Fatima Pessoa Militao de Albuquerque PhD, [1] Rosa Legood PhD, [1] Laura C Rodrigues PhD, [1]Andreia Costa Santos PhD

[1]London School of Hygiene and Tropical Medicine (LSHTM), UK; [2]Centro de Pesquisa Aggeu Magalhaes, Fundação Oswaldo Cruz (FIOCRUZ-PE), Brazil

Publication status: accepted for publication at the Journal Public Health, December/2017

Reference: de Siqueira Filha NT, de Fatima Pessoa Militao de Albuquerque M, Legood R, Rodrigues L, Santos AC. The economic burden of tuberculosis and latent tuberculosis in people living with HIV in Brazil: a cost study from the patient perspective. Public Health. 2018;158.

Contributions: The study was designed by NTSF, MFPMA and ACS. NTSF was responsible for data collection, analysis and writing the manuscript. ACS, LR, RL and MFPMA reviewed the manuscript.

5.1 Abstract

Objective: The main objective of this study was to evaluate the direct and indirect costs of tuberculosis (active and latent TB infection) and HIV co-infection from the patient perspective. We have also assessed whether the proportion of out-of-pocket spending with TB during diagnosis and treatment, relative to patients' declared income, have led individuals into catastrophic costs, as defined by the World Health Organization.

Study design: Costing study conducted alongside a pragmatic clinical trial.

Methods: The study was conducted in Brazil in a referral service for HIV/AIDS. We applied a standardised questionnaire to collect data about out-of-pocket expenses and indirect cost. The questionnaire was applied at every patients' appointment in the referral service after TB diagnosis. We followed all patient's pathway during the pre-diagnosis period and treatment period. For patients on sickness benefit due to TB/HIV, income loss was calculated as the difference between an employee's wages forgone and the sickness benefit received. The monetary value of the time loss was calculated based on the Brazilian minimum wage for 2015. Total cost exceeding the World Health Organization's 20% threshold for an annual family income was defined as catastrophic and used as the main outcome in a stratified analysis.

Results: Among 239 PLHIV recruited in the first year of the trial, 31 patients were included into the costing study, 26 TB/HIV and five LTBI/HIV. TB/HIV patients incurred higher total costs when compared with LTBI/HIV (US$ 1,429 *vs* US$ 166). The main cost component for TB/HIV was indirect costs, especially income loss (US$ 749). About forty-eight percent (n=15) of the patients incurred catastrophic costs. However, when comparing mean out-of-pocket costs between TB/HIV and LTBI/HIV, statistically significant difference was only found for time loss. No statistical association was found between hospitalisation and catastrophic costs for different exposures, although data suggest that TB status and alcoholism may play a role in differentiate those incurring catastrophic costs during hospitalisation

Conclusions: Public health policies should address both, economic and clinical aspects associated to the disease through the introduction of more accurate algorithms for TB diagnosis to prevent delays in the diagnosis and treatment, and high costs to patients.

Key words: HIV, Tuberculosis, Latent Tuberculosis, Coinfection, Costs and Cost Analysis

5.2 Highlights

- TB/HIV patients can face high costs associated to TB diagnosis and treatment.
- Indirect costs, especially income loss, accounted for more than half (52.4%) of the total cost and may be linked to delays in TB diagnosis and treatment.
- Despite free universal care for TB, data suggest that almost half of patients have incurred catastrophic costs.
- Public health policies should address both, economic and clinical aspects associated to the disease through the introduction of more accurate algorithms for TB diagnosis to prevent delays in the diagnosis and treatment, and high costs to patients.

5.3 Introduction

The economic consequences of the vicious cycle of tuberculosis (TB) and poverty in low- and middle-income countries are well known. It is estimated that tuberculosis consumes about $ 12 billion of the income of the world's poorest communities every year. Furthermore, TB patients can lose three to four months of work time and the loss of earnings can achieve up to 30% of the annual household income[143]. This scenario can be even worse for people living with HIV (PLHIV) co-infected with TB. Patients with concurrent diseases can face catastrophic costs during their diagnosis and treatment. In addition, catastrophic costs could lead to worse outcomes, such as treatment abandonment and death[36].

The World Health Organisation (WHO) has recommended cost studies as a way to support strategies aiming the end of catastrophic health expenditures due to TB by 2020, as part of the Sustainable Development Goals (SDGs)[36]. Brazil is one of the 30 countries with the highest TB/HIV burden worldwide[114], and is committed to the goals stated by the WHO through its 2017 National Plan entitled “Brazil free of TB”. The plan aims to reduce TB incidence and mortality rates to less than 10 cases/100,000 inhabitants and less than one death/100,000 inhabitants, respectively, by 2035. Another goal is to reduce to zero the number of families facing catastrophic cost due to TB by 2020[48]. However, there is a lack of information in the literature addressing costs for TB and latent TB/HIV (LTBI/HIV) co-infection in the country, especially from the patient perspective.

The main objective of this study was to evaluate the direct and indirect costs of tuberculosis (active and latent TB) and HIV co-infection from the patient perspective. We have also assessed whether the proportion of out-of-pocket spending with TB during diagnosis and treatment, relative to patients’ declared income, has led individuals into catastrophic costs, as defined by the World Health Organization[26]. This study is the first investigation of patients’ costs involving co-infection in Brazil.

5.3 Methods

Study location

The study was conducted in the city of Recife, capital of the state of Pernambuco, Brazil. The data collection was conducted in a referral service for PLHIV, Correia Picanco Hospital (CPH), which provides care for about 60% of all individuals with HIV/AIDS in the state.

Sample size calculation

The costing study was conducted alongside a pragmatic clinical trial, designed to evaluate the effectiveness and cost-effectiveness of a protocol for TB diagnosis in PLHIV. The two arms trial compares the hospital routine for TB diagnosis which follows the Brazilian Ministry of Health (MoH) protocol and advocates TB diagnosis through sputum smear microscopy (SSM), chest X-ray (CXR) and sputum culture (SC), with a new protocol comprising a screening by clinical algorithm in every appointment to examine the presence of cough, weight loss, fever and night sweets plus confirmatory tests (SSM, SC, CXR, gene Xpert MTB/RIF and liquor aspiration for extra pulmonary TB) in those patients with any one of the symptoms. The sample size for the epidemiological pragmatic trial was calculated using the mortality rate estimated for a cohort study of TB/HIV co-infected patients treated in the CPH[23]. The sample size calculation did not take into account parameters related to TB status, such as expected proportions of TB or LBTI patients. The sample size was determined using the following parameters: (1) estimated mortality rate of 20% in one year (80% survival rate in 400 days) for TB/HIV co-infected patients; (2) study power of 80%; (3) Alpha error of 5%; (4) assumed Relative Risk (RR) of 0.5 comparing the rate in both groups, intervention (protocol) and control arm (hospital routine), reduction of 50% (assumption). The hypothesis was that the intervention arm would detect more TB cases and have a lower mortality rate when compared with the routine arm. Thus, a proportion of 2:1 patients in the intervention:routine arms was applied to obtain a smaller confidence interval. The total sample size was 483 HIV positive patients (322 in the intervention group and 161 in the routine group). We used data from the first year of the trial to conduct the costing study.

Study population, inclusion and exclusion criteria

We followed the same exclusion and inclusion criteria established for the clinical trial. We included adult participants with HIV positive status recruited for the epidemiological study, who developed TB or performed isoniazid preventive therapy (IPT) during the first year of the trial. Participants were excluded if they were in TB treatment at the research enrolment or had been treated in the previous three months. Patients with multidrug resistant TB, with preliminary known status or diagnosed during the trial, should be also excluded from the study, as well as those who had started antiretroviral therapy (ART) before their first visit to CPH, those registered only to collect ART and those transferred to another health service during the study period.

Study procedures

HIV positive patients had a first appointment with a nurse to collect data for the epidemiological study. Patients were followed-up for one year and those diagnosed with TB co-infection, active TB or LTBI, were invited to take part in the costing study. TB diagnosis was established through a screening by clinical algorithm, clinical assessment and confirmatory tests (gene Xpert, sputum smear microscopy and chest X-ray) for patients in the intervention arm, or through clinical assessment and sputum smear microscopy and chest X-ray for patients in the routine arm. IPT was provided for LTBI/HIV patients with tuberculin skin test (TST) higher than 5 mm or for those who had contact with TB patients.

We followed all patient's pathway during the pre-diagnosis period (retrospectively) and treatment period (prospectively). Pre-diagnosis was the period between the onset of TB symptoms until TB/LTBI diagnosis. The treatment period was the time from the beginning of the treatment until cure, death or treatment abandonment. We considered loss of follow-up those patients who did not attend ambulatory appointments at CPH for six months after starting the treatment.

Questionnaire to collect patients' costs

A standardised questionnaire based on "The tool to estimate patient cost" was applied to collect data about out-off-pocket expenses (direct medical and non-medical costs) and indirect cost[144]. The questionnaire covered demographic and socio-economic data; TB characteristics (first symptoms, diagnostics tests, type of TB); type of health care (inpatient, outpatient and emergency care); direct costs (transport, food, caregiver, drugs, tests); indirect costs (income and time loss travelling to the hospital for appointments, tests and to collect drugs, waiting and consultation time, inpatient care). Sources of income were not explored during interview. Trained nurse technician conducted the interviews after every patient appointment at the CPH. Parents or carers of infirm patients were asked to complete the questionnaire on their behalf, if necessary.

Direct medical and non-medical costs were referred by patients during the interviews. Indirect costs - income and time loss - was also reported by patients. For those patients who were on sickness benefit due to TB/HIV, income loss was calculated as the difference between an employee's wages forgone and the sickness benefit received[59]. The monetary value of the time loss was calculated based on the Brazilian minimum wage/2015 (monthly: US$273.95; daily:

US$9.13; hourly: US$1.31)[145]. All costs were calculated in local currency (Brazilian Real, 2015 prices) and converted to US dollars using an average exchange rate for the period of study as calculated by OANDA (R$1= US$0.34765).

Data analysis

Questionnaires were double entered in a virtual platform hosted by Fundacao Oswaldo Cruz (FIOCRUZ-PE - patient costs). Data analyses were undertaken in Stata/IC 14. The primary outcome was mean costs per TB/HIV and LTBI/HIV patient. We calculated the costs by disease category and period of analysis (pre-diagnosis and treatment period). We used the threshold of 20% established by WHO to describe whether patients have incurred catastrophic costs: if the proportion of patients' income consumed by the total costs incurred by patients, from the first TB symptoms until the end of TB treatment equalled 20% or higher, then the costs were considered catastrophic. We compared two main groups in terms of direct and indirect costs: those with TB/HIV and those with LBTI/HIV. To test difference in proportions, we used Fisher's exact for dichotomy variables and a non-parametric Wilcoxon-Mann-Whitney test for continuous variables (costs). We also divided the patients into those who have incurred or not catastrophic costs, and compared them in terms of socio-economic characteristics, lifestyle, TB and other clinical status, including hospitalisation, and costs. An assessment of the association between catastrophic costs and hospitalisation was conducted aimed at evaluating whether hospitalisation stratified by different exposure would explain differences in costs; the crude and adjusted odds ratios (ORs) were calculated for this analysis. Due to a small sample size (N=31) and the possibility of sample bias, we decided for a simple stratification of data over a multi-regression analysis[146]. All *P*-values below 0.05 were considered statistically significant, although we are aware about the caveats of the interpretation of *P*-values related to sample sizes and sizes of compared groups[147].

5.4 Results

Among 239 PLHIV recruited in the first year of the trial, 31 patients were included into the costing study: 26 patients who were diagnosed and treated for TB/HIV and five who were given IPT. No major differences between patients being treated by TB/HIV and patients under LTBI/HIV treatment were observed, apart from difference in gender: in the TB/HIV category, the majority of patients were male, whilst most of LTBI/HIV patients were female ($P = 0.005$). The age group of 18-39 years old was more frequent and more than 50% of the patients had a monthly income lower than the Brazilian minimum wage. The majority of patients (84% of the

total sample) had a minimum of four years of study in both groups. The proportion of alcohol dependence and use of illicit drugs was similar between TB/HIV and LTBI/HIV groups; smoking seemed to differ between groups, although no statistically significance difference was observed (Table 1).

TB/HIV patients were more likely to attend emergency care during both pre-diagnosis (P = 0.001) and treatment period (P = 0.005) and being hospitalised during the treatment period (P = 0.027). Furthermore, TB/HIV presented lower CD4 count (<200 cells/m^3) at the first appointment at CPH when compared with LTBI/HIV patients (P = 0.013). Eight deaths occurred in the TB/HIV group and no death occurred in LTBI/HIV group, however, the difference in the death's outcome between the groups was not statistically significant (Table 2). The length of hospitalisation for TB/HIV patients was, on average, 11 days at the pre-diagnostic period and 28 days at the treatment period. Only one LTBI/HIV patient was hospitalised at the treatment period.

The mean cost of treatment period was higher when compared with pre-diagnosis period for both TB/HIV (US$840 *vs* US$589) and LTBI/HIV (US$127 *vs* US$39). TB/HIV patients incurred higher costs during pre-diagnosis and treatment when compared to LTBI/HIV patients: it was almost nine times higher than the latter (US$1,429 *vs* US$166, P = 0.001) (Table 3). The main cost component for TB/HIV was indirect costs for pre-diagnosis (78%) and treatment periods (73%), respectively. Whilst, the higher costs for LTBI/HIV were mainly on direct non-medical costs (50%) and direct medical costs (50%) during pre-diagnosis and treatment period, respectively (Figure 1).

Overall, 15 (48%) patients incurred catastrophic costs with total out-of-pocket expenditure equalling or exceeding 20% of the annual patients' family income. Among TB/HIV patients, 54% have incurred catastrophic costs (14/26=54%), while 20% of LTBI/HIV faced these costs (1/5=20%). Those who were not classified as facing catastrophic costs seemed to have a total mean costs more than three times higher than those classified as facing catastrophic costs, nonetheless no statistically significance difference was found. Among those patients who incurred catastrophic costs, the majority were TB/HIV patients (93%), male (73%), who used illicit drugs during the last year (67%), were hospitalised during the course of the disease (80%) and had a monthly income lower than the Brazilian minimum wage (60%), although those socio-economic and lifestyle characteristics have not statistically differed from those who did not incurred in catastrophic costs. Statistical significance between the two groups was only

found for those with monthly income lower or equal/higher than the Brazilian minimum wage (P = 0.006) (Table 4).

Patients incurring catastrophic costs also differed from those not incurring those costs in terms of time loss (US$396 *vs* US$152) - (P = 0.011) – Table 5. Income loss seemed to be higher among those not incurring catastrophic costs when compared to those incurring these costs (US$1,102 *vs* US$184), but no statistically significance difference was observed.

The stratified analysis has not showed any statistical difference for catastrophic costs between hospitalised and non-hospitalised patients during pre-diagnosis and treatment periods. However, the data suggest that those hospitalised seemed to have 1.8 higher chance to incur in catastrophic costs when compared with those non-hospitalised. Most variables could be considered confounder in this analysis, as almost all adjusted OR were different from the crude OR, by more than 10% and 20%, with the exception of CD4 count levels (change-in-estimate)[148]. However, because of the small sample size, this study had not enough power to detect a meaningful difference between groups.

5.5 Discussion

Our results suggest that patients with TB/HIV co-infection face much higher costs than those being treated as LTBI/HIV. In our study, TB/HIV patients incurred almost 9 times higher total costs than LTBI/HIV (US$1,429 *vs* US$169). Furthermore, almost half of all patients (48%) have occurred in catastrophic costs. The main cost component for TB/HIV was indirect costs (US$1,071 in total), especially income loss (US$749). High indirect cost may be linked to delays in TB diagnosis and treatment, which can also lead to patient's health state deteriorates and, consequently, more complications during the treatment, such as hospitalisations, side effects and more visits to emergency and outpatient care.

Indirect costs to patients in the Brazilian's context seem to be much higher than those presented in the international literature. In Cambodia, the mean indirect cost was estimated in US$176 and US$517 during the pre-diagnosis and treatment, respectively [99]. The indirect cost varied from US$171 to US$253 during the treatment in Nigeria. In Ethiopia it was US$117 during the pre-diagnosis [108,109,112]. Conversely, some of these countries presented similar or higher direct costs when compared with Brazil. Direct costs in Nigeria variated from US$62 to US$379. Nigeria provides free diagnostic testing and treatment free of charge to all TB patients in decentralised services [110,112]. Direct costs in Cambodia and Burkina Faso were also similar to

Brazil, US$137 and US$120, respectively (all costs adjusted by inflation, 2015 prices). These countries also adopt free TB diagnosis and treatment [99,111]. Lower human and infrastructure capital and variations in methodological approaches for cost assessment may explain the difference in results.

Although our study has not showed any statistically significant difference in catastrophic costs between hospitalised and non-hospitalised for a number of different categories of variables in a stratified analysis, the proportion of all patients facing catastrophic costs was relatively high (48%), with 54% of TB/HIV patients facing these costs. A study conducted in Peru, including TB and MDR/TB patients, found that 39% of patients have faced catastrophic costs. The study also shows that being male (OR 2.16 [95% CI = 1.57–2.96 p<0.001) and poorer (OR 1.25 [95% CI = 1.15–1.36], p<0.001) were also associated with these costs. Our study did not assess the association between MDR/TB and catastrophic costs because those patients were not included in the trial. The non inclusion of MDR/TB patients in our cohort is a clear limitation for the economic study, as MDR/TB is associated with a higher likelihood of incurring catastrophic costs[149].

Our study has some other limitations; the first being the use of data from a pragmatic clinical trial. Some patients in the intervention group had their diagnosis earlier than those enrolled into the routine, what has likely reduced their cost of the treatment due to early TB diagnosis and reduction of complications, such as hospitalisation. However, the objective of this study was to give a general picture of the costs involved in TB/HIV diagnosis and care. A second limitation was the small size, especially for the LTBI/HIV group, which had only five patients. Results of inferential statistics in our stratified analysis for the association of catastrophic costs and different variables by hospitalisation status should be interpreted with caution. Although some *P*-values were not statistically significant, some variables seemed to play an important role in explaining differences of costs between groups, such as lifestyle (e.g. alcoholism) and TB status. Further research is necessary to better understand the role of these confounders in influence costs to patients. A third limitation was a potential recall bias, especially for the pre-diagnosis period. Recall bias also affected the measurement of costs during the treatment period if there was a long interval between the appointments at CPH and long-term hospitalisation in other health services. In a recent publication, Sweeney and colleagues (2016) mentioned recall bias as a significant concern in surveys aiming to estimate the impact of disease on poverty. The authors suggested the follow-up of a cohort along the clinical pathway [150]. Our study adopted this strategy. The interviews were conducted at every patient appointment at CPH from

the beginning of TB/LTBI treatment until patient discharge or death. Thus, the interval between interviews was reduced and, consequently, memory bias was better controlled.

Our study is the first costing study conducted from the patient perspective addressing TB/HIV co-infection in the country. The study is directly linked to the goal of the Brazilian National Plan and with the global target to end catastrophic costs due to TB for patients and families. It is clear that the free access to TB care is not enough to prevent patients from facing financial costs, especially due to indirect and direct non-medical costs. TB/HIV co-infected patients facing high costs can suffer worsening health outcomes, which can be a barrier to reduce TB deaths among PLHIV, one of the milestone of the United General Assembly, as part of the Sustainable Development Goals [151]. Public health policies may address ways to prevent high patients' costs through the introduction of more accurate algorithms for TB diagnosis in PLHIV to prevent delays in the diagnosis and treatment. Further studies should expand the investigation of catastrophic health expenditures and effect of social protection on patients costs in the Brazilian context.

Conflict of interest: We declare no competing interests.

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Ethical approval

The study was approved by the Fundacao Oswaldo Cruz (No 279.324) and the London School of Hygiene and Tropical Medicine (Ref: 7371) ethics committees. The clinical trial was registered at Brazilian Registries for Clinical Trials (RBR-22t943).

Table 1. Socio-economic, demographic and lifestyle characteristics of the study population, Correia Picanco Hospital, Recife/Brazil.

Variable	Total (N=31)		TB/HIV (N=26)		LTBI/HIV (N=5)		*P*- value[1]
	N	%	N	%	N	%	
Socio-economic							
Gender							
Female	7	23	3	12	4	80	0.005
Male	24	77	23	88	1	20	
Age							
18-28	9	29	8	31	1	20	0.821
29-39	12	39	10	38	2	40	
40-50	7	23	6	23	1	20	
≥51	3	10	2	8	1	20	
Literate[2]							
Yes	26	84	21	81	5	100	0.560
No	5	16	5	19	0	0	
Income							
No income	3	10	3	12	0	0	1.000
< Minimum wage	16	52	13	50	3	60	
≥ Minimum wage	12	39	10	38	2	40	
Life style habits							
Smoking							
Current	6	19	6	23	0	0	0.075
Never	15	48	10	38	5	100	
Former	10	31	10	38	0	0	
Alcohol[2]							
Low risk	12	39	9	35	3	60	0.337
Hazardous drinking	7	23	5	19	2	40	
Harmful drinking	4	13	4	15	0	0	
Alcohol dependence	8	26	8	31	0	0	
Illicit drug use – last year							
Cannabis							
Yes	4	13	3	11	1	20	0.525
No	27	87	23	88	4	80	
Cocaine							
Yes	4	13	3	12	1	20	0.525
No	27	87	23	88	4	80	
Glue							
Yes	2	6	2	8	0	0	1.000
No	29	94	24	92	5	100	
Crack							
Yes	4	13	4	15	0	0	1.000
No	27	87	22	85	5	100	

[1] Fisher exact
[2] Minimum of four years of study (mec.gov.br)
[3] Brazilian minimum wage, 2015 = US$ 251·7
[4] As defined by the WHO: The Alcohol Use Disorders Identification Test (AUDIT), 2011

Table 2. Characteristics of treatment and health outcomes for patients treated at the Correia Picanco Hospital, Recife/Brazil.

Variables	**TB/HIV (N = 26)**		**LTBI/HIV (N = 5)**		***P*- value[1]**
Emergency care	**N**	**%**	**N**	**%**	
Pre-diagnosis period					
Yes	21	81	0	0	0.001
No	5	19	5	100	
Treatment period					
Yes	19	73	0	0	
No	7	27	5	100	0.005
Hospitalisation					
Pre-diagnosis period					
Yes	11	42	0	0	0.133
No	15	58	5	100	
Treatment period					
Yes	20	77	1	20	0.027
No	6	33	4	80	
CD4 count (1st appointment)					
>500	2	8	2	40	
200-499	5	19	1	20	0.018
<200	16	62	0	0	
Outcome	**N**	**%**	**N**	**%**	
Cure or end of follow-up	18	69	5	100	0.291
Death	8	31	0	0	

[1] Fisher exact
[2] Five missing data. CDC classification system for HIV-infected adults and adolescents[152]

Table 3. Mean direct and indirect cost (US$) of TB/HIV and LTBI/HIV patients per period of analysis from the patient perspective, Correia Picanco Hospital, Recife/Brazil.

Period of analysis	**TB/HIV**	**LTBI/HIV**	***P*-value[1]**
Pre-diagnosis	**(N = 26)**	**(N = 5)**	
Drugs	16.3	0.0	0.286
Tests	18.3	7	0.712
Caregiver	43.1	3.7	0.194
Total direct medical costs	*77.7*	*10.8*	*0.544*
Transport	37.2	8.6	0.080
Food	17.5	10.8	0.648
Total direct non-medical costs	*54.7*	*19.4*	*0.132*
Income loss	335.8	0	0.163
Time loss	121.3	8.4	0.002
Total indirect costs	*457.1*	*8.4*	*0.002*
Total costs pre-diagnosis period	***589.5***	***38.6***	***0.003***
Treatment			
Drugs	18.7	27.6	0.933
Tests	4.1	35.5	0.346
Caregiver	71.8	0.5	0.245
Total direct medical costs	*94.6*	*63.6*	*0.587*
Transport	66.3	23	0.418
Food	65.2	4.7	0.724
Total Direct non-medical	*131.5*	*27.7*	*0.387*
Income loss	413.6	0	0.132
Time loss	200.1	35.9	0.096
Total indirect costs	*613.7*	*35.9*	*0.032*
Total costs treatment period	***839.8***	***127.2***	***0.0601***
Total costs Pre-diagnosis + treatment	***1,429.3***	***165.8***	***0.001***

[1] Wilcoxon-Mann-Whitney test

Figure 1a. Proportion of direct and indirect costs for TB/HIV and LTBI/HIV at the pre-diagnosis period from the patient perspective, Correia Picanco Hospital, Recife/Brazil.

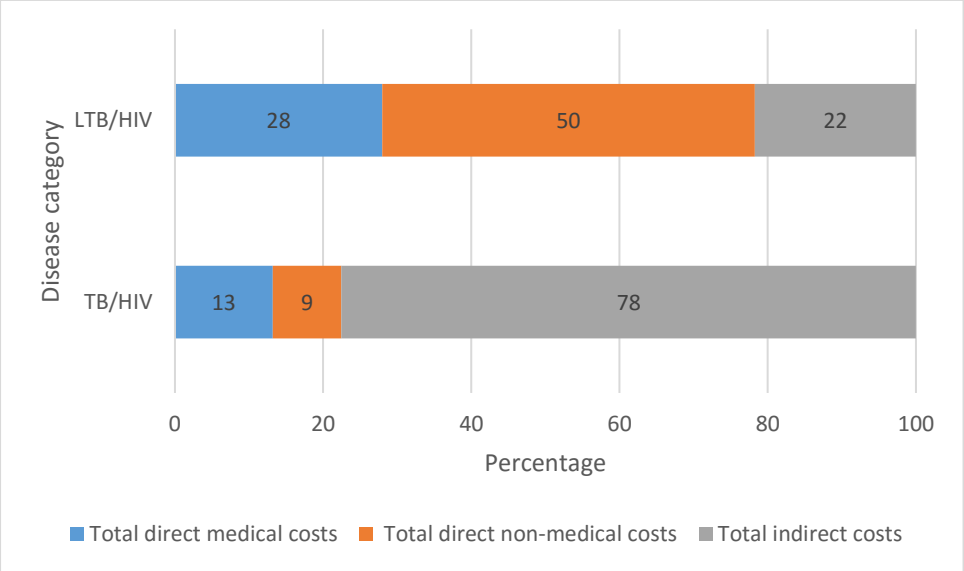

Figure 1b. Proportion of direct and indirect costs for TB/HIV and LTBI/HIV at the treatment period from the patient perspective, Correia Picanco Hospital, Recife/Brazil.

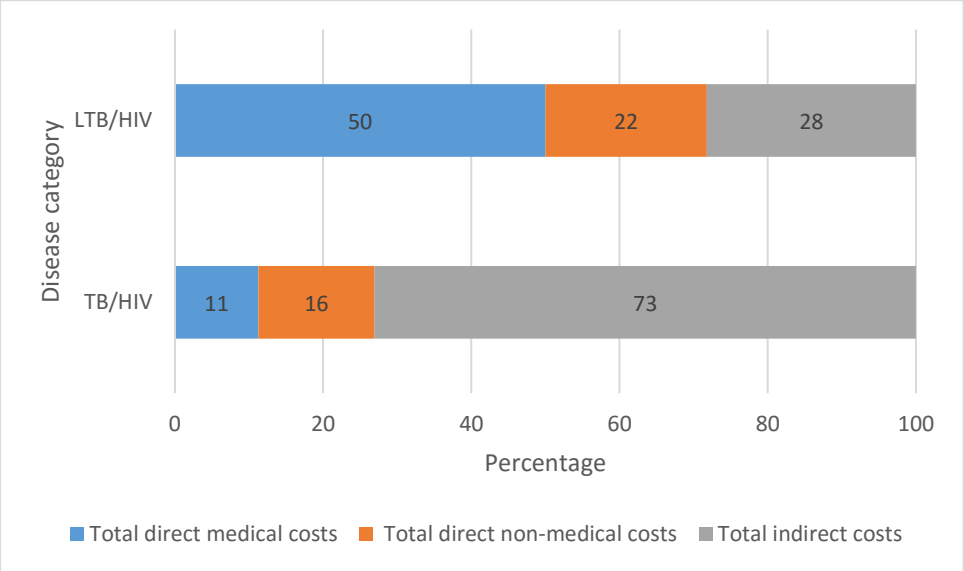

Table 4. TB status, socio-economic, life style and treatment characteristics of patients incurring catastrophic costs, Correia Picanco Hospital, Recife/Brazil.

Variable	Catastrophic costs				P-value[1]
	Yes (N = 15; 48%)		No (N = 16; 52%)		
TB status	*N*	*%*	*N*	*%*	
TB/HIV	14	93	12	75	0.333
LTBI/HIV	1	7	4	25	
Gender					
Male	11	73	13	81	0.685
Female	4	27	3	19	
Patient monthly income[2]					
< Minimum wage	12	80	5	31	0.006
≥ Minimum wage	3	20	11	69	
Illicit drug use – last year[3]					
Yes	10	67	15	94	0.083
No	5	33	1	6	
Alcohol[4]					
Low risk	4	27	8	50	0.449
Hazardous drink	3	20	4	25	
Harmful	3	20	1	6	
Alcohol dependence	5	33	3	19	
Hospitalisation[5]					
Yes	12	80	11	69	0.685
No	3	20	5	31	
CD4 count (1st appointment)[6]					
>500	2	17	2	14	0.953
200-499	3	25	3	24	
<200	7	58	9	64	

TB/HIV = patient with active tuberculosis and HIV co-infection; LTBI/HIV = patients with latent tuberculosis infection and HIV co-infection

[1] Fisher exact

[2] Brazilian minimum wage, 2015 = US$ 251.7

[3] Crack, glue, cocaine, cannabis

[4] As defined by the WHO: The Alcohol Use Disorders Identification Test (AUDIT), 2011

[5] Hospitalisation occurred since the first TB symptoms until the end of treatment. Hospitalisations to treat complications related to TB or HIV.

[6] Five Missing data. CDC classification system for HIV-infected adults and adolescents[152]

Table 5. Mean direct and indirect costs according to occurrence of catastrophic costs, Correia Picanco Hospital, Recife/Brazil.

Cost item	Catastrophic costs		P-value[1]
	Yes (N = 15)	No (N = 16)	
Direct non-medical costs			
Transport			
Mean cost	87.7	86.2	0.874
Standard deviation	120.0	95.7	
Food			
Mean cost	131.2	16.2	0.332
Standard deviation	396.3	21.3	
Direct medical costs			
Medicines			
Mean cost	30.8	36.5	0.396
Standard deviation	69.1	42.2	
Tests			
Mean cost	9.5	40.7	0.175
Standard deviation	36.8	84.7	
Indirect costs			
Income loss			
Mean cost	1,102.2	184.3	0.125
Standard deviation	2,489.5	407.4	
Time loss			
Mean cost	396.0	152.2	0.011
Standard deviation	257.2	150.1	
Total costs			
Mean cost	1,896.7	583.5	0.179
Standard deviation	3,075.0	472.5	

[1]Two-sample Wilcoxon rank-sum (Mann-Whitney) test

Table 6. Association between catastrophic costs and hospitalisation stratified for each exposure variable at a time, Correia Picanco Hospital, Recife/Brazil.

Variable	Cases of catastrophic costs per hospitalisation n/N (%)		OR (confidence interval)		Change-in-estimate
	Hospitalised N= 23	Not hospitalised N= 8	Crude	Adjusted	
Total population	11/23 (48)	2/8 (25)	1.8 (0.27; 14.29)		
Variables					
Gender					
Female	1/3 (33)	1/4 (25)	2.0 (0.05;176.16)	2.59 (0.39; 17.35)	-30.5%
Male	10/20 (50)	1/4 (25)	3.0 (0.19; 172.94)		
TB status					
LTBI/HIV	0/1 (0)	0/4 (0)	0.0 (0)	0.95 (0.12; 7.16)	90%
TB/HIV	11/22 (50)	2/4 (50)	1.2 (0.07; 19.27)		
Illicit drug use – last year[2]					
Yes	3/4 (75)	1/2 (50)	0.0 (0.0)	2.45 (0.37;16.12)	-26%
No	8/19 (42)	1/6 (17)	4.5 (0.37;236.02)		
Alcohol[3]					
Low risk	3/8 (37)	1/4 (25)	1.8 (0.80;125.54)	1.40 (0.25; 7.90)	30%
Hazardous drink	2/5 (40)	0/2 (0)	0.7 (0.0; 78.25)		
Harmful	2/3 (67)	0/0 (0)	0 (0.0)		
Alcohol dependence	4/7 (57)	1/2 (50)	2 (0.02; 195.67)		
Patient monthly income[4]					
< minimum wage	8/19 (42)	2/4 (50)	0.0 (0.0)	3.2 (0.41; 25.12)	-43%
≥ Minimum wage	3/4 (75)	0/4 (0)	2.0 (0.11;28.28)		
CD4 count (1st appointment)[5]					
>500	1/3 (33)	0/0 (0)	0.0 (0.0)	1.45 (0.20;10.34)	-6%
200-499	2/4 (50)	0/0 (0)	1 (0.008;117.32)		
<200	6/14 (43)	1/2 (50)	0.75 (0.008;68.58)		

TB/HIV = patient with active tuberculosis and HIV co-infection; LTBI/HIV = patients with latent tuberculosis infection and HIV co-infection

[1] Ratio = (Crude-Adjusted)/Adjusted*100

[2] Crack, glue, cocaine, cannabis

[3] As defined by the WHO: The Alcohol Use Disorders Identification Test (AUDIT), 2011

[4] Brazilian minimum wage, 2015 = US$ 251.7

[5] Five Missing data. CDC classification system for HIV-infected adults and adolescents[152]

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SECTION A – Student Details

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Thesis Title	COST-EFFECTIVENESS OF A PROTOCOL FOR TUBERCULOSIS DIAGNOSIS IN PEOPLE LIVING WITH HIV: AN ECONOMIC STUDY ALONGSIDE A PRAGMATIC CLINICAL TRIAL IN BRAZIL

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
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SECTION C – Prepared for publication, but not yet published

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Please list the paper's authors in the intended authorship order:	Noemia Teixeira de Siqueira Filha, Maria de Fatima Pessoa Militao de Albuquerque, Andreia Costa Santos, Laura C Rodrigues, Rosa Legood
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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	The study was designed by NTSF, RL, ACS and MFPMA. NTSF was responsible for data collection, analysis and writing the manuscript. RL gave guidance to develop the decision analysis model, probabilistic sensitivity analysis and interpreting the results. ACS, LR, and MFPMA reviewed the manuscript.

Student Signature: [redacted] **Date:** 03/04/2018

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CHAPTER 6. RESEARCH PAPER 4: COST-EFFECTIVENESS OF A PROTOCOL FOR TB DIAGNOSIS IN PEOPLE LIVING WITH HIV IN BRAZIL: AN INTERIM ANALYSIS OF TWO YEARS OF A PRAGMATIC CLINICAL TRIAL

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Contributions: The study was designed by NTSF, RL, ACS and MFPMA. NTSF was responsible for data collection, analysis and writing the manuscript. RL gave guidance to develop the decision analysis model, probabilistic sensitivity analysis and interpreting the results. ACS, LR, and MFPMA reviewed the manuscript.

6.1 Abstract

The objective of this study is to assess the cost-effectiveness of a protocol for tuberculosis (TB) diagnosis in people living with HIV (PLHIV) in Brazil. The protocol comprises a screening by clinical algorithm at every patient appointment and complementary TB tests in those with a positive screening (gene Xpert, sputum smear microscopy and culture and chest X-ray). The cost-effectiveness study was conducted alongside a pragmatic clinical trial in a referral hospital for PLHIV. We developed a decision analytic model using cost per Disability Adjusted Life Years (DALYs) averted as primary outcome. We compared the TB protocol with the hospital routine where a screening by clinical algorithm is not mandatory and the gene Xpert test is not used for TB diagnosis. Costs were estimated from the public health system perspective. Data on costs and probabilities were collected during the first year of the pragmatic clinical trial. When compared with routine hospital care, the protocol saved US$ 1,963 and averted 0.4 DALYs. The protocol was considered cost saving because it was cheaper overall and averted more DALYs than routine care. Further studies should address affordability to implement the protocol at the Brazilian national level, taking into account different epidemiological profiles and health service organisation.

6.2 Introduction

Tuberculosis (TB) diagnosis in People Living with HIV (PLHIV) is still a challenge worldwide. Some technologies and algorithms have been developed to improve the accuracy of the diagnosis. The success of these methods in reducing the burden of TB/HIV co-infection will depend on countries' laboratory capacity, health care infrastructure, TB/HIV collaboration activities and political will [153]. Most TB/HIV high burden countries also face an extra difficulty, very scarce resources. Thus, the introduction of cost-effective technologies is mandatory for the sustainability of policies to reduce the burden of TB/HIV co-infection worldwide. Furthermore, many PLHIV still do not have access to isoniazid preventive therapy (IPT) and antiretroviral therapy (ART). Both treatments are recommended by the World Health Organization (WHO) as crucial steps to reduce the burden of TB in PLHIV and to reach the Stop TB Partnership and Sustainable Development Goals (SDGs) to end the TB epidemic by 2030[20,153].

Brazil figures among the 30 countries with a high burden of TB/HIV co-infection and, in the Latin America region, Brazil and Haiti together accounted for nearly half of all HIV-positive TB incident cases [142,154]. Between 2002 and 2012, the country saw an increase of 3.8% in the incidence of co-infection per 100,000 population. The crude incidence also increased from 5,943 to 6,846 in the same period [155]. Currently, the proportion of co-infection is 9.9% and ranges from 1.7% to 19.7% among Brazilian states [39]. TB screening using clinical algorithms and IPT is not routine in all referral services for PLHIV. The country introduced the gene Xpert in 2012; however, the test is still not available for PLHIV. Additionally, there is a lack of scientific evidence addressing cost-effectiveness of TB diagnosis in PLHIV in Brazil. A recent publication analysed the cost-effectiveness of Xpert for TB diagnosis, including TB and TB/HIV co-infection patients, but the result was not stratified by HIV status and screening by clinical algorithm was not addressed [126].

The objective of this study is to perform an interim analysis of a pragmatic clinical trial in Brazil to assess the cost-effectiveness of a protocol for TB diagnosis in PLHIV comprising screening by clinical algorithm and complementary tests, such as gene Xpert, sputum smear microscopy (SSM) and culture (SC) and chest X-ray (CXR). We compare the intervention with routine hospital care to evaluate the cost per Disability Adjusted Life Years (DALYs) averted.

6.3 Methods

Study design

We conducted the cost-effectiveness study alongside a pragmatic clinical trial at the Correia Picanço Hospital (CPH), the main referral service for PLHIV in the city of Recife, Brazil. The trial evaluated the effectiveness, cost and cost-effectiveness of a new protocol for TB diagnosis in PLHIV. The protocol included screening by clinical algorithm (investigation of symptoms such as cough, weight loss, fever and night sweats) at every patient appointment plus complementary tests in those patients with any one of the above symptoms (tests included SSM, CXR, SC and Xpert).

Inclusion and exclusion criteria

We included newly diagnosed HIV infected patients admitted at CPH, aged 18 years or over, not on TB treatment. We excluded patients who had visited CPH only to collect medicines, but received the treatment in the private sector for difficulties in follow-up and patients with multidrug resistant TB, with preliminary known status or diagnosed during the trial.

Modelling approach

We conducted an interim analysis of the pragmatic clinical trial with patients recruited and followed-up from March 2014 to March 2016. We developed a decision analytic model to estimate the cost-effectiveness of a protocol for TB diagnosis in PLHIV compared with routine hospital care. We included both pulmonary and extra-pulmonary TB and LTBI patients co-infected with HIV. Our model does not include multi-resistant TB as these patients were not covered by the referral hospital where the study was carried out. The primary outcome was cost per DALYs averted. We applied a 5% discount rate for DALYs calculation, as recommended by the Brazilian guidelines for heath technology assessment [156]. We calculated the cost-effectiveness ratio as the difference between the total costs of the intervention and control divided by the difference in DALYs. We use an Excel spreadsheet to develop the model following a cohort of newly diagnosed PLHIV during the entire pathway of TB and LTBI diagnosis and LTBI/HIV, TB/HIV, HIV/AIDS treatment. The analytical horizon of our model was one year after admission at CPH. Figure 1 shows the model description.

Comparators

In the intervention group, a nurse carried out TB screening by clinical algorithm using a standardised form and requested monitoring tests, such as CD4, viral load, tuberculin skin test (TST) and viral hepatitis, at the patient's admission to CPH. Those with a negative screening were referred to an infectious disease specialist physician at the same hospital to start HIV/AIDS treatment. These patients continued to be TB screened at every appointment at the CPH and some had a TB diagnosis during the follow-up period. Patients who were categorised as TB suspect and presented at least one TB symptom, were referred to a pulmonologist for further TB investigation, which included clinical evaluation and TB tests. Patients whose TST test showed a result of > 5mm or those who had been in contact with TB patients were diagnosed and treated as LTBI/HIV after ruling out active TB. These patients received six months IPT with isoniazid (100m). Patients with at least 2 mm of sputum were given an Xpert test, SC and CXR. Those with insufficient sputum for the Xpert test or without sputum were given a CXR and/or SSM and SC. Patients diagnosed with TB through clinical judgment and/or tests received two months of rifampicin treatment (150 mg) + isoniazid (75 mg) + pyrazinamide (400 mg) + ethambutol (275 mg) plus four to seven months of rifampicin (150 mg) + isoniazid (75 mg). TB treatment was self-administered and patients collected the drugs monthly at the CPH pharmacy to carry out the treatment at home.

In the control group, patients were not routinely screened for TB at admission to CPH. They had a first appointment with a nurse to perform the monitoring tests (the same as the intervention group) and then were referred to an infectious disease specialist physician who decided whether or not to conduct a TB investigation. We collected information on a possible TB screening by clinical algorithm from the patient's records after every appointment at CPH. Provision of IPT was based on medical decision and this treatment was not provided in the control group, even for those patients with a TST > 5 mm. The TB diagnosis included SSM, SC and CXR. Xpert was not available for the patients in the control group because the test was not implemented in routine hospital care. TB treatment comprised the same drugs as the intervention group.

Cost parameters

Details of the methodology applied in the costing studies will be published elsewhere, but in short, we estimated the cost from the health system perspective for each arm of the trial and for TB/LTBI diagnosis and treatment of TB/HIV, LTBI/HIV and HIV/AIDS patients. For

TB/LTBI diagnosis we included costs of tests, such as gene Xpert, SSM, SC, and CXR. We also included staff costs and overheads. For TB, LTBI and HIV/AIDS treatment we included healthcare use costs with drugs (TB, LTBI, ART, and all other drugs administered during treatment), tests (CD4, viral load and all other tests performed during treatment), staff wages (appointments at outpatient and emergency care and hospital day) and overheads (utility bills and contracts) incurred during the entire pathway of care (emergency, inpatient and outpatient care). We followed-up patients for one year or until death if it occurred before the end of one year.

Technical nurses conducted interviews after every patient appointment at CPH to collect data on the occurrence of hospitalisation and emergency care and use of medical resources at CPH and other health services in the metropolitan region. We also reviewed patients' notes at CPH and other health services used by patients during the follow-up period. We applied a mix of bottom-up and top-down approaches to capture and estimate the direct costs [51,75,133]. Unit costs were estimated by multiplying *quantity x price* for each cost category. We obtained drug prices from the Brazilian Ministry of Health database [134]. The cost of tests came from health system records [135]. Staff wages, hospital productivity and values of contracts and utility bills were collected from the CPH administrative division. We measured the average number of screens performed in the intervention and control group and then multiplied this value by the cost of an outpatient appointment (medical staff + overheads) to obtain the average cost of screening. Costs were calculated in local currency (Real, 2015 prices) and converted to US dollars using an average exchange rate from the period of study as calculated by OANDA [78] (www.oanda.com; R$1= US$0.34765).

Probabilities

The survival rates and probabilities used throughout the model pathway were also collected during the first year of the study. For the intervention arm, we collected the screening result from the standardised form used by nurses and doctors for the screening procedure. In the control arm, we collected this information from medical records. Information about TB diagnosis and treatment for both arms was collected from medical records or from the patient after the appointment at CPH. We recorded deaths through patient notes at CPH, participant nominated contacts, the CPH Epidemiology Centre, and by accessing the Mortality Information System reports.

DALYs calculation

DALYs is the outcome recommended by WHO for cost-effectiveness analysis studies addressing TB interventions. DALY is a measurement of lost health and it is calculated by the sum of years lived with disability (YLD) and years of life lost (YLL). We used the formulas described below to calculate YLD and YLL:

$$YLLs = (KCe^{ra})/(r+\beta)_2\{e^{-(r+\beta)(L+a)}[-r+\beta)(L+a)-1]-e^{-(r+\beta)a}[-r+\beta)a-1]\}+(1-k)/r(1-e^{rL})$$

Where:

K (age-weighting modulation factor) = 1, C (age-weighting correction constant) = 0.1658, r (discount rate) = 0.05, a = age of death, β (age-weighting function) = 0.04, L = standard life expectancy in Brazil

$$YLD = DW \times (KCe^{ra})/(r+\beta)_2\{e^{-(r+\beta)(L+a)}[-r+\beta)(L+a)-1]-e^{-(r+\beta)a}[-r+\beta)a-1]\}+(1-k)/r(1-e^{rL})$$

Where:

DW = disability weight, K (age-weighting modulation factor) = 1, C (age-weighting correction constant) = 0.1658, r (discount rate) = 0.05, a = age of death, β (age-weighting function) = 0.04, L = standard life expectancy of HIV/AIDS and TB/HIV patients in Brazil

We collected the average age of TB/HIV and HIV/AIDS deaths from the epidemiological study. We applied an average standard life expectancy in Brazil (men 72 years; women 79 years), which is 75.5 years[157]. The life expectancy figures for people with TB/HIV and HIV/AIDS in Brazil were collected from published studies [85,158]. The disability weight was based on the WHO Global Burden of Disease and published studies. We applied the disability weight for HIV cases of 0.135 to calculate DALYs for LTBI/HIV as these patients did not present AIDS symptoms at CPH admission. We applied the disability weight for AIDS on ART cases (0.167) to calculate DALYs for HIV/AIDS as the Brazilian Ministry of Health guidelines for HIV/AIDS treatment recommend starting ART immediately after HIV diagnosis [43,159]. The disability weight for TB/HIV co-infection was obtained from a published study (0.399) [160].

Sensitivity analysis

We conducted a one-way sensitivity analysis varying all parameters of the intervention arm according to the confidence interval. Results for this analysis were presented in a tornado diagram. We also ran a probabilistic sensitivity analysis to explore the joint uncertainty in costs and effects. We applied gamma distribution for costs to represent the usual skewness in cost. We applied beta distribution for probabilities parameters, which is ideal for binomial data. We estimated α and β using mean and standard error values. We calculated alpha as the number of events (i.e. positive or negative screening, TB/LTBI diagnosis, death, alive) and beta as the total sample less the number of events [66,161]. We ran the model 1,000 times in Excel software. Results were presented in a cost-effectiveness scatter plane and in a cost-effectiveness acceptability curve graph. We used the literature and the epidemiological study to calculate DALYs (Table 1).

Ethics

The study was approved by the Fundacao Oswaldo Cruz (No 279.324) and the London School of Hygiene and Tropical Medicine (Ref: 7371) ethics committees. All patients signed a consent form. The clinical trial was registered at the Brazilian Registries for Clinical Trials (RBR-22t943).

6.4 Results

During the study period, we recruited 315 PLHIV, with 15 patients excluded at the randomisation stage, 25 transferred to another health service and 37 considered lost to follow-up. The final sample for this study was 239 PLHIV (79 - control group and 160 - intervention group). In total, 23% and 65% of patients presented a positive screening at admission or during the follow-up period in the control and intervention group, respectively. Nineteen TB (12%) and five LTBI (3%) cases were diagnosed and treated in the intervention group, whilst seven TB (9%) cases were diagnosed and treated in the control group. There were eight (10%) and thirteen (8%) deaths in the control and intervention group, respectively. Figure 2 shows the trial profile.

The mean cost of TB/LTBI diagnosis was higher in the intervention group when compared with the control for screening positive TB/HIV patients (US$ 129 *vs* US$ 126) and HIV/AIDS (US$ 81 *vs* US$ 67) and for screening negative TB/HIV patients (US$ 310 *vs* US$ 154). In the treatment pathway, the control group presented higher costs in almost all categories, screening positive TB/HIV patients (US$ 9,397 *vs* US$ 3,070), screening negative TB/HIV (US$ 7,634 *vs* US$ 1,675) and HIV/AIDS (US$ 1,428 *vs* US$ 995) (Table 1).

When compared with current practice, the protocol saved US$ 2,069 and averted 0.4 DALYs. The protocol for TB diagnosis in PLHIV was considered cost saving because it was cheaper overall and averted more DALYs when compared with the routine. We also found a lower proportion of hospitalisations and deaths in the protocol arm (Table 2).

The sensitivity analysis confirmed our results. When we varied each parameter in the one-way sensitivity analysis the final result remained cost saving. In the probabilistic sensitivity analysis, the scatter plan shows that our model is robust as the simulations are concentrated in the cost-saving quadrant. Additionally, WHO establishes that for countries without a cost-effectiveness threshold, the Gross Domestic Product per capita (GDP per capita) should be applied in the willingness to pay threshold, and that a cost-effectiveness ratio below three times the GDP per capita is considered cost-effective. The acceptability curve analysis shows a 100% chance of the protocol being cost-effective with a willingness to pay threshold of US$ 8,538.6 (Brazilian GDP per capita). The Supplementary material (Figure S1, S2, S3, S4) shows the one-way and probabilistic sensitivity analysis.

6.5 Discussion

Our interim analysis suggests that the protocol for TB diagnosis in PLHIV, including a screening by clinical algorithm and complementary investigation of those with a positive result, is a cost-saving intervention when compared with the hospital routine for TB diagnosis in the Brazilian context. Although the protocol resulted in higher costs for TB diagnosis in PLHIV when compared with the routine arm, it had a major impact on decreasing treatment costs and DALYs. The mean cost to treat a screening positive TB/HIV co-infected patient was 2.5 times higher for the routine arm when compared with the protocol. It may indicate delays in TB diagnosis in the routine arm and, consequently, more complications such as hospitalisations, and adverse events during the TB/HIV treatment in this group. Indeed, in the routine arm, 80% of screening positive TB/HIV patients were hospitalised during the treatment with an average length of hospitalisation of 60 days. In the protocol arm, 71% of patients were hospitalised and the average length of stay was 17 days.

Studies conducted in other TB/HIV high burden countries that included screening in the diagnostic method have shown a lower impact on DALYs and deaths averted when compared to the current study. In Botswana, an algorithm including screening by clinical symptoms plus CXR and tracking policy resulted in only 0.1% fewer deaths when compared with an algorithm with screening plus CXR only [115]. In Uganda, the only study including both pulmonary and

extra-pulmonary TB, a screening by clinical algorithm plus the combination of Xpert and lateral-flow immune-chromatographic assay (LF-LAM), was considered highly cost-effective and resulted in an ICER of US$82/DALY averted [117]. Another study carried out in Sub-Saharan Africa found that the cost-effectiveness of a screening by clinical symptoms plus Xpert will depend on the prevalence of TB among PLHIV and volume of testing and varied from US$ 1,414/DALYs averted to 3,658/DALYs averted [84].

Our study has some limitations. Our model did not include secondary transmission due to the lack of, or delays in, TB diagnosis and treatment. However, as TB/HIV patients are usually paucibacillary and, consequently sputum smear negative (SSN), they are less likely to transmit TB. Thus, the impact of a TB protocol on TB transmission would be insignificant. Additionally, a study which simulated TB incidence three decades after the introduction of Xpert found that TB incidence remains substantial due to the lower probability of SSN patients transmitting TB and the high pool of latent TB patients who will progress to active TB irrespective of the improvement in TB diagnosis [127].

We did not include start-up costs and cost of scaling-up of medical staff in our analysis. Also, we applied the amount paid by the Brazilian Ministry of Health to calculate costs of TB and other diagnostic tests. These values represent amounts paid to providers to partially cover their laboratory costs and do not include transportation costs for Xpert samples (as it was not used as a point of care), quality control assurance and maintenance costs. To partly compensate for this limitation, we added the costs of staff and overheads to these estimates. Our final results were similar to another Brazilian study where the full costs of these tests were estimated [126]. In addition, the one-way sensitivity analysis did not show a significant impact on the final cost-effectiveness result when we varied diagnostic costs.

Another limitation is that we collected screening data for the control group from the patients' medical records as some doctors could conduct a screening without taking notes about this procedure. Thus, we may have added bias to the probability of having a screening positive or negative for the routine arm. It shows the importance to have standardised forms to collect information about TB symptoms during the medical appointment. WHO also recommends the monitoring of the full cascade of investigation through the identification of TB in patients with a positive screening and documentation of the type of investigation performed [2]. Finally, our analysis covers only a one year time horizon. A further cost-effectiveness analysis covering the

life of the cohort is planned after the end of the clinical trial, using the final analysis from the epidemiological study.

Although the study has limitations, our model is robust and the use of primary data collection to measure costs and probabilities of diagnosis and treatment was a strength of our analysis. Another benefit of our study is the inclusion of both pulmonary and extra-pulmonary TB/HIV co-infected patients. The rate of extra-pulmonary and disseminated TB in PLHIV is higher than the general population [6]. Thus, it is important to include strategies targeting these patients who are less likely to produce sputum and usually have false negative TB tests. Our study generated important information to contribute to the end of the TB epidemic in a sustainable way, as stated by the Stop TB Partnership and SDGs. Nevertheless, the success of this intervention will also depend on the scaling-up of IPT and improvement of the laboratory infrastructure to deal with an increased demand for Xpert tests for PLHIV. Further studies should address the affordability of implementing the protocol at the national level, taking into account different epidemiological profiles and health service organisation.

Figure 1. TB diagnostic scenarios in newly diagnosed PLHIV.

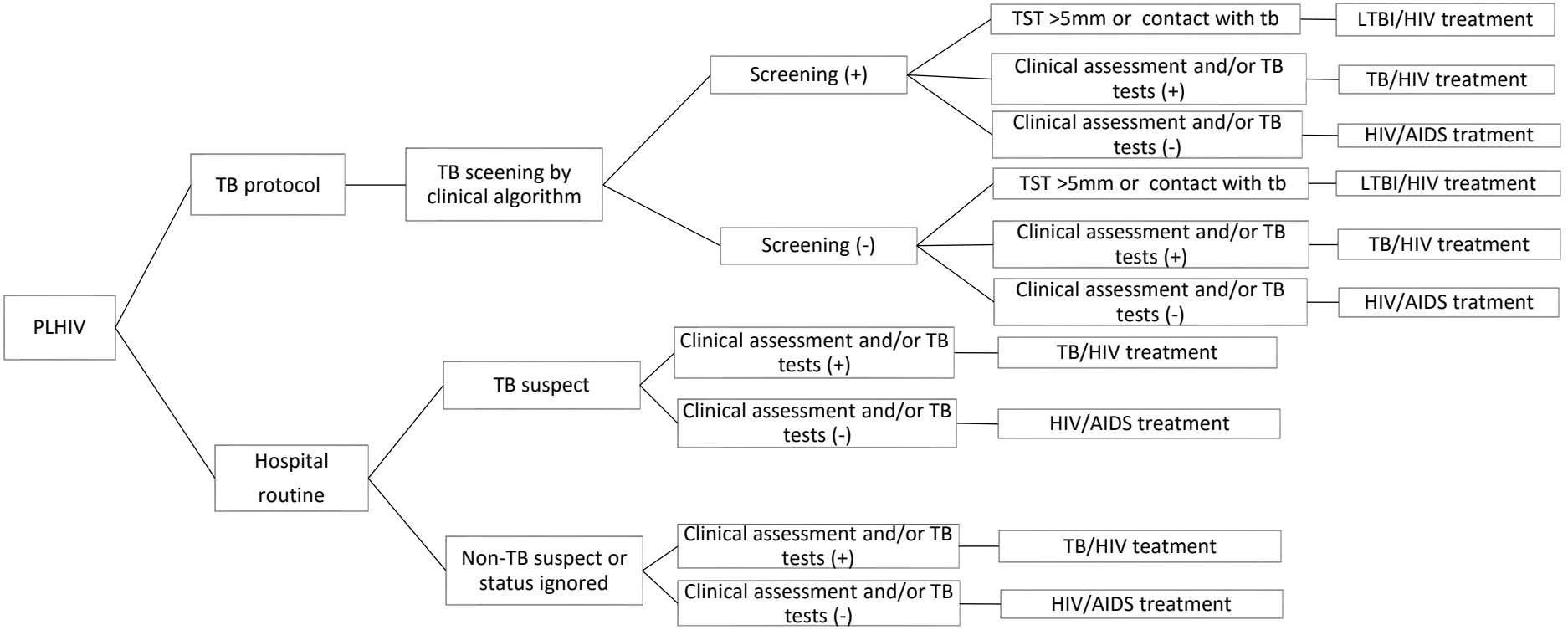


Figure 2. Trial profile

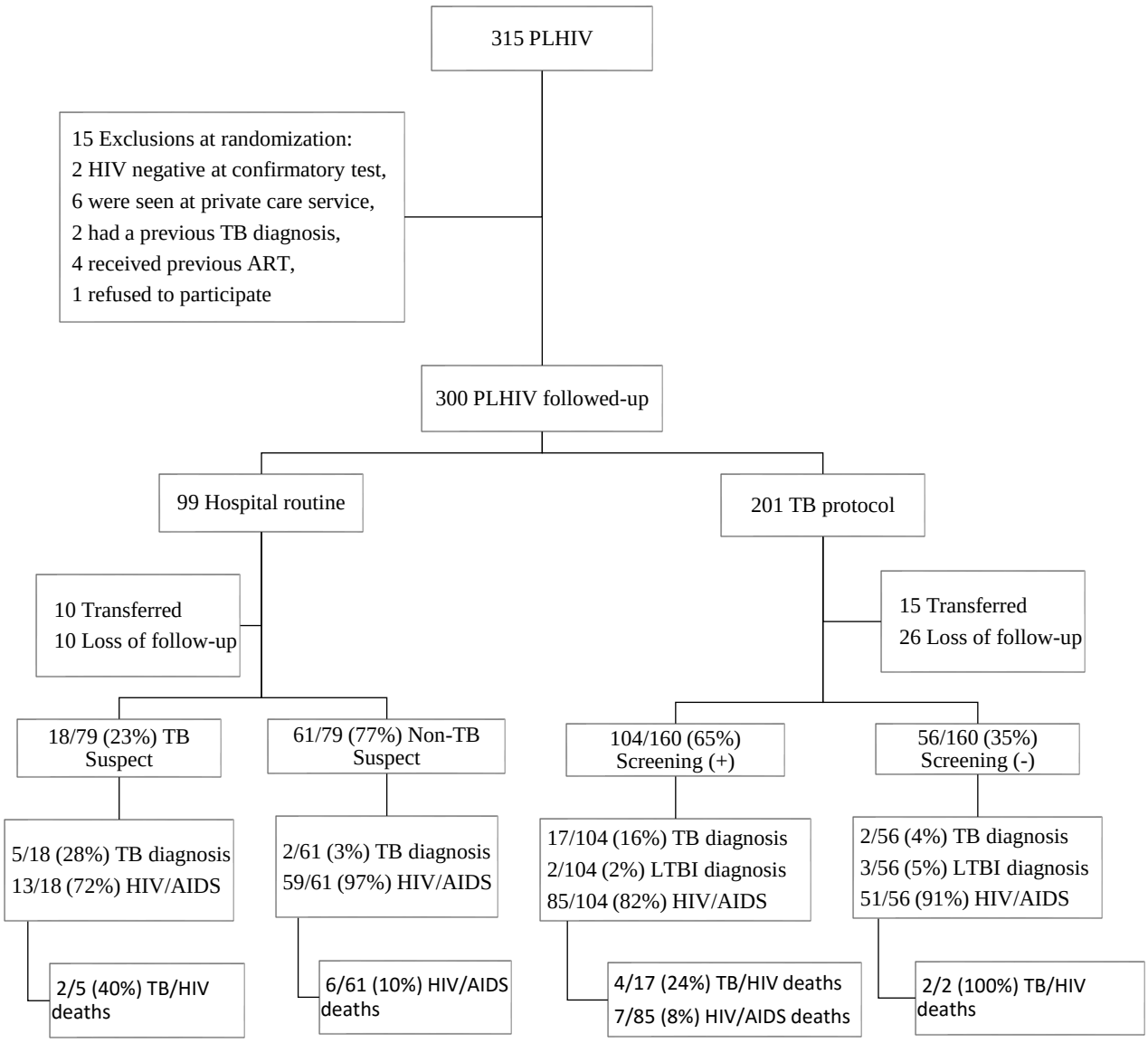


Table 1. Costs and probabilities applied in the decision analysis model

Cost parameters	US$ (2015)	Source
Intervention arm		
Screening	91.1	Cost study
LTBI/HIV screening (+)		
TB/LTBI investigation	47.0	Cost study
TB/LTBI treatment	1,324.7	Cost study
TB/HIV screening (+)		
TB/LTBI investigation	129.1	Cost study
TB/HIV treatment	3,070.1	Cost study
HIV/AIDS screening (+)		
TB/LTBI investigation	81.4	Cost study
HIV/AIDS treatment	1,613.5	Cost study
LTBI/HIV screening (-)		
TB/LTBI investigation	44.1	Cost study
LTBI/HIV treatment	315.5	Cost study
TB/HIV screening (-)		
TB/LTBI investigation	310.5	Cost study
TB/HIV treatment	1,675.1	Cost study
HIV/AIDS screening (-)		
TB/LTBI investigation	64.9	Cost study
HIV/AIDS treatment	994.7	Cost study
Control arm		
Screening	85.3	Cost study
TB/HIV, TB suspect (+)		
TB/LTBI investigation	126.2	Cost study
TB/HIV treatment	9,397.2	Cost study
HIV/AIDS, TB suspect (+)		
TB/LTBI investigation	67.3	Cost study
HIV/AIDS treatment	1,317.2	Cost study
TB/HIV, TB suspect (-)		
TB/LTBI investigation	154.3	Cost study
TB/HIV treatment	7,634.3	Cost study
HIV/AIDS TB suspect (-)		
TB/LTBI investigation	91.7	Cost study
HIV/AIDS treatment	1,428.3	Cost study
Probabilities parameters		
Intervention arm		
Screening (+)	0.65	Epidemiological study
LTBI/HIV diagnosis	0.02	Epidemiological study
TB/HIV diagnosis	0.16	Epidemiological study
HIV/AIDS diagnosis	0.82	Epidemiological study
Screening (-)	0.35	Epidemiological study
LTBI/HIV diagnosis	0.05	Epidemiological study
TB/HIV diagnosis	0.04	Epidemiological study
HIV/AIDS diagnosis	0.91	Epidemiological study
Control arm		
TB suspect	0.23	Epidemiological study
TB/HIV diagnosis	0.28	Epidemiological study
HIV/AIDS diagnosis	0.72	Epidemiological study
No TB suspect or status ignored	0.77	Epidemiological study
TB/HIV diagnosis	0.03	Epidemiological study
HIV/AIDS diagnosis	0.97	Epidemiological study

Continued

DALYs parameters		
Maximum life expectancy, Japan	84	[162]
Mean age of death (TB/HIV)	35	Epidemiological study
Mean age death (HIV/AIDS)	43	Epidemiological study
Life expectancy of patient diagnosed with TB (years) Brazil	19.5	[85]
Life expectancy of HIV/AIDS (years) Brazil	27	[158]
Disability weight TB/HIV co-infection	0.399	[160]
Disability weight AIDS on ART	0.167	[159]
Disability weight HIV cases	0.135	[159]

Table 2. Expected outcomes and cost-effectiveness of a protocol for TB diagnosis in PLHIV, Brazil.

Variables	Routine	TB protocol
Total cost (US$)	3,785.2	1,716.6
N. of total deaths	13/160 (10.1%)	8/79 (8.1%)
Difference in total deaths	-	-0.2
N. of TB/HIV deaths	2/7 (29%)	6/24 (25%)
Difference in TB/HIV deaths	-	-0.2
N. of total hospitalisations (TB/HIV, LTBI/HIV and HIV/AIDS)	20/79 (25%)	40/160 (25%)
N. of TB/HIV hospitalisations	6/7 (86%)	14/19 (74%)
N. of LTBI/HIV hospitalisations	-	1/5 (20%)
Difference in TB/HIV hospitalisations	-	-0.2
Average TB/HIV length of hospitalisation	56 days	16 days
DALYs	4.45	4.06
Incremental cost/DALYs averted	Dominated[1]	-

[1] Strategy with lower DALYs averted and higher cost.

6.6 Supplementary file

Figure S1. One-way sensitivity analysis, costs (US$)

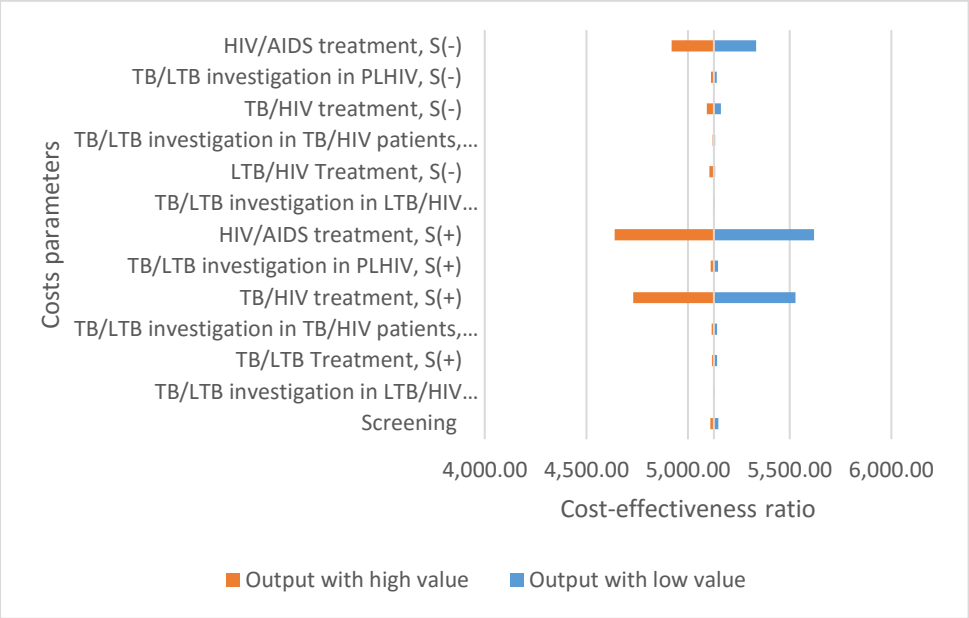
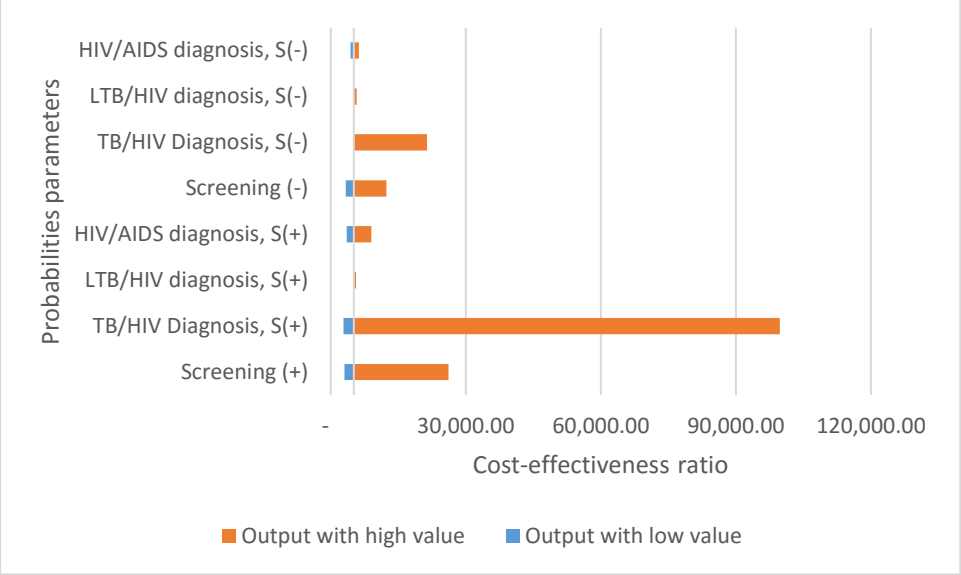


Figure S2. One-way sensitivity analysis, probabilities



S(-) = patients who were screening negative throughout the study period;
S(+) = patients who had at least one positive screening during the study period

Figure S3. Scatter plane

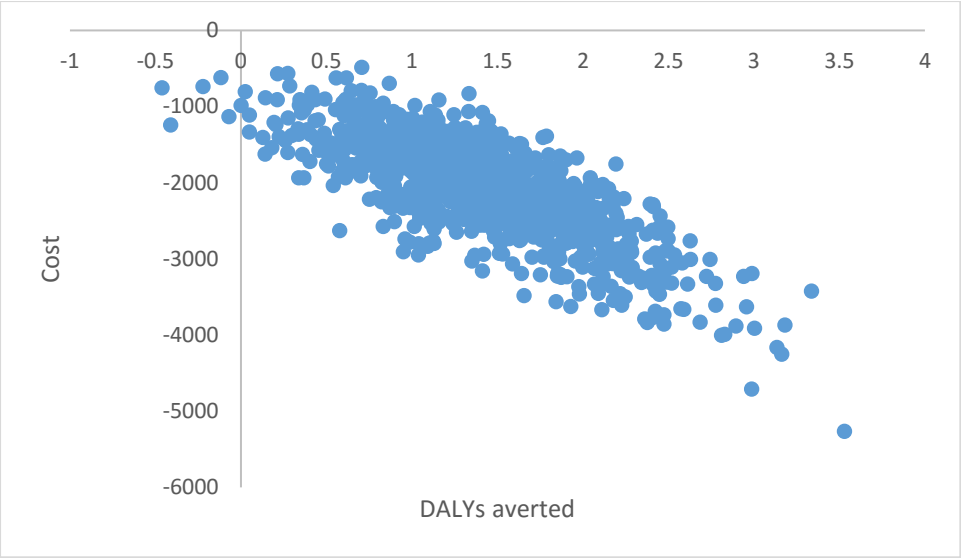
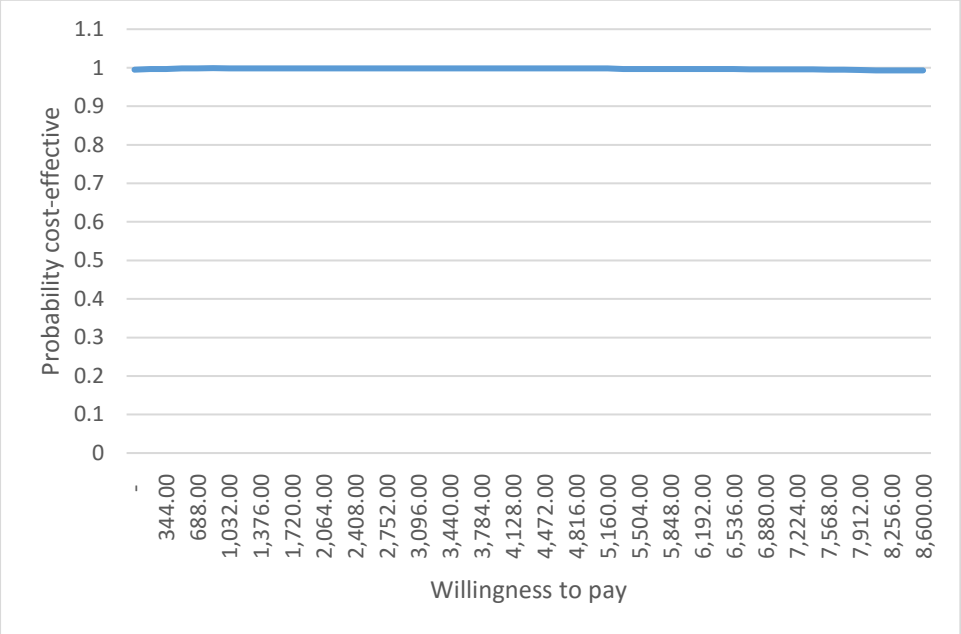


Figure S4. Cost-effective curve



CHAPTER 7. DISCUSSION

7.1 Introduction

TB is the main opportunistic infection and main cause of death in PLHIV. Although the latest WHO reports have shown a decreasing trend in incidence rates and deaths worldwide, there is a long way to go to achieve the end of the TB epidemic, as advocated by the main international organisations [15]. The main challenges are to speed up the decrease in TB incidence and mortality rates (from the current 1.5% to 6% annually), accelerate TB/HIV response (scale-up of ART, IPT and other key interventions) and address the gap in the funding available to deal with the disease [21].

Brazil also faces these challenges and the National Plan to end TB states two main goals: reduce the TB incidence rate to less than 10/100,000 inhabitants and the TB mortality rate to less than 1/100.000 inhabitants by 2035 [48]. The improvement of technologies and strategies for TB diagnosis in PLHIV is a key element to achieve these goals. However, there is a lack of evidence concerning the cost and cost-effectiveness of these interventions in PLHIV at national level. This lack of evidence was clearly apparent in both the literature and systematic reviews, which are part of this thesis.

The overall aim of this thesis was to evaluate the cost-effectiveness of a protocol for TB diagnosis in PLHIV in Brazil. To achieve this aim, four specific objectives were covered:

- To perform a review of the literature to evaluate gaps in costing studies and economic evaluations addressing TB/HIV co-infection
- To estimate the costs of PLHIV with or without active or latent TB, from the symptomatic phase until the first year of treatment from the perspective of the Brazilian public health system;
- To estimate direct and indirect costs of TB/HIV and LTBI/HIV co-infection from the patient perspective during the pre-diagnosis and treatment period;
- To perform an interim analysis of a pragmatic clinical trial in Brazil to assess the cost-effectiveness of a protocol for TB diagnosis in PLHIV.

The next section summarises the overall findings from the thesis, limitations of the studies and further research raised, addressing each research paper individually.

7.2 Overall findings and main contributions of the thesis

The Brazilian National Plan to end TB (National Plan) launched in 2017 establishes three goals to be achieved by 2035: (1) reduce TB incidence; (2) reduce TB deaths and (3) avoid catastrophic costs faced by patients and families. The aim is for these goals to be achieved through the development of three pillars: (1) prevention and integrated care for TB patients; (2) bold policies and supportive systems; (3) innovation and research intensification. TB/HIV co-infection is clearly addressed in the first pillar, but the actions in (2) and (3) are also indirectly linked to the co-infection. The first pillar highlights four action points: (1) early TB diagnosis, universal offer of sputum culture, sensitivity, and rapid tests; (2) timely and correct treatment of all TB cases; (3) intensification of collaborative TB/HIV activities and (4) intensification of TB prevention. The second pillar also has four action points: (1) ensure the offer of prevention activities; (2) strengthen actions to guarantee human rights; (3) strengthen the participation of civil society and (4) improve the quality of the national information system. Finally, the third pillar has two action points: (1) establish partnerships to promote public health research in the country and (2) promote the introduction of strategies and policies to improve TB control [48]. The results provided by this thesis can guide, directly or indirectly, the three pillars of the National Plan. The next paragraphs will summarise the main findings and the individual contributions of each research paper to the National TB policy.

Research paper 1. Cost of tuberculosis diagnosis and treatment in HIV patients: a systematic literature review

This systematic review included 34 articles with 24 addressing costs to treat TB/HIV co-infection and 10 addressing TB diagnosis in HIV patients. Most of the studies were carried out in high TB/HIV burden countries (82%), mainly in the African region (59%). From the health system perspective, the mean cost of TB diagnosis per positive result varied from 4 USD to 348 USD in high TB/HIV burden countries. Additionally, the mean cost to treat TB/HIV hospitalised patients in low/medium TB/HIV burden countries was higher when compared with high TB/HIV burden countries (75,407 USD *vs* 2,474 USD). From the patient perspective, the mean direct cost of TB/HIV co-infection was similar during the pre-diagnosis and treatment period, 313 USD and 278 USD, respectively in high TB/HIV burden countries. Also, the indirect cost was higher in the treatment period than the pre-diagnosis period, 314 USD *vs* 147 USD.

The systematic review found only one study conducted in Brazil. It addressed the cost of different methods of sputum culture for TB diagnosis in PLHIV and it was published in 2008. This shows the need to strengthen the third pillar of the National Plan: "innovation and research intensification", including the dissemination and use of research results and introduction of new technologies for TB diagnosis and treatment of active and latent infection.

Sputum smear microscopy and culture are still the main technologies adopted in the country for TB diagnosis in PLHIV. As described in previous chapters of the thesis, these methods have low accuracy in PLHIV. Preliminary data from the Brazilian National Disease Notification System (Sistema Nacional de Agravos de Notificacao - SINAN) showed that 6,800 PLHIV were reported to have TB in 2015. Other data from SINAN showed that the proportion of deaths due to TB was higher in PLHIV when compared with HIV negative patients (5.2% *vs* 2.4%). However, these numbers may be even higher if we consider undiagnosed TB cases, which are still common in PLHIV. The assessment of new technologies is therefore paramount for the success of the National Plan.

The gene Xpert has been introduced and disseminated in the country but no recent study evaluating the cost of this technology in PLHIV has been found. This scenario shows the urgent need for costing studies addressing TB diagnosis in PLHIV in the national context. These studies must address gene Xpert and other new technologies being recommended by WHO to increase the accuracy of extra pulmonary TB diagnosis, such as LF-LAM assay.

The lack of costing studies addressing TB/HIV and LTBI/HIV treatment from the patient and public health system perspective is also an issue tackled in the third pillar of the National Plan. The strategy to introduce new technologies for the treatment of active and latent infection may be supported by economic evaluations. It is important to highlight that Brazil is a country with a continental dimension and huge regional differences in the epidemiological profile of TB/HIV co-infection. Thus, the introduction or scaling-up of interventions should consider the health care and laboratory infra-structure available, the strength of collaborative TB/HIV activities and the political will in each state of the country. Also, the third goal of the National Plan, which advocates the avoidance of catastrophic costs borne by families, will be harder to achieve without understanding and knowledge of the out-of-pocket expenditures and indirect costs faced by TB/HIV co-infected patients and their families.

This systematic review thus contributes to summarising the (lack) of published information available in the country (and similar settings) and pointing to the need to produce more

evidence on interventions to diagnose and treat TB/HIV co-infected patients – to which the whole thesis contributes.

Research paper 2. The economic burden of HIV and TB/HIV co-infection in a middle-income country: a costing analysis alongside a pragmatic clinical trial in Brazil

The study analysed the cost of 239 PLHIV, 26 of whom had TB co-infection and five LTBI/HIV. Compared with the HIV/AIDS category, TB/HIV co-infected patients presented higher rates of hospitalisation (pre-diagnosis: 42% *vs* 8%; treatment period: 77% *vs* 19%) and were seen more frequently at emergency care (pre-diagnosis: 81% *vs* 41%; treatment period: 73% *vs* 59%); arrived at CPH for the first appointment with lower CD4 count (>200 cells/µl: 12% *vs* 7%), and had a higher rate of life style vulnerability (alcohol dependence: 31 *vs* 9%; use of crack: 15% *vs* 2%). Furthermore, the length of hospitalisation and proportion of death (31% *vs* 6%) was higher among the TB/HIV group than the HIV/AIDS category. TB/HIV co-infected patients presented higher costs in all types of care (emergency, inpatient and outpatient care) when compared with HIV/AIDS and LTBI/HIV. This difference was more pronounced in inpatient care during the treatment period when the mean cost per TB/HIV was 1.5 times higher than the mean cost of HIV/AIDS. LTBI/HIV patients presented the lowest mean costs in all types of care. Analysing the cost per disease category, TB/HIV co-infected patients presented the highest mean cost during the entire pathway of care, especially the category TB/HIV death, whose total mean cost was three times the cost of AIDS death. The total median cost for the TB/HIV category was almost six times higher than the HIV or AIDS category (US$ 6,039 *vs* US$ 1,080).

The results of this study reinforce the need for actions targeting the first pillar of the National Plan: “Prevention and integrated care for TB patients”. The fourth action point of this pillar recommends surveillance of latent infection, introduction of new technologies to diagnose and treat LTBI and scale-up of IPT. In this study, TB/HIV patients imposed a high economic burden on the public health system in Brazil, whilst LTBI/HIV patients presented the lowest costs of all disease categories in the entire pathway of care.

Although the WHO recommendation to offer IPT to all PLHIV who active TB was ruled-out, the Brazilian MoH recommended that IPT be offered only to those patients with TST≥ 5mm or who had been in recent contact with TB patients. Therefore, IPT was offered to only five patients during the study period. It represents only 2.3% of all eligible patients, if we consider

the WHO recommendation. The country also faced a shortfall of TST for more than one year due to problems in the supply chain of the test. During this period, the MoH recommended IPT for vulnerable individuals (eg prisoners), patients with low CD4 count (≤ 350 cells/μL), patients with detectable viral load and patients who had had previous contact with TB patients [163]. However, the lack of TST supply seems to have impaired the offer of IPT. At CPH, the main referral service in the city of Recife, only one patient received the treatment during the shortfall period. The low-cost TST has been used for more than 100 years and it is the main technology available in the country for the diagnosis of latent infection.

In addition, and despite Brazilian MoH claims that there is a lack of evidence about the accuracy and cost-effectiveness of other tests, such as gama-interferon (IGRAs), in order to give IPT to patients, [164]an alternative would be to produce and scale-up IPT to all PLHIV in the country, regardless of TST result. This would also avoid shortages of medication. Besides the prevention of TB cases, which is important to stop the chain of TB transmission, IPT can avert further expenditure in the treatment of TB/HIV co-infection.

Other findings of this costing study also address the first pillar of the National Plan in its first and second action points: "Early TB diagnosis" and "Timely and correct treatment". The study found worse outcomes in the TB/HIV category (i.e. more hospitalisations and deaths) and more deteriorated health status in those patients that came for their first visit to the health service (low CD4 count). These findings are very likely to be linked with delay in TB diagnosis. The challenge is to increase the coverage of the gene Xpert test as a point of care and active case finding to increase the chance of early diagnosis and timely treatment.

The focus on vulnerable patients is also a relevant point since those patients represented an important proportion of TB/HIV patients. These patients usually have more difficulty in accessing health care and concluding long-term treatment. These actions are key to achieving the National Plan goal of reducing TB deaths.

Research paper 3. The economic burden of tuberculosis and latent tuberculosis in People Living with HIV in Brazil: a cost study from the patient perspective

Among 239 PLHIV included during the first year of the pragmatic clinical, 26 were diagnosed and treated for TB/HIV and five were given IPT during follow-up. TB/HIV patients incurred higher total costs than LTBI/HIV in both the pre-diagnosis and treatment periods (pre-

diagnosis: US$ 589 *vs* US$ 39; treatment: US$ 840 *vs* US$ 127). The main cost component for TB/HIV was indirect costs (US$ 1,071 in total), especially income loss (US$ 749). The main cost component for LTBI/HIV was direct non-medical costs in the pre-diagnosis period (US$ 19) and direct medical costs during the treatment period (US$ 64). Although our study has not showed any statistically significant difference in catastrophic costs between hospitalised and non-hospitalised for a number of different categories of variables in a stratified analysis, the proportion of all patients facing catastrophic costs was relatively high (48%), with 54% of TB/HIV patients facing these costs. In conclusion, the high costs faced by TB/HIV co-infected patients are potentially a barrier to reducing TB incidence and death among PLHIV.

This is the first costing study conducted from the patient perspective addressing TB/HIV co-infection in the country. The study is directly linked to the third goal of the National Plan and with the global target to end catastrophic costs due to TB for patients and families. Furthermore, WHO has recommended data collection on costs and evaluation of catastrophic costs faced by TB patients and their households through periodic surveys[15]Although we have collected data on patients' average monthly income, we have not explored the sources of declared income by patients. Furthermore, a good proportion of patients were not employed in the formal market which makes collection of data on annual household income and assessment of catastrophic costs even more challenging. However, the study is an important approach to understanding the dynamics of direct and indirect costs involved in the diagnosis and care of TB/HIV co-infection. Although the Brazilian Health System provides free access to medication, tests and professional care for patients affected by TB/HIV, it is clear that the care provided is not enough to prevent patients from facing catastrophic costs, especially due to indirect costs.

The study points out for the need for policies to prevent high costs for TB/HIV patients. Social protection has been discussed as a pathway to reduce high relative costs faced by patients. Devereux and Sabates-Wheeler (2004) show three areas where social protection [f]can act: social assistance, social services, social insurance and social equity. The authors also define the main targets of social protection programmes: extremely poor individuals and households and groups who need special care and access to basic services [165]. Studies conducted in middle income countries, including Brazil, have shown a direct impact of cash transfer[g] policies on

[f] Range of policies directed to people facing risks and adversities, with the objective of achieving poverty reduction and sustainable and inclusive economic growth [165].

[g] Form of social protection based on the conditional or unconditional provision of cash to vulnerable people. For the conditional cash transfer recipients may adopt a specific behaviour, such as education or health actions, to be able to receive the payment [179].

reducing TB incidence and mortality, improving treatment compliance and TB cure and mitigating costs [166–169]. One challenge is the production of scientific evidence on effectiveness and cost-effectiveness of different schemes of social protection for TB/HIV patients [167].

Research paper 4. Cost-effectiveness of a protocol for TB diagnosis in people living with HIV in Brazil: an interim analysis of two years of a pragmatic clinical trial

The analysis used the same cohort as the costing study to evaluate the cost per DALY of a protocol for TB diagnosis in PLHIV. Patients in the intervention arm were more likely to have a positive TB screening at admission or during the follow-up period than patients in the control arm (65% *vs* 23%). There were more cases of TB/HIV co-infected patients diagnosed and treated in the intervention arm than in the control arm (12% *vs* 9%). Furthermore, five patients received IPT in the intervention arm, whilst in the control arm this treatment was not offered. There was a lower proportion of TB hospitalisations (58% *vs* 86%) and deaths (8% *vs* 10%) in the intervention arm than in the control arm. The mean cost of TB/LTBI diagnosis was higher in the intervention group than in the control for screening (+) TB/HIV patients (US$ 141 *vs* US$136) and HIV/AIDS (US$90 *vs* US$72) and for screening negative TB/HIV patients (US$306 *vs* US$166). In the treatment pathway, the control group presented higher costs in almost all categories, screening positive TB/HIV patients (US$ 9,163 *vs* US$ 3,589), screening negative TB/HIV (US$7,298 *vs* US$1,624) and HIV/AIDS (US$1,400 *vs* US$990). When compared with the current practice, the protocol saved US$1,963 and averted 0.4 DALYs. Thus, the protocol for TB diagnosis in PLHIV was considered cost saving compared with the hospital routine. The PSA confirmed the robustness of the model and the acceptability curve shows a 99% probability of the protocol being cost-effective at a willingness to pay threshold of US$8,538.6 (Brazilian GDP per capita). In conclusion, the cost-effectiveness analysis performed through a decision-analysis model suggests the protocol for TB diagnosis in PLHIV, comprising screening by clinical algorithm at every patient appointment at the health service and supplementary TB investigation with gene Xpert, SSM, SC and CXR, is a cost saving intervention compared with routine hospital care from the public health system perspective in Brazil.

The modelling study also complements the pillars and action points established by the National Plan to end TB. The study shows a cost saving intervention which is aligned with several strategies proposed in the National Plan: expanded access to rapid tests; use of Xpert; promoted

prevention and integrated care through offering IPT and providing an early TB diagnosis and timely treatment; intensified TB case finding in PLHIV through the introduction of screening based on a clinical algorithm with further investigation of patients with positive screening; intensified collaborative TB and HIV activities through the investigation of TB in PLHIV at every appointment.

The study was also a way to promote partnership between academic institutions and the health service. All steps of the trial were discussed with key stakeholders of the health service and preliminary results were communicated regularly. The positive and robust findings generated in this preliminary analysis are encouraging, and might be source of evidence to support the use of the protocol in routine health service care.

7.3 Limitations

The main limitation of the systematic review addressing cost of TB diagnosis and treatment in PLHIV (Research paper 1) is that the search of papers was limited to the English, Portuguese and Spanish languages, and had not included grey literature. Thus, the comprehensiveness of the review was limited. Other limitations not linked to the study design, but to the findings, are likely to restrict the generalisability of the review: (1) variation in the methodological rigour evidenced by the quality assessment of the papers; (2) variation in the methodological approaches applied to measure similar costs, which can generate variation in the results; (3) exclusion of a considerable number of studies (N = 33) because they did not present disaggregated findings (did not separate TB outcomes for diagnosis and treatment of PLHIV); (4) concentration of studies in the African region, almost 60% of all studies included in the review; (5) lack of studies in 29 high TB/HIV burden countries. All these limitations should be addressed in further economic evaluations. Thus, more robust cost estimates can be generated and applied in the decision-making process upon the introduction of new technologies or scale-up of the existing ones.

All research papers generated by this thesis, except the systematic literature review, were based on primary data collection in a referral hospital for PLHIV in Brazil. Also, the economic study was conducted alongside a pragmatic clinical trial, which is considered the gold standard for hypothesis testing and has the advantage of being free of selection bias due to the randomisation

process [170]. Although the primary data collection is a strength of the economic evaluation, some limitations are intrinsic to the methodological approaches applied in this study.

Research papers 2, 3 and 4 have methodological limitations due to the use of data from a pragmatic clinical trial. In the study addressing costs of TB/HIV, LTBI/HIV and HIV/AIDS (research paper 2) from the health system perspective, some patients received more expensive tests, for instance gene Xpert in the intervention group. However, some patients in the intervention group had the cost of the treatment reduced because early TB diagnosis resulted in fewer complications, such as hospitalisation. This limitation was evidenced in the modelling study (Research paper 4), when the intervention group presented higher costs during the pre-diagnosis period and lower costs during the treatment period when compared with the routine group. However, the objective of this study was to give a general picture of the costs involved in TB, HIV/AIDS and LTBI diagnosis and care. Additional evidence needs to be generated by taking into account the performance of the gene Xpert test in routine health service practice.

Another limitation of Research paper 2 is the methodological approach used to measure the costs of tests. The price of laboratory tests was collected from the Brazilian MoH database and these values do not represent the full cost of the tests. In order to obtain a more reliable estimate of these costs, a micro-costing approach could have been used. However, the micro-costing approach was not feasible in this case due to the high number of tests received by patients (more than 100) and limitations of time and field staff. To minimise the underestimation of these costs, we added the costs of overheads and staff to the estimates, and the final result was similar to previous estimates conducted in the country. In addition, to deal with uncertainties regarding these estimates, a one-way sensitivity analysis was performed varying all cost components by ± 50%. The results of this analysis did not show any important impact of the item "tests" on the cost estimates for the pre-diagnosis and treatment periods and disease categories.

A final identified limitation of Research paper 2 is the possibility of misdiagnosis of MDR/TB patients. We have not identified or diagnosed any MDR/TB patient during the period of study. The lack of sputum for culture and gene Xpert testing might have contributed for the non-identification of MDR/TB patients. Brazil is considered a high burden MDR/TB country and, like other Latin American country, did not reach the 2015 goals for MDR/TB detection and treatment, which advocated 100% of cases detected and treatment success above 75% [15,154]. Brazil has faced difficulties in the MDR/TB diagnosis, and an increment of only 12% in the

number of cases detected was observed between 2011 and 2015. The proportion of sputum culture performed has increased in the country, but achieved only 38% of new cases detected in 2015 [39]. MDR/TB diagnosis is even more difficult in PLHIV due to the lack of sputum in many of these patients. In those patients, the treatment for MDR/TB starts only after failure of the conventional treatment for drug sensitive TB, after two months, in average. During this time, patients can develop more complications and, consequently, can face longer and more complex treatment, resulting in higher costs from both patients and health system perspective [171]. Advanced methods to diagnosis these patients are thus paramount for the success of policies aimed at reducing TB deaths.

The main limitation of the study addressing costs of TB/HIV and LTBI/HIV from the patient perspective (Research paper 3) is the small size of the study sample, especially for the LTBI/HIV group, which had only five patients. Another limitation was a potential recall bias, especially for the pre-diagnosis period. Recall bias also affected the measurement of costs during the treatment period if there was a long interval between the appointments at CPH and long-term hospitalisation in other health services. The use of diaries would potentially have been an option to deal with this limitation; however, it was unlikely to prove useful for this specific population because of the high proportion of patients with social and life style vulnerabilities, as they are less likely to take notes about the cost of disease using diaries. The study found that literacy was low among the patients (19% illiterate in the TB/HIV group and 9% in the HIV/AIDS group), alcohol dependency was high (31% in the TB/HIV group and 9% in the HIV/AIDS group), as was use of crack (15% in the TB/HIV group and 4% in the HIV/AIDS group) and use of glue (8% in the TB/HIV group and 0% in the HIV/AIDS group). In a recent publication, Sweeney and colleagues (2016) mentioned recall bias as a significant concern in surveys aiming to estimate the impact of disease on poverty. The authors suggested the follow-up of a cohort along the clinical pathway [150]. The cost study presented in this thesis adopted this strategy. The interviews were conducted at every patient appointment at CPH from the beginning of TB/LTBI treatment until patient discharge or death. Thus, the interval between interviews was reduced and, consequently, memory bias was better controlled.

The modelling study (Research paper 4) was an interim analysis of one year of the pragmatic clinical trial. The one year time horizon is one limitation of this study. The final model, expected to be run after the end of the clinical trial, will expand the time horizon.

The limitation regarding the use of macro-costing was discussed previously (research paper 2). Another possible limitation in the model is the non-inclusion of secondary transmission due to the lack of, or delays in, TB diagnosis and treatment. However, there is no consensus in the literature on the inclusion of secondary transmission from TB/HIV patients because these patients are less likely to transmit TB due to the paucibacillary nature of the disease. An additional limitation in the modelling study was the non-inclusion of start-up costs, costs for scaling-up of medical staff to deal with a higher demand for tests and appointments, transportation costs (specimens); quality control maintenance, and calibration costs. As discussed in the limitations for Research paper 2, these costs would be included if a micro-costing approach was adopted. However, the use of this method was not feasible in the current context due to the limitations of field work staff and budget.

7.4 Further research

This thesis, addressing costs and cost-effectiveness of TB diagnosis and treatment in PLHIV, provides significant and timely information for the decision-making process in Brazil. It also raises questions to be addressed in further research. Both the literature and systematic literature reviews (Research paper 1) clearly show a gap in the literature addressing TB/HIV co-infection in Brazil and a concentration of studies in the African region, especially South Africa. In addition, many studies were excluded from the reviews because they did not provide disaggregated information for TB/HIV co-infected patients, although these patients were included in the analysis. Thirty-three studies were excluded from the systematic review because the costs of TB/HIV were presented aggregated with the cost of TB or HIV/AIDS. The review points to the need for generation of cost studies addressing TB/HIV co-infection in a disaggregated manner and in other high burden countries. Future studies also should apply more standardised economic methods to allow generalisability and use of results in the decision-making process.

Research paper 2, addressing costs of LTBI/HIV, TB/HIV and HIV/AIDS form the public health system perspective, indicates that TB/HIV co-infected patients start the treatment in more advance stages of HIV, and therefore are more likely to have complications and higher costs during the treatment of the disease. TB/HIV patients also have high proportion of social and life style vulnerability. Based on these findings, further research should address costs of active TB case finding algorithms in vulnerable populations, such as the homeless and people

living in poverty; cost of more accurate TB diagnosis among PLHIV addressing both pulmonary and extra-pulmonary TB (LF-LAM and new versions of gene Xpert); and cost and budget impact of scaling-up of Xpert as a point of care in specialised care services for PLHIV using a micro-costing approach for the cost study.

Another finding of this study is that IPT is not implemented in the routine treatment of PLHIV and it has not been offered to patients who met the WHO and Brazilian protocol criteria for LTBI treatment. Besides the fact that these patients presented the lowest cost among all categories analysed, prevention of TB is the main alternative to stopping the spread of disease and, consequently, reduce TB incidence. Thus, further research should focus on IPT for PLHIV. Other gaps include the study of costs and budget impact of scaling-up of IPT for the scenario where treatment starts regardless of TST result; cost of new and/or more accurate technologies for LTBI diagnosis, such as IGRAs; and cost of shorter and safer treatment for LTBI to reduce adverse events and treatment abandonment. Brazil also needs to plan and start national surveys to analyse treatment coverage and be in a position to communicate the results internally and to international agencies such as WHO and UNAIDS. One methodology proposed by WHO is the survey of medical records [15], which is not very suitable for the Brazilian context due to the current low quality of this documentation. However, the problem could be overcome by the national plan of computerise all records and integrate patients notes, although this plan has not been completely implemented yet [172].

Research paper 3, addressing the economic burden of TB/HIV co-infection from the patient perspective pointed out that the Brazilian Universal Health System and free access to diagnosis and treatment are not enough to prevent catastrophic costs due to TB/HIV co-infection. WHO has recommended the "monitoring of a proposed post-2015 TB target of no TB-affected family facing catastrophic costs due to TB by 2020"[36]. However, researches produced with Brazilian data have not yet demonstrated enough scientific evidence of catastrophic costs faced by TB/HIV co-infected patients. Results of our stratified analysis indicate that some lifestyle conditions (e.g. alcoholism) and TB status may play an important role in explaining differences in costs between hospitalised and non-hospitalised patients. In fact, most all variables assessed in the stratified analysis could have explained difference in costs between the groups. Due to small sample size, results should be interpreted with caution. Further research is necessary to better understand the role of these confounders in influencing higher costs to patients.

Our study did not assess the association between MDR/TB and catastrophic costs because the latter patients were not included in the trial. The non inclusion of MDR/TB patients in our cohort is a clear limitation for the economic study, as MDR/TB is associated with a higher likelihood of incurring catastrophic costs. The results shown in this thesis indicate that patients are still paying a significant amount of direct and indirect costs related to the diagnosis and treatment of TB/HIV co-infection.

Research paper 3 shows that indirect costs, especially income loss, represent the higher proportion of the total costs faced by patients. This finding reinforces the need for further studies addressing social protection programmes for co-infected patients.

Brazil has a very strong cash transfer programme called "Bolsa Familia[h]". Currently covering 13.9 million families, Bolsa Familia is the largest cash transfer program in the world [173]. Recent studies have shown the positive impact of this program on the outcomes of TB and other neglected diseases in Brazil [167,174]. Also, there is a vast literature addressing social protection for PLHIV in other countries [175,176]. However, the impact of social protection on co-infected patients and the economic impact of the expansion of this programme for TB/HIV patients in vulnerable positions are still to be assessed in the Brazilian context.

Another important issue is to consider the way in which the interventions for TB diagnosis and treatment are delivered to avoid high costs for patients due, for instance, to the need for multiple visits to health care services. In this context, home-based care interventions are more likely to reduce costs from the patient perspective. Also, the way in which interventions are financed should protect TB/HIV patients from out-of-pocket and other expenditure. Therefore, further studies should evaluate the potential for an intervention to lift families from poverty or to prevent families' impoverishment (poverty cases averted). A recent modelling study developed by the TB Modelling and Analysis Consortium has analysed catastrophic health expenditure averted by TB control in India and South Africa (in submission, Vassal et al); thus this kind of analysis is a potential field of research in Brazil.

Research paper 4 "Cost-effectiveness of a protocol for TB diagnosis in people living with HIV in Brazil: an interim analysis of a pragmatic clinical trial" has found encouraging results regarding the benefits of a potential introduction of the protocol in the routine care of PLHIV.

[h] Bolsa Família is a conditional cash transfer programme intended to help families facing poverty or extreme poverty. The programme aims to combat hunger and promote food and nutritional security; to combat poverty and other forms of deprivation in families; to promote access to public services, especially health, education, food security and social assistance

The protocol was cost-saving and averted more DALYs and deaths than routine hospital care. Also, the decision-analysis model adopted seems to be suitable for this type of analysis. Despite the robustness of the decision-analysis model, the study is an interim analysis of the first year of a pragmatic clinical trial. Therefore, further research should consider the final result of this trial and the adoption of larger time horizon, such as the life time of the cohort. Currently, patient recruitment has finished (October/2016) and the trial will follow-up these patients for another year (up to October/2017). The next step is to collect information on the outcomes (screening result, number of deaths, TB cases diagnosed) to populate and run the final model.

Another research question raised by this last research paper, is the affordability of implementing the protocol at the national level, taking into account different epidemiological profiles and health service organisation. Future analyses should consider the resource requirements to adapt and implement the protocol at national level, considering the scaling-up of IPT, as discussed before, and improvement of the laboratory infrastructure to deal with an increase demand for gene Xpert tests for PLHIV.

The inclusion of constraints (from the demand and supply side) is another challenge for health economic evaluations, especially in middle and low-income countries. Constraints can be related to budget, health system, policy or information [177]. In a recent publication, Vassall and colleagues recommend the incorporation of demand[i] and supply[j] constraints in economic evaluations addressing TB diagnosis in middle and low-income countries. The authors argue that constraints can interfere with the entire pathway of TB diagnosis and care and give some examples of demand constraints, such as distance to facility, ability to pay, knowledge of symptoms and ability to adhere to treatment; and supply constraints, such as staff and supplies availability, provider knowledge of guidelines and clinical skills and provider behaviour (i.e. adherence to guidelines) [178]. It was possible to identify demand and supply constraints in both the cost and cost-effectiveness studies presented in this thesis. On the supply side, low availability of IPT (only five patients performing IPT) and shortfall of TST were observed during the study period. On the demand side low knowledge of symptoms (TB/HIV patients arriving for the first appointment in advanced stages of HIV) was observed. All these elements

[i] Factors that restrict the ability of an individual in seeking and using healthcare services in order to maximise the individual's utility

[j] Factors that restrict the ability of a supplier in providing efficient services with sufficient coverage and quality in order to achieve an optimal impact

of constraint should certainly be considered in further economic evaluations and in the introduction of the protocol or other interventions at national level.

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APPENDIX

Clinical Trial Protocol

Title: The impact on mortality and the cost- effectiveness of implanting a protocol for the diagnosis and treatment of tuberculosis in people living with HIV

Coordinators:

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Summary

The aim of this research is to investigate the impact on mortality and the incremental cost-effectiveness ratio of adopting a standardized protocol for the investigation of tuberculosis (TB) in PLHIV. If, as expected, the study indicates a reduction in mortality, this protocol may then be implemented in all HIV/AIDS referral units within the Brazilian Unified Health System (SUS), thus strengthening guidelines for controlling these two conditions.

Since 2012, the World Health Organization (WHO) has recommended the initiation of concurrent antiretroviral therapy (ART) and TB treatment, based on evidence that this procedure reduces mortality in patients with both diseases. The diagnosis of pulmonary TB is strongly dependent on the sputum smear test, which has a low sensitivity in PLHIV. As a consequence, this may lead to a delay in diagnosing TB, and therefore results in missed opportunities to initiate treatment. This has led to the suggestion that empirical treatment for TB, that is, without bacteriological confirmation, is necessary in some circumstances, given the existing limitations for the diagnosis of smear-negative pulmonary TB in PLHIV and the high rates of mortality amongst this population. The proposal presented herein is to conduct a pragmatic clinical trial, with individual randomization, at the Correia Picanço Hospital, an HIV referral centre in the state of Pernambuco. Patients allocated to the intervention group will be investigated for TB from their first appointment within the health service, based on the presence of at least one of the four clinical symptoms (cough, fever, night sweats and weight loss), as recommended by WHO. Those with suspected smear-negative TB will follow a clinical protocol of systematized investigation, the result of which could be empirical treatment for TB. Those patients allocated to the comparison group (control) will be referred for appointments with the attending doctors according to routine practice within the health service. The primary

outcome being studied is mortality: the mortality rate of PLHIV who initiated empirical treatment in the intervention and control groups. Amongst the secondary (intermediate) outcomes is the proportion of patients diagnosed with confirmed and suspected TB (without bacteriological confirmation) and TB treatment outcomes (cure and abandonment) of confirmed and suspected TB in the intervention and control groups.

Furthermore, an economic study will be conducted through an analysis of incremental cost-effectiveness. In this analysis, the additional costs incurred by introducing a new strategy for investigating TB on the first appointment at the HIV referral service following a systematised clinical protocol (early diagnosis of tuberculosis), together with the additional health results (decreased mortality, increased detection of TB in PLHIV) will be calculated using the ratio between the cost of the new strategy minus the cost of the existing strategy and the result of the new health strategy minus the result of the existing health strategy.

Rationale and justification for implementing the project and its application to the Brazilian unified health system (SUS):

The widespread use of ART has led to a decline in the mortality rate of people living with HIV/AIDS (WHO, 2011), although mortality rates are still very high when compared to the general population (Ewing, 2008 ; Lohse, 2007). The mortality of PLHIV is higher in developing countries than in developed countries (Braitstein, 2006), especially during the first year of using ART (Marazzi, 2008; Lawn, 2008; Braitstein, 2006). Many of these deaths in patients with advanced immunosuppression are attributed to undiagnosed and therefore, untreated TB (Lawn, 2011).

TB is the leading cause of HIV-related deaths worldwide (Lawn, 2011; WHO, 2010; Grinsztejn, 2009; Corbett, 2006; López-Gatell, 2008) and TB patients infected with HIV present higher mortality rates than those not infected with HIV (WHO, 2011; CDC, 2007). In 2009, TB accounted for 24% of estimated HIV-related mortality (WHO, 2011). Mortality due to TB in PLHIV could well be an obstacle for achieving the global target of halving TB mortality by 2015, as set by WHO in 2010.

The concomitant initiation of antiretroviral therapy and treatment for TB has proven effective in reducing mortality in patients with both diseases in observational studies (Manosuthi, 2006; Sanguanwongse, 2008; Velasco, 2009) and in controlled clinical trials (Karim, 2010), and has been recommended by WHO since 2010 (WHO, 2010). However, difficulties have been

encountered in establishing criteria for suspected and confirmed TB, especially in patients with severe immunosuppression.

Population surveys and autopsy studies have shown that a substantial number of TB cases in PLHIV remains undiagnosed (Bradshaw, 2004; Lawn, 2008), as recently confirmed by a study that encountered a high prevalence of TB in PLHIV at their first appointment to initiate ART at an HIV referral service (Hanifa, 2012).

In developing countries, the diagnosis of pulmonary TB is strongly dependent on the sputum smear test, which has little sensitivity for PLHIV, who often present smear-negative pulmonary and/or extrapulmonary TB (Hanifa, 2012; Getahun, 2007) resulting in treatment delay or no treatment for TB (Harries, 2011). This evidence has led to the suggestion of introducing empirical treatment, i.e. TB treatment without microbiological confirmation in order to reduce mortality from undiagnosed tuberculosis in this population (Lawn, 2011). Recently, a meta-analysis of observational studies was undertaken to identify a set of symptoms for investigating TB in PLHIV. The combination of cough of any duration, fever, night sweats and weight loss presented a sensitivity of 78.9%. Abnormal findings in chest X-rays increased the sensitivity by 11% (Getahun, 2011). Furthermore, a recent WHO publication recommended that HIV-infected adults and adolescents, for whom the disease had been excluded and who presented either a positive or unknown tuberculin skin test (TST), should receive 300 mg daily dose of isoniazid for at least six months, irrespective of the degree of immunosuppression and whether they had previously been treated for TB (WHO, 2011).

In a recent cohort study (still unpublished) conducted by the team of the present research project in HIV referral services in Recife, a mortality rate of 4.6 per 100 person-years was reported among PLHIV with presumptive smear-negative pulmonary TB, corresponding to a 50% increase in the general mortality of individuals in the cohort. Although there are recommendations from national and international health organizations for investigating active and latent TB (Mycobacterium tuberculosis infection without clinical disease) in HIV/AIDS referral centres, a cross-sectional study of PLHIV treated at two HIV referral services in the State of Pernambuco indicated that only 47.5% of the indicated individuals underwent the tuberculin skin tests (TST) (Moura, 2011). Of these, 20.4% presented a positive TST. In the absence of sputum smear-positive examination, currently, TB investigations and treatment are conducted non-systematically at the decision of the attending doctor, and often at a late stage.

The mean time from clinical suspicion of TB until initiating treatment is almost six months (unpublished data).

Evidence demonstrates that systematically investigating TB in PLHIV from the very first appointment at the health service may increase the proportion of diagnosed individuals and those receiving specific treatment for TB (Hanifa, 2012). With regard to the treatment of latent tuberculosis infection (LTBI), there is a consensus in the literature that treatment reduces the risk of developing TB, as reported by the summarized evidence of a systematic review of clinical trials on this matter (Akolo, 2010).

The aim of the present research project is to investigate the impact of adopting a standardized clinical protocol for investigating TB from the first appointment at the HIV/AIDS referral service and early empirical treatment of TB (without bacteriological confirmation) on the mortality of PLHIV. The study also aims to assess the impact of the standardized protocol on the early diagnosis of presumptive and confirmed TB and LTBI, as well as the incremental cost-effectiveness ratio of the new treatment strategy. The diagnosis of active TB should indicate the initiation of ART regardless of the CD4+ T-cell count, although the initiation of the two treatments should not be simultaneous, in order to prevent adverse effects and to facilitate adherence to the treatment (WHO, 2010).

The study will set out to answer the following research questions: What is the mortality reduction in PLHIV associated with implementing a standardized TB investigation from the first appointment at the health service and the introduction of systematic empirical treatment for smear-negative TB compared to the routine procedures conducted at HIV/AIDS referral centres? Is it cost-effective to implement a screening program with standardized procedures for the investigation and treatment of suspected and confirmed TB?

Objectives and aims to be achieved:

Primary objective:

To compare the mortality rate of PLHIV who are investigated for TB from their first appointment using a standardized protocol, and who present smear-negative TB and initiate empirical TB treatment (intervention) with the mortality rate of PLHIV who are treated within the routine HIV/AIDS referral service and initiate empirical TB treatment (control), and the incremental cost-effectiveness ratio of this protocol from the perspective of SUS and society.

Secondary objectives:

- In PLHIV, to compare the intervention and control groups in relation to:
  The proportion of patients diagnosed with LTBI, bacteriologically confirmed TB and presumptive tuberculosis;
- The proportion of patients receiving treatment for LTBI, for bacteriologically confirmed TB and empirical treatment for TB;
- To estimate the mortality rate in the intervention and control groups according to whether they are receiving treatment for LTBI and confirmed TB;
- To compare the direct and indirect costs of treatment protocols for TB in PLHIV;
- To assess the cost-effectiveness of incorporating protocols that reduce mortality from TB in PLHIV.

Methodology

Study design:

This is a pragmatic clinical trial with individual randomization.

Study location:

The Correia Picanço Hospital (CPH) is the main HIV/AIDS Referral Service in the state of Pernambuco, and is responsible for the care of 50% of all individuals with HIV and AIDS in the state. Currently, the service is responsible for around 5,000 patients, of which approximately 85% use antiretroviral therapy.

Approximately 700 new patients are registered annually, at the ratio of two men per woman. Patients are seen on a basis of outpatients, inpatients and day patients. Outpatient care, exclusively for HIV/AIDS patients, is undertaken by a multidisciplinary team comprised of doctors, nurses, psychologists, social workers, pharmacists, nutritionists and dentists who conduct around 3,000 consultations per month.

Study population:

HIV-infected individuals aged 18 years or over, attended at the Correia Picanço Hospital before initiating antiretroviral therapy.

Exclusion criteria:

Those who are currently undergoing TB treatment or have done so in the last 3 months and those diagnosed with MDR-TB will be excluded.

Recruitment:

Patients will be recruited for the study during their first appointment at the CPH. After receiving an explanation on the purpose of the study and signing the informed consent form (Appendix 1), participants will be invited to answer a questionnaire specifically designed for the study (Appendix 2).

Allocation:

The study population will be randomly allocated to the intervention group and the control group.

Intervention:

The intervention consists of standardized TB investigation, from the first appointment in the health service and empirical treatment for presumptive TB based on the outcome of the investigation. The standardized TB investigation is based on four questions regarding complaints of cough (of any duration), fever, night sweats and weight loss. Those who on the first investigation, report at least one of the four symptoms, will undergo sputum collection (in the presence of sputum) for two smear tests (one performed on the same day and the second on the next), a culture for M. tuberculosis (in the presence of sputum), gene Xpert test (if they have at least 2ml of sputum) and a chest X-ray. Patients who on the initial investigation report any of these symptoms and have at least one positive sputum smear microscopy or Xpert test should start TB treatment defined as confirmed TB.

Patients who, under investigation during the first appointment, report one symptom and present two sputum smear-negative or Xpert tests (or do not present sputum) with abnormalities in the chest X-ray, will receive antibiotic treatment to prevent bacterial pneumonia. If there is no response to antibiotic treatment and after ruling out other opportunistic diseases, they should initiate empirical TB treatment if they meet at least one of the criteria for clinical severity (CD4 <200 cells/mm^3, anaemia and a BMI <18.5 kg/m2). Symptomatic patients with sputum smear or Xpert negative (or without sputum) who present no changes in the chest X-ray should initiate empirical treatment if they meet at least one of the above-mentioned criteria for clinical severity, after ruling out other opportunistic diseases.

Patients who do not present any of the above-mentioned symptoms and who present a TST ≥ 5 mm, should start preventive treatment for TB and will be investigated once again (together with those presenting a TST <5mm) for the presence of TB disease at the next appointment with the same protocol as the first. Antiretroviral therapy should be initiated between two to eight weeks after initiating TB treatment.

Comparison group (control):

Patients in the comparison group will be referred to the attending doctors working within the normal hospital routine. The procedures for TB investigation will be under the responsibility of the attending doctor.

Follow-up:

There will be a follow-up period of one years for patients in both groups and the intermediate and final outcomes will be monitored each six months.

Final outcome:

Mortality rate of PLHIV, from any cause and from TB.

Intermediate outcomes:

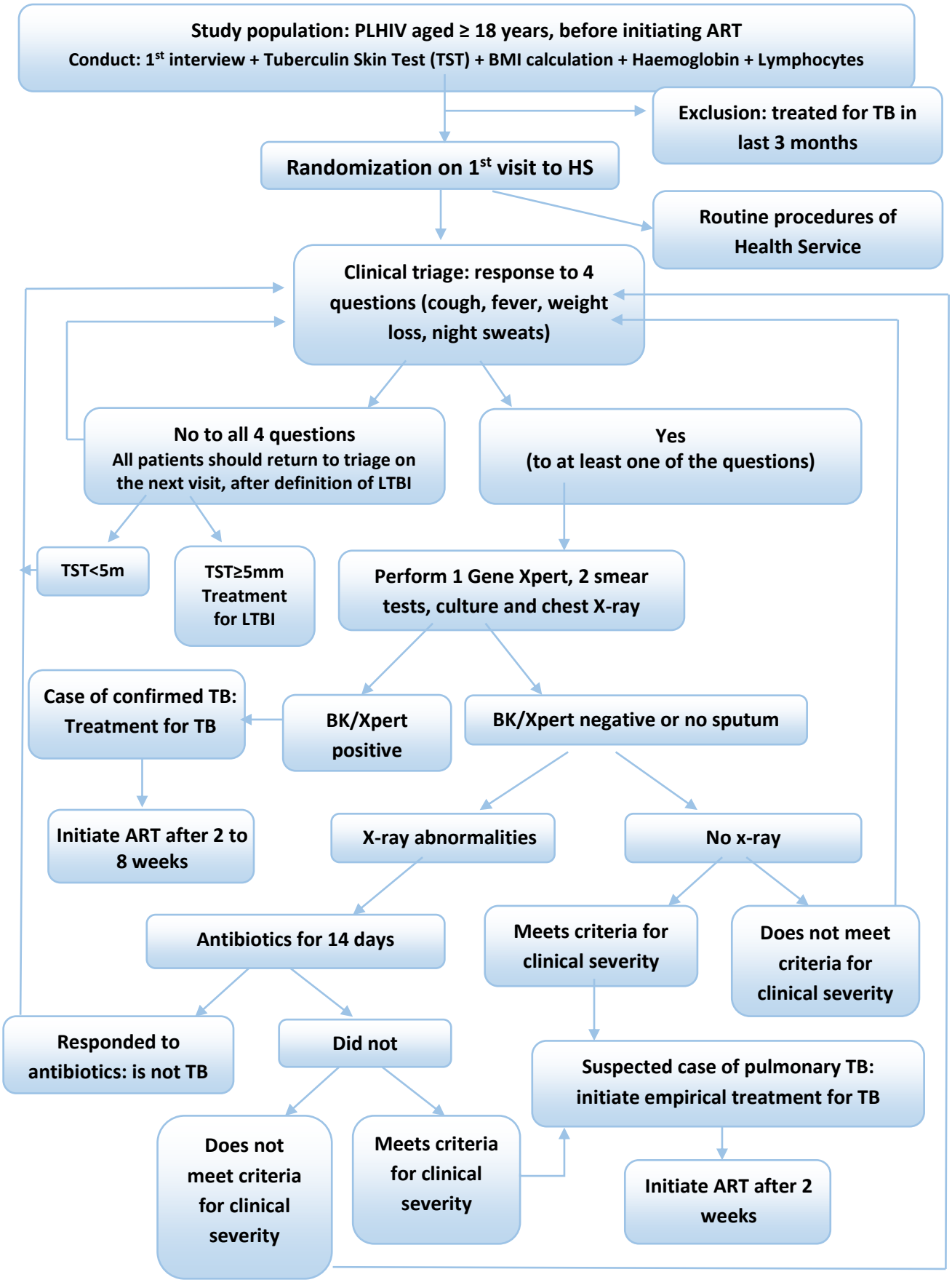
Diagnostic percentages of LTBI, confirmed TB and presumptive TB, treatment outcomes (cure and abandonment) of LTBI, confirmed TB and suspected TB; Proportion completing each of these treatments.

Sample size calculation:

The sample size for the epidemiological study was calculated for the primary analysis and used the mortality rate estimated by a cohort study of TB/HIV co-infected treated in CPH (Maruza, 2012). The sample size was determined using the following parameters:

- Mortality rate in one year (80% survival rate in 400 days): 20%
- Proportion exposed and unexposed: 2:1
- Study power: 80%
- Alpha error: 5%
- Relative Risk (RR) = 0.5 comparing the rate in both groups, reduction of 50% (assumption)

Figure 2. Research flowchart.



Economic assessment

Costs will be collected by means of a specific instrument for this purpose and will be completed by the field team, consecutively to the development of the study. A cost inventory will be drawn up, which consists of a list of all resources required for the deployment and execution of a given healthcare intervention (Haddix, 1996). Direct medical and nonmedical costs and indirect costs will be assessed. Direct costs include the value of all resources and services consumed in providing the intervention or treating adverse effects, as well as any other present or future monetary consequences involved. Indirect costs primarily include gains and losses of productivity of patients related to the intervention (BRAZIL, 2008). Productivity is herein measured in terms of lost days or hours of salary or earnings or losses incurred due to the disease or the control thereof.

Study perspective

The economic analysis will include an assessment of costs within the perspectives of SUS and patients. Estimates are calculated for unit cost of the procedure. Costs will be adjusted for inflation taking into consideration the nation's official rates for the period. An annual discount rate of 5% will be considered for future costs.

Analysis plan:

- **Assessment of mortality**

To estimate and compare the mortality rates of PLHIV with presumptive TB in the intervention and control groups;

To compare the proportion of PLHIV diagnosed with TBLI, bacteriologically confirmed TB and suspected TB, in the intervention and control groups;

To compare the proportion of PLHIV receiving treatment for LTBI, bacteriologically confirmed TB and empirical treatment in the intervention and control groups;

- **Economic assessment**

The cost-effectiveness study will aim to compare two intervention strategies for treating TB in PLHIV. The cost-effectiveness will be assessed of the protocol that recommends the standardized TB investigation at the first appointment and at each visit to the health service

and empirical TB treatment versus the routine procedure within the health service. Death will be the considered outcome.

The economic analysis includes the assessment of costs incurred with the two strategies and the cost-effectiveness from the perspective of SUS and of society. To estimate the effects of empirical treatment for TB in the long term, a mathematical model will be constructed that represents the relevant events of the natural history of the disease, and the effects of interventions. The Markov model will be employed in the present study, where patients may be classified into a specific number of states, which will be defined as parameters of the disease (e.g. severity). The development of a disease and the effects of treatment are represented as the transition from one state to another (Kobelt, 2008). To measure the effects of parameter variations used in the model, a sensitivity analysis will be performed, taking into account different cost scenarios and complication rates.

The incremental cost-effectiveness ratio will be calculated through the following formula:

$$ICER = \frac{C_2 - C_1}{R_2 - R_1}$$

Where ICER = incremental cost-effectiveness ratio; $C_{1,2}$ = cost of first and second intervention; $R_{1,2}$ = health result

Expected results:

- A reduction of the mortality rate in the intervention group that received empirical treatment for TB.
- A reduction of the mortality rate in the intervention group that received treatment for bacteriologically confirmed TB;
- A reduction of the mortality rate in the intervention group that received treatment for LTBI;
- A higher proportion of bacteriologically confirmed TB cases in the intervention group compared to the group routinely investigated in the health services.
- A higher proportion of cases of LTBI in the intervention group compared to the group routinely investigated in the health services.
- Higher cure rates and lower dropout rates of treatment for TB and LTBI in the intervention group compared to the group routinely treated in the health services.

Ethical issues of the project:

The procedures employed in this study are in accordance with Resolution 196 (10th October 1996) of the National Health Council, which is the regulating body for standards and guidelines for research involving humans. The Project will be submitted to the Research Ethics Committee at the Aggeu Magalhaes Research Center, Fiocruz-Pernambuco and London School of Hygiene and Tropical Medicine.

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Methodological, Epidemiological support and Interpretation of results

- Isabella Coimbra

Researcher and Attending Doctor

- Noêmia Teixeira de Siqueira Filha

Researcher in the area of health economics

- Andréia Costa Santos

Researcher in the area of health economics

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Search strategies for the systematic and literature reviews

What is the cost of tuberculosis diagnosis and treatment in HIV patients?

PubMed//Embase/Econlit/ CINAHL plus

1	**cost*.mp.**
2	cost analysis.mp.
3	direct cost*.mp.
4	indirect cost*.mp.
5	cost to treat.mp.
6	cost to diagnosis.mp.
7	tuberculosis.mp.
8	tb.mp.
9	pulmonary tuberculosis.mp.
10	pulmonary TB.mp.
11	sputum smear negative.mp.
12	sputum negative.mp.
13	smear negative.mp.
14	smear negative tb.mp.
15	afb negative.mp.
16	negative for afb.mp.
17	abacillary.mp.
18	hiv.mp.
19	human immunodeficiency virus.mp.
20	aids.mp.
21	people living with hiv.mp.
22	acquired immunodeficiency syndrome.mp.
23	acquired immunodeficiency syndrome.mp.
24	coinfection.mp.
25	coinfected patients.mp.
26	hiv infected patients.mp.
27	"Review"/
28	1 or 2 or 3 or 4 or 5 or 6
29	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
30	18 or 19 or 21 or 22 or 23 or 24 or 25 or 26
31	28 and 29 and 30
32	31 not 27

LILACS

(cost$ OR cost$evaluation OR health$care$costs OR cost$analysis) AND (mycobacterium$tuberculosis OR tuberculosis OR tuberculosis$symptoms OR TB OR sputum$smear$negative) AND (HIV$ OR acquired$immunodeficiency$syndrome OR aids OR co$infection OR (human AND immunodeficiency AND virus) OR (people AND living AND HIV)

(1) What is the cost-effectiveness of TB diagnosis algorithms in PLHIV?

(2) Which modelling approaches are applied in cost-effectiveness studies addressing TB diagnosis in PLHIV?

Medline/Embase/Econlit

1 **cost*.mp.**
2 cost analysis.mp.
3 cost effectiveness analysis.mp.
4 incremental cost effectiveness analysis.mp.
5 direct cost*.mp.
6 indirect cost*.mp.
7 economic evaluation.mp.
8 health economics.mp.
9 cost to treat.mp.
10 cost to diagnosis.mp.
11 health technology evaluation.mp.
12 diagnos*.mp.
13 sputum smear.mp.
14 sputum culture.mp.
15 sputum smear microscopy.mp.
16 chest radiography.mp.
17 chest x ray.mp.
18 xray.mp.
19 xpert.mp.
20 gene xpert.mp.
21 xpert mtb rif.mp.
22 clinical algorithm.mp.
23 algorithm*.mp.
24 systematic investigation.mp.
25 pcr.mp.
26 point of care.mp.
27 current practice.mp.
28 tb screening.mp.
29 tb case finding.mp.
30 treat*.mp.
31 empirical treatment.mp.
32 presumptive treatment.mp.
33 urine antigen.mp.
34 tuberculosis.mp.
35 tb.mp.
36 pulmonary tuberculosis.mp.

37 pulmonary TB.mp.
38 sputum smear negative.mp.
39 sputum negative.mp.
40 smear negative.mp.
41 smear negative tb.mp.
42 afb negative.mp.
43 negative for afb.mp.
44 abacillary.mp.
45 hiv.mp.
46 human immunodeficiency virus.mp.
47 aids.mp.
48 people living with hiv.mp.
49 acquired immuno deficiency syndrome.mp.
50 acquired immunodeficiency syndrome.mp.
51 coinfection.mp.
52 coinfected patients.mp.
53 hiv infected patients.mp.
54 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
55 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
56 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
57 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
58 54 and 55 and 56 and 57
59 "Review"/
60 58 not 59

LILACS

(cost$ OR (cost AND effectiveness) OR cost$evaluation OR health$care$costs OR cost$analysis) AND (mycobacterium$tuberculosis OR tuberculosis OR tuberculosis$symptoms OR TB OR sputum$smear$negative) AND (HIV$ OR acquired$immunodeficiency$syndrome OR aids OR co$infection OR (human AND immunodeficiency AND virus) OR (people AND living AND HIV) AND (diagnos$ OR screen$ OR treat$)

Informed consent form

Research: Cost-effectiveness of a protocol for tuberculosis diagnosis in People Living with HIV. An economic study alongside a pragmatic clinical trial in Brazil

Principal investigator: Noemia Teixeira de Siqueira Filha

About this consent form

Please read this form carefully. It gives you important information about a research study. If you have any questions about the research or about this form, please ask us. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a copy of this form to be kept by you.

Purpose and Description

The purpose of this study is to estimate the direct and indirect costs for patients, families and the health system of diagnosis and treatment for TB in PLHIV. Also, we will analyse the cost-effectiveness of a protocol for TB diagnosis in PLHIV. To do that, you will be invited to answer a questionnaire to inform us about some aspects of your disease and all expenditures incurred by you and your family due to the tuberculosis. The process takes about one hour and you do not need to perform any experimental procedures. You will be interviewed every three months to give us information about costs incurred during the course of the disease until your discharge. We will ask you about treatment, visits to ambulatory and admission to hospital. If you were admitted to hospital we would like permission to consult your notes to find out about your hospital stay including the investigations that were made to identify problems and the treatment you received.

All the information you give us will be entirely confidential. All questionnaires will receive a code and data will not be identified by any personal details. The list of names and codes will be kept locked securely at the FIOCRUZ and LSHTM and be accessed only by myself, the principal investigator. No names will be used on any paper or electronic records. No one will be identifiable in research reports or publications. The findings of this study will be available for all participants on the FIOCRUZ web site.

Taking part in the study is entirely voluntary and will not affect your treatment in any way. We do however hope that greater understanding of the disease will contribute to decisions about ways of improving the diagnosis of tuberculosis in the future.

If you have any queries relating to the questionnaire or on any aspect of the study please ring Noemia Teixeira de Siqueira Filha at FIOCRUZ- Centro de Pesquisa Aggeu Magalhaes, Av. Prof. Morais Rego - Cidade Universitária Recife - PE, 50670-420, Brazil (81) 2101-2500.

Many thanks for your attention. We do hope you will agree to participate in the project.

Noemia Teixeira de Siqueira Filha

Principal investigator of the economic study

<u>Consent form to participate in study</u>: Cost-effectiveness of a protocol for tuberculosis diagnosis in People Living with HIV. An economic study alongside a pragmatic clinical trial in Brazil

- I have read the information about the study and understand why it is being undertaken.
- I understand that all questionnaires will be coded and no identification details will be available either on paper or electronic records.
- I agree that if I have been in hospital the study team would like my permission to access my hospital records to find out how long I was in hospital, the tests that were undertaken and the treatments that were given.
- I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
- I understand that my details will be treated in strictest confidence and kept securely.
- I agree to participate in the study.
- I agree to details of my hospital stay being obtained from my hospital notes.

Signed …… Date ……..

Patient's details

Title …… First Name…… Surname ……

Address…… Postcode ……

Telephone number Home ……..…….. Mobile…….

If you are answering the questionnaire on behalf of the patient please state your name and address and relationship to patient (please tick):

☐ Parent

☐ Next of kin, friend and carer of a patient able to give consent but not able to answer the questionnaire

☐ Other (please specify): _____

Title …… First Name…… Surname ……

Address…… Postcode ……

Telephone number Home ……..…….. Mobile…….

Questionnaires

Questionnaire 1 - Pre-diagnosis period

Information about the TB treatment

Patients' information

Q01 Date: / /

Q02 Interviewer`s name: _____

Q03 Patient's name: _____

Q04 Gender: 1. M 2. F

Q05 Research number: _____

Q06 Medical record: _____

Q07 Address: _____

Q08 Telephone number: _____

Q09 Profession: _____

Q10 Individual income: _____

Q11 Family income: _____

Q12 Schooling: _____

Q13 Is the patient answering the questionnaire? If so, go to question Q16. 1. Yes 2. No

Q14 If not, what is your relationship with the patient? _____ 9. NA

Q15 You are answering this questionnaire in on behalf of the patient because he/she is 1. Weak 2. Illiterate 3. Other: _____ 9. NA

Current TB treatment – information collected from the medical record

Q16 Type of TB 1. Active TB 2. Presumptive TB 3. Latent TB

Q17 Estimated treatment time: 1. (6 months) 2. (8 months) 3. Other:

Q18 Treatment schemes (drugs): _____

Q19 Current phase: 1. Intensive 2. Maintenance 9. NA

Q20 Start date of TB investigation (sputum smear microscopy, chest x ray, other): / /

TB signs and symptoms

Q21 Which symptoms did you present? 1. Cough 2. Fever 3. Night sweats 4. Weight loss 5. Other: _____

Q22 When did these symptoms start? /

Q23 Tests performed: 1. Sputum smear 2. Sputum culture 3. Chest X-ray 4. Xpert 5. PPD 6. Other: _____

Q24 Date of starting the TB treatment: /

Q25 Days / months elapsed between onset of symptoms and initiation of treatment:

Appointment at Emergency care

Q26 Have you visit the emergency care since the beginning of the symptoms? If not go to Q44.1. Yes 2. No

Q27 If so, how many times? _____ 9. NA

Q28 How did you get to the service? 1. Walking 2. Car 3. Bus 4. Moto 5. Taxi 6. Other: _____ 9. NA

Q29 How long did you take to (minutes/hours):

Item	Time spent								
	1ª Visit	2ª Visit	3ª Visit	4ª Visit	5ª Visit	6ª Visit	7ª Visit	8ª Visit	9ª Visit
Get to the service									
Waiting for the appointment or during the appointment									
Go back home									
Total									

Q30 Did you have any tests at the service? If not, go to Q32. 1. Yes 2. No 9. NA

Q31 If so, which tests?

Tests*	Quantity

* Covered by SUS

Q32 Did you use any medication at the service? If not, go to Q34. 1. Yes 2. No 9. NA

Q33 If so, which medications

Medication *	Dosage	Quantity

* Covered by SUS

Q34 Did you lose working time due to the appointment? If not go to Q37. 1. Yes 2. No 9. NA

Q35 If so, how much time did you lose? _____ 9. NA

Q36 Was there a deduction in your salary due to your appointment? 1. Yes 2. No 9. NA

Q37 Did someone accompany you to the service? If not, go to Q41. 1. Yes 2. No 9. NA

Q38 If so, did she/he lose working time? If not, go to Q41. 1. Yes 2. No 9. NA

Q39 If so, how much time did she/he lose? _____ 9. NA

Q40 Was there a deduction in her/his salary due to your appointment? 1. Yes 2. No 9. NA

Q41 Did you miss school due to the appointment? If not, go to Q43. 1. Yes 2. No 9. NA

Q42 If so, how many school days did you miss? _____ 9. NA

Q43 Summary of costs due to the appointment at the service

Item	Cost								
	1ª Visit	2ª Visit	3ª Visit	4ª Visit	5ª Visit	6ª Visit	7ª Visit	8ª Visit	9ª Visit
Transport									
Meal									
Lodging									
Caregiver									
Deduction in salary – patient									
Deduction in salary – family member									
Medicines *									
Tests *									
Other									
Total									

* Paid by the patient/family member

Hospitalisation

Q44 Have you been <u>hospitalised</u> since the beginning of the TB symptoms? If not, go to Q63. 1. Yes 2. No

Q45 If so, where? _____

Q46 How many days did you stay in the hospital? _____ 9. NA

Q47 How did you get to the service? 1. Walking 2. Car 3. Bus 4. Moto 5. Taxi 6. Other: _____ 9. NA

Q48 How long did you take to (minutes/hours):

Item	Time spent								
	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª
Get to the service									
Go back home									
Total									

Q49 Did you have any tests during the hospitalisation? If not, go to Q51. 1. Yes 2. No 9. NA

Q50 If so, which tests (**Information collected from the medical record**)?

Tests*	Quantity

* Covered by SUS

Q51 Did you use any medication during the hospitalisation? If not, go to Q53. 1. Yes 2. No 9. NA

Q52 If so, which medications (**Information collected from the medical record**)?

Medication *	Dosage	Quantity

* Covered by SUS

Q53 Did you lose working time due to the hospitalisation? If not go to Q56. 1. Yes 2. No 9. NA

Q55 If so, how much time did you lose? _____ 9. NA

Q55 Was there a deduction in your salary due to your hospitalisation? 1. Yes 2. No 9. NA

Q56 Did someone accompany you during the hospitalisation? If not, go to Q60. 1. Yes 2. No 9. NA

Q57 If so, did she/he lose working time? If not, go to Q60. 1. Yes 2. No 9. NA

Q58 If so, how much time did she/he lose? _____ 9. NA

Q59 Was there a deduction in her/his salary due to your hospitalisation? 1. Yes 2. No

Q60 Did you miss school due to the hospitalisation? If not go to Q62. 1. Yes 2. No 9. NA

Q61 If so, how many school days did you miss? _____ 9. NA

Q62 Summary of costs due to the Hospitalisation

Item	Cost								
	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª
Transport									
Meal									
Lodging									
Caregiver									
Deduction in salary – patient									
Deduction in salary – family member									
Medicines *									
Tests *									
Other									
Total									

* Paid by the patient/family member

Outpatient care

Q63 How many times have you visited <u>outpatient care</u> since the beginning of the symptoms? _____

Q64 How did you get the service? 1. Walking 2. Car 3. Bus 4. Moto 5. Taxi 6. Other: _____ 9. NA

Q65 How long did you take to (minutes/hours):

Item	Time spent								
	1ª Visit	2ª Visit	3ª Visit	4ª Visit	5ª Visit	6ª Visit	7ª Visit	8ª Visit	9ª Visit
Get to the service									
Waiting for the appointment or during the appointment									
Go back home									
Total									

Q66 Did you have any tests at the service? If not, go to Q68. 1. Yes 2. No

Q67 If so, which tests?

Tests*	Quantity

* Covered by SUS

Q68 Did you use any medication at the service? If not, go to Q70. 1. Yes 2. No

Q69 If so, which medications

Medication *	Dosage	Quantity

* Covered by SUS

Q70 Did you lose working time due to the appointment? If not go to Q73. 1. Yes 2. No

Q71 If so, how much time did you lose? _____ 9. NA

Q72 Was there a deduction in your salary due to your appointment?1. Yes 2. No 9. NA

Q73 Did someone accompany you to the service? If not, go to Q77. 1. Yes 2. No 9. NA

Q74 If so, did she/he lose working time? If not, go to Q77. 1. Yes 2. No 9. NA

Q75 If so, how much time did she/he lose? _____ 9. NA

Q76 Was there a deduction in her/his salary due to your appointment? 1. Yes 2. No 9. NA

Q77 Did you miss school due to the appointment? If not, go to Q79. 1. Yes 2. No 9. NA

Q78 If so, how many school days did you miss? _____ 9. NA

Q79 Summary of costs due to the appointment at the service

Item	Cost								
	1ª Visit	2ª Visit	3ª Visit	4ª Visit	5ª Visit	6ª Visit	7ª Visit	8ª Visit	9ª Visit
Transport									
Meal									
Lodging									
Caregiver									
Deduction in salary – patient									
Deduction in salary – family member									
Medicines *									
Tests *									
Other									
Total									

* Paid by the patient/family member

Other costs

Q80 How many days were you away from your job due to the disease? _____

Q81 During this time were you away from

Q81a Paid work: 1. Yes 2. No

Q81b School: 1. Yes 2. No

Q81c Leisure: 1. Yes 2. No

Q82 Did you need a caregiver or a family member to look after you? If not, go to Q85. 1. Yes 2. No

Q83 If so, she/he lose working time? If not, go to Q85. 1. Yes 2. No 9. NA

Q84 If so, how much time did she/he lose? _____ 9. NA

Q85 Summary of other costs during the pre-diagnosis period

Item*	Cost
Transport	
Meal	
Lodging	
Caregiver	
Deduction in salary – patient	
Deduction in salary – family member	
Medicines *	
Tests *	
Other	
Total	

* Paid by the patient/family member

Q86 Next appointment: _____

Q87 Doctor: _____

Q88 Comments: _____

_____

_____

Questionnaire 2 - Treatment period

Patients' information

Q01 Date: / /

Q02 Interviewer`s name: _____

Q03 Patient's name: _____

Q04 Research number: _____

Q05 Medical record: _____

Q06 Is the patient answering the questionnaire? If so, go to question Q9. 1. Yes 2. No

Q07 If not, what is your relationship with the patient? _____ 9. NA

Q08 You are answering this questionnaire in on behalf of the patient because he/she is 1. Weak 2. Illiterate 3. Other: _____ 9. NA

Information about the TB treatment

Appointment at Emergency care

Q9 Have you visited emergency care since your last interview? If not go to Q28. 1. Yes 2. No

Q10 If so, how many times? _____ 9. NA

Q11 How did you get to the service? 1. Walking 2. Car 3. Bus 4. Moto 5. Taxi 6. Other: _____ 9. NA

Q12 How long did you take to (minutes/hours):

Item	Time spent								
	1ª Visit	2ª Visit	3ª Visit	4ª Visit	5ª Visit	6ª Visit	7ª Visit	8ª Visit	9ª Visit
Get to the service									
Waiting for the appointment or during the appointment									
Go back home									
Total									

Q13 Did you have any tests at the service? If not, go to Q15. 1. Yes 2. No 9. NA

Q14 If so, which tests?

Tests*	Quantity

* Covered by SUS

Q15 Did you use any medication at the service? If not, go to Q17. 1. Yes 2. No 9. NA

Q16 If so, which medications

Medication *	Dosage	Quantity

* Covered by SUS

Q17 Did you lose working time due to the appointment? If not go to Q20. 1. Yes 2. No 9. NA

Q18 If so, how much time did you lose? _____ 9. NA

Q19 Was there a deduction in your salary due to your appointment? 1. Yes 2. No 9. NA

Q20 Did someone accompany you to the service? If not, go to Q24. 1. Yes 2. No 9. NA

Q21 If so, did she/he lose working time? If not, go to Q24. 1. Yes 2. No 9. NA

Q22 If so, how much time did she/he lose? _____ 9. NA

Q23 Was there a deduction in her/his salary due to your appointment? 1. Yes 2. No 9. NA

Q24 Did you miss school due to the appointment? If not, go to Q26. 1. Yes 2. No 9. NA

Q25 If so, how many school days did you miss? _____ 9. NA

Q26 Summary of costs due to the appointment at the service

Item	Cost								
	1ª Visit	2ª Visit	3ª Visit	4ª Visit	5ª Visit	6ª Visit	7ª Visit	8ª Visit	9ª Visit
Transport									
Meal									
Lodging									
Caregiver									
Deduction in salary – patient									
Deduction in salary – family member									
Medicines *									
Tests *									
Other									
Total									

* Paid by the patient/family member

Hospitalisation

Q28 Have you been hospitalised since your last interview? If not, go to Q47. 1. Yes 2. No

Q29 If so, where? _____

Q30 How many days did you stay in the hospital? _____ 9. NA

Q31 How did you get to the service? 1. Walking 2. Car 3. Bus 4. Moto 5. Taxi 6. Other: _____ 9. NA

Q32 How long did you take to (minutes/hours):

Item	Time spent								
	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª
Get to the service									
Go back home									
Total									

Q33 Did you have any tests during the hospitalisation? If not, go to Q35. 1. Yes 2. No 9. NA

Q34 If so, which tests (**Information collected from the medical record**)?

Tests*	Quantity

* Covered by SUS

Q35 Did you use any medication during the hospitalisation? If not, go to Q37. 1. Yes 2. No 9. NA

Q36 If so, which medications (**Information collected from the medical record**)?

Medication *	Dosage	Quantity

* Covered by SUS

Q37 Did you lose working time due to the hospitalisation? If not go to Q40. 1. Yes 2. No 9. NA

Q38 If so, how much time did you lose? _____ 9. NA

Q39 Was there a deduction in your salary due to your hospitalisation? 1. Yes 2. No 9. NA

Q40 Did someone accompany you during the hospitalisation? If not, go to Q44. 1. Yes 2. No 9. NA

Q41 If so, she/he lose working time? If not, go to Q44. 1. Yes 2. No 9. NA

Q42 If so, how much time did she/he lose? _____ 9. NA

Q43 Was there a deduction in her/his salary due to your hospitalisation? 1. Yes 2. No

Q44 Did you miss school due to the hospitalisation? If not go to Q46. 1. Yes 2. No 9. NA

Q45 If so, how many school days did you miss? _____ 9. NA

Q46 Summary of costs due to the Hospitalisation

Item	Cost								
	1ª	2ª	3ª	4ª	5ª	6ª	7ª	8ª	9ª
Transport									
Meal									
Lodging									
Caregiver									
Deduction in salary – patient									
Deduction in salary – family member									
Medicines *									
Tests *									
Other									
Total									

* Paid by the patient/family member

Outpatient care

Q47 How many times have you visited outpatient care since your last interview? _____

Q48 How did you get to the service? 1. Walking 2. Car 3. Bus 4. Moto 5. Taxi 6. Other: _____ 9. NA

Q49 How long did you take to (minutes/hours):

Item	Time spent								
	1ª Visit	2ª Visit	3ª Visit	4ª Visit	5ª Visit	6ª Visit	7ª Visit	8ª Visit	9ª Visit
Get to the service									
Waiting for the appointment or during the appointment									
Go back home									
Total									

Q50 Did you have any tests at the service? If not, go to Q52. 1. Yes 2. No

Q51 If so, which tests?

Tests*	Quantity

* Covered by SUS

Q52 Did you use any medication at the service? If not, go to Q54. 1. Yes 2. No

Q53 If so, which medications

Medication *	Dosage	Quantity

* Covered by SUS

Q54 Did you lose working time due to the appointment? If not go to Q57. 1. Yes 2. No

Q55 If so, how much time did you lose? _____ 9. NA

Q56 Was there a deduction in your salary due to your appointment?1. Yes 2. No 9. NA

Q57 Did someone accompany you to the service? If not, go to Q61. 1. Yes 2. No 9. NA

Q58 If so, did she/he lose working time? If not, go to Q61. 1. Yes 2. No 9. NA

Q59 If so, how much time did she/he lose? _____ 9. NA

Q60 Was there a deduction in her/his salary due to your appointment? 1. Yes 2. No 9. NA

Q61 Did you miss school due to the appointment? If not, go to Q63. 1. Yes 2. No 9. NA

Q62 If so, how many school days did you miss? _____ 9. NA

Q63 Summary of costs due to the appointment at the service

Item	Cost								
	1ª Visit	2ª Visit	3ª Visit	4ª Visit	5ª Visit	6ª Visit	7ª Visit	8ª Visit	9ª Visit
Transport									
Meal									
Lodging									
Caregiver									
Deduction in salary – patient									
Deduction in salary – family member									
Medicines *									
Tests *									
Other									
Total									

* Paid by the patient/family member

Other costs

Q64 How many days were you away from your job due to the disease? _____

Q65 During this time were you away from

Q65a Paid work: 1. Yes 2. No

Q65b School: 1. Yes 2. No

Q65c Leisure: 1. Yes 2. No

Q66 Did you need a caregiver or a family member to look after you? If not, go to Q85. 1. Yes 2. No

Q67 If so, she/he lose working time? If not, go to Q85. 1. Yes 2. No 9. NA

Q68 If so, how much time did she/he lose? _____ 9. NA

Q69 Summary of other costs during the pre-diagnosis period

Item*	Cost
Transport	
Meal	
Lodging	
Caregiver	
Discount on salary – patient	
Discount on salary – family member	
Medicines *	
Tests *	
Other	
Total	

* Paid by the patient/family member

Q70 Next appointment: _____

Q71 Doctor: _____

Q72 Comments: _____

_____

_____