ABSTRACT

Cryptococcal infection is a frequent cause of mortality in Brazilian HIV-infected patients. The present study aimed to evaluate the cost-effectiveness and budgetary impact of four cryptococcosis screening strategies in HIV-infected patients with CD4+ ≤ 200 cells/mm³, in Brazil. A Monte Carlo microsimulation was used to compare the following diagnostic tests: a systematic serum cryptococcal antigen (CRAG) screening with latex agglutination (CRAG-LA), a lateral flow immunochromatographic test (CRAG-LFA), India ink staining and no intervention. The rationale was that of the Unified Health System (SUS), and the time horizon was of one year for the intervention and of five years for the budgetary impact analysis (BIA). The effectiveness outcomes were years of life and years of life adjusted for quality (QALY). The cost-effectiveness analysis showed that the two cryptococcal antigen tests were cost-effective, presenting with superior results in comparison with India ink and no screening. CRAG-LFA, compared to CRAG-LA, has an incremental cost of US$0.25 and an incremental cost-effectiveness ratio of US$73.36 (considering the US dollar equal to 5 reais, the Brazilian current money). The probabilistic sensitivity analysis between CRAG-LFA and CRAG-LA, despite showing a high agreement between the two tests, indicated the superiority of CRAG-LFA. The BIA estimated that the incorporation of CRAG-LFA would have an additional cost of approximately US$ 10.4 million dollars in five years. These findings suggest that, for the group of studied patients, the adoption of CRAG-LFA and CRAG-LA are cost-effective, while the India ink test and no intervention are less effective strategies. The BIA showed that using the CRAG-LFA test for people living with HIV (PLHIV) with CD4+ ≤ 200 cells/mm³ could reduce costs for the Brazilian Unified Health System (SUS).

KEYWORDS: Cost-benefit analysis. Diagnostic test approval. Cryptococcus. HIV infections.

INTRODUCTION

Cryptococcosis is a systemic mycosis caused by fungi of the genus *Cryptococcus*. The infection typically affects the central nervous system (CNS) and the respiratory tract, commonly presenting as cryptococcal meningitis (CM). HIV infection with a CD4 count below 200 cells/mm³ and the presence of the acquired immunodeficiency syndrome (AIDS) are predisposing conditions for cryptococcosis¹.

CM is associated with about 15% of all HIV deaths. In 2014, a total of 223,100 CM cases led to 181,100 deaths, 75% of which in sub-Saharan Africa, followed by Southeast Asia and Latin America². In Brazil, the cryptococcosis mortality rate is between 45% to 65% regardless of HIV risk factors and the primary
form of the disease. Cryptococcosis occurs as the first opportunistic manifestation in about 4.4% of AIDS cases in Brazil. In addition, patients recovering from cryptococcal meningitis may experience long-term neurological and sensory impairment (≥ 3 months after the diagnosis), resulting in disability and poor quality of life, a tertiary referral hospital to HIV-infected patients serving the São Paulo State, Brazil. All patients were >18 years old without prior cryptococcal meningitis, without clinical suspicion of cryptococcal meningitis, regardless of antiretroviral (ART).

The Unified Health System (SUS) provides different methods for diagnosing Cryptococcosis. The conventional one is the direct examination of slides stained with India ink and the sample’s culture on Sabouraud dextrose agar (SDA). In the case of Cryptococcosis, the India ink method refers to the direct microscopy of the cerebrospinal fluid (CSF), secretions or exudates, subcutaneous aspirate, pus, urine, serum, plasma or blood to visualize yeasts. In contrast, the SDA culture consists of yeast culture for seven days, between 25 °C to 37 °C. Serological techniques can be used to detect antigens (CRAG) or search for antibodies. The latex agglutination test (CRAG-LA) is one of the most frequently used due to its high accuracy along with the lateral flow immunochromatographic test (LFA) the cryptococcal antigen lateral flow assay (CrAg LFA). The CRAG-LFA is a rapid diagnostic test that provides a definitive result in ≤ 10 min. with no need of specialized physical structure. The technique is stable at room temperature and easy to use and interpret results the cryptococcal antigen lateral flow assay (CrAg LFA).

The Brazilian Ministry of Health (MH) Clinical Protocol and Therapeutic Guideline (CPTG) for the treatment of adults with HIV recommends that people living with HIV (PLHIV) should be investigated for fungal etiology in all pneumonia cases in addition to the routinely performed exams. Those who are CRAG-positive and present with CD4 ≤ 100 cells/mm³ are subjected to preemptive treatment with fluconazole and antiretroviral therapy (ART) until they reach CD4 > 200 cells/mm³. The cost-effectiveness of CRAG screening, in either asymptomatic or symptomatic CM patients, has never been evaluated in Brazil.

The primary aim of this study was to model the cost-effectiveness and budget impact of implementing CRAG screening for asymptomatic cryptococcus infections in PLHIV with CD4+ ≤ 200 cells/mm³, in Brazil.

**MATERIALS AND METHODS**

A Monte Carlo analytical decision model assessed the cost-effectiveness ratio and budgetary impact of the screening of PLHIV, over 18 years old, of both genders, infected with cryptococcosis, asymptomatic, with CD4 ≤ 200 cells/mm³, using the following methods as screening strategies: (a) the point-of-care diagnostic test CRAG-LFA, (b) cryptococcus research in CSF with India ink or (c) CRAG-LA in serum, using no intervention as the baseline. Each strategy has its own accuracy value and employs different sample collection methods. This type of analysis records the patient’s history and the transition probabilities depend on the variables involved, allowing great clinical complexity in the development of the model.

The perspective adopted considered the SUS as the funding agency for the services. The horizon for the cost-effectiveness analysis was one year for the intervention, evaluating its impact on the disease’s development for five years, as many patients have life expectancies almost equal to those of people without HIV. A discount rate of 3% per year was applied.

The primary outcomes were years of life and quality-adjusted life years (QALY). Estimates referring to direct medical costs included the identification, measurement and evaluation of the applied resources. A sensitivity analysis assessed the uncertainties of the model.

According to the CPTG for the management of HIV infection in adults, the screening and preemptive treatment strategy for cryptococcosis prevent deaths in individuals with ART CD4+ ≤ 100 cells/mm³. The document highlights patients without clinical manifestations of cryptococcosis but presenting with a test showing positive detection of cryptococcal antigenemia in CSF samples obtained by lumbar puncture (LP), performed to rule out CM. Then, a preemptive treatment with 800 mg fluconazole per day for two weeks and 400 mg fluconazole per day for eight weeks is prescribed and ART will be administered after the first two weeks of antifungal treatment. All individuals with positive plasma or serum tests are investigated for CM using LP. The treatment of positive cases follow these phases: (a) induction, (b) consolidation and (c) maintenance, recommended by the Brazilian consensus and CPTG.

SUS’s reimbursement amounts for different items were used as measures of the abovementioned costs. Procedures and test values were obtained from the Ministry of Health and, when not available, from the Brazilian Hierarchical Classification of Medical Procedures of the Brazilian Medical Association (BMA) in addition to several consultations of studies by Lofgren et al. implementation studies and evaluations of how to integrate CrAg screening programs into existing HIV care infrastructure are lacking. During a CrAg screening program in Kampala, Uganda, we interviewed 15 health care workers (2 coordinating research nurses and 13 clinic personnel and Rajasinghan et al. and CrAg positivity is an independent predictor of
meningitis and death. CrAg screening for patients with advanced HIV and preemptive treatment is recommended by the World Health Organization, though implementation remains limited. Our objective was to evaluate costs and mortality reduction (lives saved Table 1 shows the values adopted for the procedures and treatments.

**Table 1 - Values of procedures, treatments, medications, and tests included in the economic model and other parameters of the model.**

| Procedures/Drugs/Treatment (the reference is no intervention) | Costs (U$S) |
|---------------------------------------------------------------|-------------|
| **Medicines** | **Concentration** | **Unit cost** | **Treatment cost** | **Source** |
| Fluconazole | 150 mg | 0.07 | - | Brasil. Ministério da Saúde12 |
| Fluconazole | 100 mg | 3.14 | - | Brasil. Ministério da Saúde12 |
| **Daily dosage** | **Duration (weeks)** | **Daily cost/patient** | **Treatment cost** | **Source** |
| Preemptive treatment | | | | |
| Fluconazole 800 mg | 2 | 6.56 | 92.00 | Brasil. Ministério da Saúde12 |
| Fluconazole 400 mg | 8 | 3.28 | 184.00 | Brasil. Ministério da Saúde12 |
| CM treatment | | | | |
| Induction phase | | | | |
| Mycoses treatment (code 03.03.01.016-9) | 2 | 23.27 | 325.72 | Brasil. Ministério da Saúde15 |
| Consolidation phase | | | | |
| Fluconazole 600 mg/day | 8 | 0.29 | 17.23 | Brasil. Ministério da Saúde15 |
| Maintenance phase | | | | |
| Fluconazole 200 mg | 48 | 6.28 | 2,293.66 | Brasil. Ministério da Saúde12 |
| **Tests and culture** | **Amount** | **Unit cost** | **Cost / patient** | **Source** |
| CRAG-LFA | 1 | 6.00 | 6.00 | Brasil14 |
| CRAG-LA | | | | |
| Cryptococcus research - latex (code 4.03.09.05-3) | 1 | 0.36 | 0.36 | Associação Médica Brasileira15 |
| Cryptococcus research – India ink (code 4.03.10.10-0) | 1 | 0.14 | 0.14 | Associação Médica Brasileira15 |
| Culture for fungi identification (code 02.02.08.13-7) | 1 | 0.84 | 0.84 | Brasil. Ministério da Saúde13 |
| **Procedures** | **Amount** | **Unit cost** | **Cost / patient** | **Source** |
| Collection of samples for laboratory examination (code 02.01.02.004-1) | 2 | 0 | 0 | Brasil. Ministério da Saúde13 |
| Specialized medical attention (code 03.01.01.007-2) | 2 | 2.00 | 4.00 | Brasil. Ministério da Saúde15 |
| Individuals with CRAG-LA test, India’s ink (LP) | | | | |
| Lumbar puncture (code 02.01.01.063-1) | 1 | 1.41 | | Brasil. Ministério da Saúde15 |
| Induction phase | | | | |
| Mycoses treatment (code 03.03.01.016-9) | 2 | 23.27 | 325.72 | Brasil. Ministério da Saúde15 |
| Consolidation phase | | | | |
| Specialized medical attention (code 03.01.01.007-2) | 2 | 2.00 | 4.00 | Brasil. Ministério da Saúde15 |
| Maintenance phase | | | | |
| CD4 Lymphocyte count (code 02.02.03.002-4) | 2 | 3.00 | 6.00 | Brasil. Ministério da Saúde13 |
| Collection of samples for laboratory examination (code 02.01.02.004-1) | 2 | 0 | 0 | Brasil. Ministério da Saúde13 |
Table 1 - Values of procedures, treatments, medications, and tests included in the economic model and other parameters of the model. (cont.)

| Procedures/Drugs/Treatment (the reference is no intervention) | Costs (U$S) |
|---------------------------------------------------------------|-------------|
| Specialized medical attention (code 03.01.01.0072 -) | 3 | 2.00 | 6.00 |
| Brasil. Ministério da Saúde |

| Parameters | Probability (%) | CI (95%) | Distribution | Source |
|------------|-----------------|----------|--------------|--------|
| Percentage of CD4 ≤ 100 in cryptococcosis | 40 | 30–70 | Rajasingham et al. |
| Percentage CD4 ≤ 200 cells/mm³ in cryptococcosis | 60 | 30–70 | Rajasingham et al. |
| Developed CM after preemptive treatment | 14 | | Meya et al. |
| Died after preemptive treatment | 29.1 | | Meya et al. |
| Developed CM after hospital treatment | 8 | 0–20 | Beta | Meya et al. |
| CRAG+ among those who developed CM | 33 | 25–41 | Beta | Rajasingham et al. |
| CRAG+ among those who developed MC and died | 40 | 34–46 | Beta | Rajasingham et al. |
| CM progression in CRAG+ without preemptive treatment | 70 | 56–82 | Beta | Rajasingham et al. |
| Survived after hospital treatment | 45 | 38–52 | Beta | Ramachandran et al. |
| Developed CM after hospital treatment | 32 | | Ramachandran et al. |
| PLHIV CD4 ≤ 200 cells/mm² CRAG+ asymptomatic with CM | 2.3 | | Meya et al. |
| PLHIV CD4 ≤ 100 cells/mm³ CRAG+ asymptomatic with CM | 8.04 | 5.8–12.6 | Beta | Morawski et al., Meya et al. |
| CM mortality (fatality ratio) | 26–63 | | | Vidal and Boulware |
| Utility | | | | |
| Stable with HIV | 0.95 | 0.8–0.98 | Beta | Miot et al. |
| CM patient (induction phase) | 0.5 | 0.43–0.58 | Beta | Miot et al. |
| Stable with CM (maintenance phase) | 0.8 | 0.68–0.92 | Beta | Miot et al. |
| Cryptococcus accuracy tests | | | | |
| CRAG-LFA | 100 (98-100) | 99 (97-99.4) | | Vidal and Boulware |
| CSF | | | | |
| CRAG-LA | 97.1 (91.9-99.0) | 99.1 (93.8-99.9) | | Temfack et al. |
| India ink | 86.1 | 97.3 | | Nalintya et al., Boullware et al. |
| CSF culture | 95-100 | | | Consensus on cryptococcosis |

CI = confidence interval.

Assumptions

The parameter assumptions was based on prospective CRAG studies and Brazilian consensus4,17-23 with a cohort of HIV-infected patients with CD4 < 100 cells/μL. Primary outcomes were expected costs, DALYs, and incremental cost-effectiveness ratios (ICERs). CRAG-positive individuals (CRAG+) may be asymptomatic and eligible for the preventive treatment with fluconazole in the model. International studies were used11,17-19,24 the prevalence of cryptococcal antigenemia (CrAg+) in the absence of studies on Brazilian population’s quality of life for the outcomes described.

The model did not incorporate the ART treatment7 after using antifungals, the adverse effects resulting from amphotericin, and intracranial hypertension (CH) as a complication of CM. The use of amphotericin B deoxycholate (1 mg/kg/week) and other drugs to replace fluconazole was not considered.

Economic model

Figure 1 presents a schematic representation of the transition states for CM screening and treatment, with two residual states where the patient dies or has predominantly negative CM symptoms. Data from the Vidal et al.5 a tertiary referral hospital to HIV-infected patients serving the São Paulo State, Brazil. All patients were >18 years old without prior cryptoccocal meningitis, without clinical suspicion of cryptoccocal meningitis, regardless of antiretroviral (ART) were used to calibrate the model.

As CM and mortality progression depends on CD4 levels, the target population had two PLHIV subgroups: CD4 ≤ 100 cells/mm³ and CD4 ≤ 200 cells/mm³. For each
subgroup, after screening, those who were CRAG+ undergo preemptive treatment. After this stage, these individuals may or may not progress to CM. Those who developed CM undergo treatment consisting of induction, consolidation and maintenance. After the end of the treatment, those who did not die progress to a state without CM.

All CRAG-negative individuals, considered without CM, could develop meningitis depending on their true or false negative condition. Those who have undergone preemptive treatment could also progress to a CM status at any time, just as anyone who had finished the in-hospital therapy and may have a relapsed or contracted CM again.

Sensitivity analysis

Deterministic and probabilistic sensitivities analyzed uncertainties of the model. The discount rate varied from 0% to 5%, and medical costs were estimated by values found in public purchasing bases.

Patients’ utilities and average medical costs changed in a directly proportional manner. Medical costs are related to SUS’s services and showed similar results among patients, regardless of the therapeutic alternatives. A scatterplot was constructed in the probabilistic sensitivity analysis indicating the option that was most likely to be cost-effective.

Budget impact

The budgetary impact analysis employed the demand method. The use of the CRAG-LFA diagnostic test in SUS was simulated for five years to screen for cryptococcus infection in PLHIV with CD4+ ≤ 200 cells/mm³. The BIA adopted the SUS perspective. The price of the implemented technology was US$ 6 per test. The costs to assess the budgetary impact were as follows: screening – US$ 6, preemptive treatment – US$ 277.8, and meningitis treatment – US$ 2,644.60 dollars. Table 1 shows the costs of the screening and treatments.

In 2021, the Brazilian population was 212,601,219 inhabitants. The HIV cases considered were the mean number of cases in the period from 2018 to 2020 reported to the Notifiable Diseases Information System (SINAN), declared in the Mortality Information System (SIM), and registered in the Control System for Laboratory Examinations of the National Network of CD4+/CD8+ Lymphocyte Count and HIV Viral Load (SISCEL)/Logistics Control System for Medicines (SICLOM).

RESULTS

For the effectiveness measured in years of life, the microsimulation estimated an incremental cost-effectiveness ratio (ICER) that is shown in Table 2.

The cost-effectiveness analysis showed that the two tests, CRAG-LA and CRAG-LFA, are cost-effective, a superior performance in comparison with the India ink and the no evaluation scenario.

As the CRAG-LA and CRAG-LFA tests proved to be cost-effective, a deterministic univariate sensitivity analysis evaluated the accuracy of each of the tests, their sensitivities and specificities (Table 3). The results for sensitivity showed that both tests are no longer cost-effective for values below 0.975. For specificity, this response occurs for CRAG-LFA
above 0.9 and for CRAG-LA with values around 0.99. The price of CRAG-LA was changed to assess its impact in the result. For the same price as CRAG-LFA, of US$ 6 per test, the alternative to use CRAG-LA was superior.

The probabilistic sensitivity analysis between CRAG-LFA and CRAG-LA, although pointing to a high agreement between the two tests, indicated the superiority of CRAG-LFA (Figure 2). In approximately 38% of the cases, this test was superior to the CRAG-LA.

### Budget impact

We would have a total cost for a cohort of 45,000 patients with the hypothesis of all of them treated for meningitis of approximately US$ 34.8 million dollars for five years without screening. Using the measured demand method and a five-year time horizon, an assumed initial market share of 20% for CRAG-LFA, with annual increments of the same amount, reaching 100% in the fifth year, the estimated budget impact resulting from the incorporation...
of the test would have an additional cost of approximately USS 10.5 million dollars. For comparison, the budgetary impact of 100% adoption of screening for asymptomatic PLHIV CD4 ≤ 200 cells/mm³ is a five-year cost savings of USS 11 million dollars in this context.

**DISCUSSION**

The diagnosis and management of cryptococcosis and its outcomes are structural problems in Brazil\(^1,4,5\) and case report of the complex C. neoformans. Com o aparecimento da AIDS,houve expressivo aumento na incidência da criptococose. Posteriormente, o uso de anti-fungicos profiláticos e a introdução da HAART levaram à redução desta incidência. Objetivamos determinar o perfil epidemiológico da meningite criptócica no Estado do Rio de Janeiro no período de 1994 a 2004, com base nos dados da Assessoria de Meningite, setor do Centro de Vigilância Epidemiológica da SSE-RJ e, também, avaliar em que medida o perfil epidemiológico disponível no sistema nacional (SINAN). Our study suggests that, for PLHIV with CD4 ≤ 200 cells/mm³, the incorporation of CRAG-LFA or CRAG-LA in the patients’ screening would be advantageous compared to no screening and the India ink test. Our model predicts a reduction in mortality due to CM in PLHIV CRAG+ CD4 ≤ 200 cells/mm³ by 15%, while costs for 1,000 patients would decrease by USS 11 million dollars in five years compared to no screening.

Ramachandran et al.\(^18\) conducted a study similar to ours in Uganda, Africa. The authors assessed the costs and cost-effectiveness of implementing a CRAG screening for PLHIV in comparison with the usual practice. The CRAG screening was considered highly cost-effective and was associated with an ICER of USS 6.14 per avoided DALY compared to no screening. The implementation cost of CRAG screening was of an additional USS1.52 per person and resulted in a 40% relative reduction in disease-associated mortality. The probabilistic sensitivity analysis showed that the CRAG screening was cost-effective in 100% of the scenarios. A secondary analysis projected a total cost of USS651.454 for the 100% implementation of the screening in the country, preventing 1,228 deaths compared to no screening.

Another study carried out in Cambodia\(^27\) one time systematic serum cryptococcal antigen (CRAG) evaluated the cost-effectiveness of three alternative strategies for preventing cryptococcal infection in HIV-infected patients. Opportunistic cryptococcal infection is endemic in Cambodia and corresponds to a significant public health burden in PLHIV there and in Brazil. Over a one-year horizon, the systematic CRAG screening (for targeted treatment of positive cases) in patients with CD4 ≤ 100 cells/mm³ is more cost-effective for preventing cryptococcosis than the systematic primary prophylaxis strategy.

Tenforde et al.\(^28\) made a cost-effective model of CRAG screening for CRAG+, treatment-naïve patients with CD4 ≤ 100 cells/mm³ and CRAG+ CD4 ≤ 100 cells/mm³ with previous experience of ART in Botswana. The authors estimated that of 650,000 samples submitted to the CD4 test annually, 16,364 would have CD4 ≤ 100 cells/mm³ and would undergo a CRAG test, and 70% of patients reporting previous experience with ART at the time of screening. CRAG screening and preventive treatment in CD4 treatment-naïve patients with ≤ 100 cells/mm³ prevented 20% of MC-related deaths at the cost of USS2 per avoided DALY. The expansion of the preemptive treatment, including patients with previous ART experience and CD4 ≤ 100 cells/mm³, would generated 55 additional cost-avoided deaths with respect to no screening.

The results of the present study deserve to be analyzed carefully. Some limitations are inherent to the modeling process, which can have oversimplified the disease’s progression due to differences in real-world circumstances and the use of more than one treatment, disease complications and adverse drug effects. Different sources of international data were the basis for estimating the transition probability values\(^2,8,16,20\) and we aimed to provide an updated estimate of global incidence of HIV-associated cryptococcal disease. Methods We used 2014 Joint UN Programme on HIV and AIDS estimates of adults (aged >15 years. In the sensitivity analysis, these variables did not affect the results. We have also considered that any CM complication would lead to hospitalization or death, which may not be accurate in all cases. The model did not include effects other than meningitis caused by cryptococcal infections and the adverse effects of treatment.

Unit costs calculated from SIGTAP\(^19\) may be underestimated. Two of the technologies used for comparisons had no prices indicated in the BPS\(^12\), and the 2016 AMB table was used\(^15\), which may be out of date. Still, as the CRAG-LFA was superior than the other two tests, these prices have little influence on the result. In this analysis, we assumed equal hospitalization days for patients who underwent screening with any of the technologies. Because of the lower accuracy of a given method, the duration of admission, risk of readmission, and risk of complications that could prolong hospitalization therefore increasing hospital care costs and duration. The cheapest combination corresponding to the use of fluconazole was adopted on the list of CMED\(^29\) at a maximum price to the
CONCLUSION

An economic evaluation of the Monte Carlo microsimulation estimated the main costs and consequences of the cost-effectiveness analysis and budgetary impact of implementing the CRAG-LFA test for the screening of *Cryptococcus* infection in PLHIV with CD4+ ≤ 200 cells/mm³ in comparison with the CRAG-LA, the India ink, and no screening as the reference, from the perspective of the Brazilian Unified Health System.

Given the results of this study, the CRAG-LFA and CRAG-LA tests are potentially cost-effective to track cryptococcal infections, preventing mortality related to cryptococcal meningitis in PLHIV with CD4 ≤ 200 cells/mm³. India ink and no intervention were inferior strategies. According to the results of the model and the sensitivity analysis, CRAG screening for PLWH with CD4+ ≤ 200 cells/mm³ represents an excellent opportunity to save money with the potential to prevent CM and reduce the corresponding mortality in Brazil. The BIA showed that for a cohort of 45,000 patients without screening, we would have a total cost of approximately US$ 34.8 million dollars in five years. The budgetary impact of the 100% adoption of screening in PLHIV CD4 ≤ 200 cells/mm³ and asymptomatic CM infections would save US$ 11 million dollars in five years.

Finally, a review of epidemiology researches on the consequences of cryptococcal screening in asymptomatic patients highlighted a significant knowledge gap that exist worldwide, especially in Brazil. Now, the paucity of parameters is the main barrier for the development of simulation models that are more compatible with the knowledge accumulated in laboratory practice.

AUTHORS’ CONTRIBUTIONS

CMMV and GBGM participated in the study design; data collection, analysis, interpretation of results and the writing of the manuscript. Both authors read and approved the final version.

CONFLICT OF INTERESTS

None stated by the authors.

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