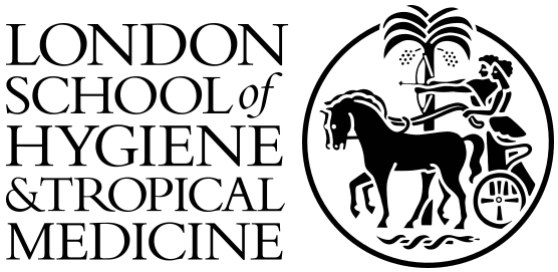

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The economic burden of tuberculosis and latent tuberculosis in People Living with HIV in Brazil: a cost study from the patient perspective.

Introduction

The economic consequences of the vicious cycle of tuberculosis (TB) and poverty in low and middle income countries is 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[1]. This scenario can be even worse for people living with HIV (PLHIV) co-infected with TB. Patients with concurrent diseases can face financial hardship during their diagnosis and treatment. In addition, financial hardship could lead to worse outcomes, such as treatment abandonment and death[2].

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 [2]. Brazil is one of the 30 countries with the highest TB/HIV burden worldwide, and is committed to the goals stated by the WHO and 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 [3]. However, there is a lack of information in the literature addressing costs for TB and Latent TB/HIV (LTB/HIV) co-infection in the country, especially from the patient perspective.

The objective of this study is to evaluate the direct and indirect costs of TB/HIV and LTB/HIV co-infection from the patient perspective from pre-diagnosis to treatment period. This study is the first investigation of patients’ costs involving co-infection in Brazil.

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 sample size for the epidemiological study was calculated using the mortality rate estimated by a cohort study of TB/HIV co-infected patients treated in CPH [4]. The sample size was determined using the following parameters: (1) mortality rate of 20% in one year (80% survival rate in 400 days); (2) study power of 80%; (3) Alpha error of 5%; (4) Relative Risk (RR) of 0.5 comparing the rate in both groups, 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. We also excluded patients 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 LTB, 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 LTB/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/LTB 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 [5]. 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). 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 [6]. 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) [7]. 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 analysis were undertaken in Stata/IC 14. The primary outcome was mean costs per TB/HIV and LTB/HIV patient. We calculated the costs by disease category and period of analysis (pre-diagnosis and treatment period). To test difference in proportions, we used Fisher's exact. We applied Wilcoxon-Mann-Whitney test for non-parametric distribution to check differences in mean and total costs between TB/HIV and LTB/HIV groups. All p-values below 0.05 were considered statistically significant.

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/IV and patients under

LTB/HIV treatment were observed, apart from difference in gender: in the TB/HIV category, the majority of patients were male, whilst most of LTB/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 smoking, alcohol dependence and use of illicit drugs was similar between TB/HIV and LTB/HIV groups (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 LTB/HIV patients ($p = 0.013$). Eight deaths occurred in the TB/HIV group and no death occurred in LTB/HIV group, however, the difference in outcomes between the groups was not statistically significant (Table 2).

The mean cost of treatment period was higher when compared with pre-diagnosis period for both TB/HIV (US$ 840 *vs* US$ 589) and LTB/HIV (US$ 127 *vs* US$ 39). TB/HIV patients incurred higher costs during pre-diagnosis and treatment when compared to LTB/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 LTB/HIV were mainly on direct non-medical costs (50%) and direct medical costs (50%) during pre-diagnosis and treatment period, respectively (figure 1).

Discussion

Our results suggest that patients with TB/HIV co-infection face much higher costs than those being treated as LTB/HIV. In our study, TB/HIV patients incurred almost 9 times higher total costs than LTB/HIV (US$ 1,429 *vs* US$ 169). 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.

International literature on patients costs seem to differ from the Brazilian context. In Cambodia, the mean indirect cost was estimated in US$ 176 and US$ 517 during the pre-diagnosis and treatment, respectively [8]. 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 [9–11]. These figures are relatively lower when compared to the Brazilian estimates. 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 [11,12]. 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 [8,13]. Lower human and infrastructure capital and variations in methodological approaches for cost assessment may explain the difference in results.

Our study has some 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 LTB/HIV group, which had only five 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 [14]. Our study adopted this strategy. The interviews were conducted at every patient appointment at CPH from the beginning of TB/LTB 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 [15]. 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 investigate 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).

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