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Title: Cost of tuberculosis diagnosis and treatment in HIV patients: a systematic literature review

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Running title: Systematic review of TB costs in HIV infected

Author 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.

Abstract

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. We include cost, cost-effectiveness and cost-utility studies that reported primary costing data, conducted worldwide and published between 1990 and August 2016. We retrieved papers in PubMed, EMBASE, EconLit, CINAHL plus, and LILACS databases. The quality assessment was performed using two guidelines, “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 hospitalisation and treatment. We analysed the data per level of TB/HIV endemicity and perspective of analysis. We included 34 articles, 24 addressing TB/HIV treatment and 10 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 USD 0.5 for sputum smear microscopy to USD 175 for intensified case finding. The cost of TB/HIV hospitalisation were higher in low/medium burden countries than in high burden countries (USD 75,406 vs USD 2,474). TB/HIV co-infection presented higher costs than TB from the provider perspective (USD 814 vs USD 604 vs USD 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.

1. Introduction

The World Health Organization (WHO) estimates 1.1 billion people worldwide are living with tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection¹. Among HIV patients the prevalence of co-infection can reach approximately 31% in African countries². Although the number of deaths due to TB/HIV co-infection has been falling, TB is still the main cause of death for HIV patients¹. 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 United Nation Sustainable Development Goals³.

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^{4,5}. 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 services⁶⁻⁸. 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.

2. Methodology

This systematic review was designed and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations⁹. A protocol for this review is registered at Prospero – International Prospective Register of Systematic Reviews - CRD42015020730.

2.1 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.

2.2 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.

2.3 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.

2.4 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)”^{10,11}. 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.

2.5 Data analysis

Costs were first inflated to 2015 prices using USD inflation rates¹². Then, costs reported in local currency were converted to US Dollars using exchange rates as reported in the OANDA website¹³. 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 country¹⁴. 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. Results

3.1 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.

3.2 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 ¹⁵.

Among those studies carried out in high burden countries ^{16–24}, we found a variety of algorithms within the diagnostic groups. The ICF category was performed through chest x-ray screening ²⁴; symptom screening plus sputum smear (SS), culture (SC) and chest x-ray (CXR) ¹⁷; symptom screening plus acid-fast bacilli (AFB) smear and PCR; symptom screening plus AFB smear and SC ²²; light-emitting diode microscopy (LED) screening; gene Xpert screening ²⁰; symptom screening plus CXR, AFB smear and SC¹⁸. The sputum culture category was performed using solid media and mycobacteria growth indicator tube (MGIT)²¹. Sputum smear category was performed through LED and Ziehl–Neelsen (ZN) light microscopy²³. Finally, histology, other cultures and smear categories were performed in pleura, pleural fluid, bone marrow, urine and blood¹⁶. 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.

3.3 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, ^{25–27} but one of them provided data only about TB drug costs in HIV patients ²⁶. 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 ²⁵. Koenig 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 USD²⁷. 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 USD²⁸.

Provider perspective:

Thirteen studies reported cost from the provider perspective disaggregated by TB/HIV status^{25-27,29-38}. 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 analysis³⁰. 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)²⁵. 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)³⁴. Another study carried out in South Africa reported the mean cost only for TB/HIV outpatients (2,831 USD)³⁸.

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 countries³⁹⁻⁴². One study carried out in Peru analysed a program for integrated care of TB/HIV patients and found a cost of 817 USD/patient/year⁴¹. Three other studies analysed the costs based on charges, the mean cost of TB/HIV hospitalisation was 75,407 USD^{39,40,42}. 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)⁴⁰. One study carried out in USA, analysed TB/HIV outpatient cost, which was 1,186 USD⁴². 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.^{35,43-48} 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, respectively⁴⁴. 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, respectively⁴³. 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).

3.4 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).

3.4.2 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^{27,43} 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)⁴⁶. 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 illness⁴⁵. Other methods applied local labour cost, minimum wage or average wage rate per day/hour reported by patients to calculate indirect costs^{25-28,48} (Table 4). Tables S2 and S3 in the Supplementary file give the detailed quality assessment of the articles.

4. 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^{15,20}. 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 ^{1,3}.

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 ⁴⁹.

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 ⁵⁰. 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 ⁵¹. 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.

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.

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