

Cost-Effectiveness of Serum Cryptococcal Antigen Screening to Prevent Deaths among HIV-Infected Persons with a CD4⁺ Cell Count ≤ 100 Cells/ μ L Who Start HIV Therapy in Resource-Limited Settings

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Background. Cryptococcal meningitis (CM) remains a common AIDS-defining illness in Africa and Asia. Subclinical cryptococcal antigenemia is frequently unmasked with antiretroviral therapy (ART). We sought to define the cost-effectiveness of serum cryptococcal antigen (CRAG) screening to identify persons with subclinical cryptococcosis and the efficacy of preemptive fluconazole therapy.

Methods. There were 609 ART-naive adults with AIDS who started ART in Kampala, Uganda, and who had a serum CRAG prospectively measured during 2004–2006. The number needed to test and treat with a positive CRAG was assessed for ≥ 30 -month outcomes.

Results. In the overall cohort, 50 persons (8.2%) were serum CRAG positive when starting ART. Of 295 people with a CD4⁺ cell count ≤ 100 cells/ μ L and without prior CM, 26 (8.8%; 95% confidence interval [CI], 5.8%–12.6%) were CRAG positive, of whom 21 were promptly treated with fluconazole (200–400 mg) for 2–4 weeks. Clinical CM developed in 3 fluconazole-treated persons, and 30-month survival was 71% (95% CI, 48%–89%). In the 5 CRAG-positive persons with a CD4⁺ cell count ≤ 100 cells/ μ L treated with ART but not fluconazole, all died within 2 months of ART initiation. The number needed to test and treat with CRAG screening and fluconazole to prevent 1 CM case is 11.3 (95% CI, 7.9–17.1) at costs of \$190 (95% CI, \$132–\$287). The number needed to test and treat to save 1 life is 15.9 (95% CI, 11.1–24.0) at costs of \$266 (95% CI, \$185–\$402). The cost per disability-adjusted life year saved is \$21 (95% CI, \$15–\$32).

Conclusions. Integrating CRAG screening into HIV care, specifically targeting people with severe immunosuppression (CD4⁺ cell count ≤ 100 cells/ μ L) should be implemented in treatment programs in resource-limited settings. ART alone is insufficient treatment for CRAG-positive persons.

The global annual burden of cryptococcal meningitis (CM) is estimated at 957,900 cases, resulting in an es-

timated 624,700 deaths within 3 months of cryptococcal infection [1]. Sub-Saharan Africa has the highest burden, with a median incidence of 3.2% among all HIV-infected people, resulting in 720,000 CM cases annually with high mortality of 20%–50% [2–5]. Even with antiretroviral therapy (ART) availability, CM-related mortality remains high [5, 6]. Most cases of CM occur in AIDS patients with advanced immunosuppression. Among patients with CM in Tanzania and Uganda, 80%–90% had a CD4⁺ T cell count ≤ 100 cells/ μ L [4, 5, 7]. Most cases of CM occur in ART-naive persons [8]; however, the unmasking of ART-associated CM within the first weeks is also com-

Received 8 February 2010; accepted 4 May 2010; electronically published 2 July 2010.

Pfizer manufactures and donates fluconazole for use in sub-Saharan Africa via the Pfizer Diflucan Partnership program. Pfizer had no role in any aspect of this project.

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Clinical Infectious Diseases 2010;51(4):000–000

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1058-4838/2010/5104-00XX\$15.00

DOI: 10.1093/cid/cir143

mon. We have previously reported a high incidence of ART-associated CM in patients positive for cryptococcal antigen (CRAG) who are not treated with fluconazole [9].

Early diagnosis and treatment are paramount to reducing CM-related mortality. CM is a subacute meningitis in which the polysaccharide CRAG is detectable in serum a median of 3 weeks prior to onset of clinical symptoms [7, 10]. The subacute nature allows for effective interventions. Methods to prevent this CM-related mortality would include (1) earlier HIV diagnosis and ART initiation prior to AIDS, (2) primary prophylaxis with fluconazole in persons with AIDS, and (3) screening and treatment for occult cryptococcosis. Both earlier ART and primary fluconazole prophylaxis are effective interventions [11–13], yet widespread implementation requires improvements in HIV testing and treatment infrastructure. For those people presenting with already advanced HIV, preventative options are limited.

Despite published data on increased mortality in patients with cryptococcal antigenemia, the utility of serum CRAG testing to identify asymptomatic cryptococcosis and the clinical impact of preemptive fluconazole treatment have not been clearly defined in the ART era [14, 15]. We analyzed the cost-effectiveness of performing routine testing of asymptomatic persons for serum CRAG at time of ART initiation in Uganda, specifically in persons with a CD4⁺ cell count ≤100 cells/μL.

METHODS

Data were collected from a prospective cohort of 609 ART-naive people who initiated ART during the period from 2004 through 2006 at the Infectious Disease Institute in Kampala, Uganda, of whom 559 had been previously clinically described [9]. In brief, ART-eligible adults (≥18 years) were enrolled if they (1) had confirmed HIV-1; (2) had a regular clinic attendance, based on ≥2 clinic visits in the prior 6 months; (3) were stable residence within ≤20 km; (4) had a willingness to exclusively receive HIV care at the clinic for ≥2 years; (5) were eligible for ART according to the World Health Organization (WHO) 2003 guidelines and the National Ministry of Health guidelines (ie, CD4⁺ cell count ≤200 cells/μL or WHO stage IV); and (6) provided informed consent.

The first-line ART regimen prescribed was stavudine or zidovudine, plus lamivudine, and either nevirapine or efavirenz. Daily cotrimoxazole prophylaxis was provided regardless of CD4⁺ cell count. The CD4⁺ cell count was measured every 3 months (Becton Dickinson). At enrollment, study physicians conducted clinical evaluations, including full medical history and physical examination. A qualitative, undiluted serum CRAG was measured at ART initiation regardless of symptoms (Wampole Laboratories). During the 2004–2006 period, no clinic-wide protocol existed for clinical intervention for a positive CRAG in an asymptomatic person, thus intervention de-

pended on physician discretion. Patients were followed for a median of 3.9 years (minimum, 2.5 years). No patients were lost to follow-up. This research was approved by the ethics committees of Makerere University and Uganda National Council for Science and Technology.

We subsequently assessed interventions and patient outcomes within this prospective cohort using chart review. We determined the mean incidence, with 95% confidence interval (CI), of symptomatic CM disease, and we determined the number needed to test and treat prior to ART initiation, to prevent 1 case of CM or 1 death, as well as the costs associated with screening. The number needed to test and treat 1 new case is 1/(CRAG incidence), excluding those cases with prior, pre-ART CM:

$$\text{NNT survival} = \frac{1}{(\text{CRAG incidence}) * (\text{proportion of survival})},$$
$$\text{NNT cost} = \frac{\text{cost per screening test}}{(\text{CRAG incidence}) * (\text{proportion of survival})},$$

where NNT is the number needed to test and treat.

The cost of CRAG testing was calculated on the basis of the current actual cost in Kampala, Uganda. In 2010, the CRAG cost was US\$16.75 at the Makerere University–Johns Hopkins University (MU–JHU) laboratory, a College of American Pathologists (CAP)–certified laboratory in Kampala, Uganda, that adheres to CAP and Good Clinical Laboratory Practice standards for all testing. This CRAG cost is a total cost encompassing reagents (\$5.43/test; 32% of CRAG cost), daily positive-negative quality controls (\$2.72; 16%), laboratory disposable supplies (\$0.95; 6%), labor (\$3.04; 18%), external quality assurance testing (\$0.62; 4%), laboratory overhead (\$3.19; 19%), and margin (\$0.80; 5%). The MU–JHU laboratory is a financially self-sustainable laboratory that is not subsidized from external sources. The laboratory survives solely on testing income to provide world-class laboratory testing in a resource-limited setting. Thus, the cost estimate used was a real-world, actual cost. Nevertheless, this real-world cost may be higher than laboratory costs in other countries. The 2010 CRAG cost in South Africa via the National Health Laboratory System is \$5.61 (33%).

The cost of fluconazole was not included in the model because the average antifungal medicine use was less in the screened and preemptively treated group (2–4 weeks) than in the untreated group, who developed clinical CM requiring longer and more expensive antifungal treatment courses (ie, 2 weeks of amphotericin induction, 8 weeks of fluconazole 400 mg consolidation, and then secondary fluconazole 200 mg prophylaxis). Amphotericin cost (\$17.50/day) is based on 2010 actual Ugandan costs, which are 2-fold higher than 2009 negotiated costs in South Africa.

RESULTS

Patients and CRAG screening. Of 609 HIV-infected adults with a CD4⁺ cell count <200 cells/ μ L, 50 (8.2%) were positive for CRAG (hereafter referred to as CRAG+) when starting HIV therapy (Figure 1). Of the cohort, 418 (69%) were women, and the mean cohort CD4⁺ cell count was 79 cells/ μ L, with 311 (51%) patients having a CD4⁺ cell count \leq 100 cells/ μ L. The median CD4⁺ cell count of CRAG+ persons was 15 cells/ μ L (interquartile range, 4–59 cells/ μ L), which was lower than the overall cohort ($P < .001$). Of 50 CRAG+ persons, 17 had pre-ART diagnosed and treated CM, and they were excluded from analysis of screening; thus, 33 (5.6%) had incident cryptococemia. Of 295 people with a CD4⁺ cell count \leq 100 cells/ μ L and without prior CM, 26 were CRAG+ and were classified as having incident cryptococcal antigenemia (8.8%; 95% CI, 5.8–12.6%). All were relatively asymptomatic, and none had clinical symptoms with regard to meningitis. Fluconazole therapy was given to 21, with doses varying in the range of 200–400 mg for 2–4 weeks duration. Only 3 persons treated with fluconazole developed CM at a median time of 4 weeks during a median follow-up time of 47 months (minimum, 30 months).

Mortality. There were 77 HIV-related deaths in the overall cohort, with 19 (25%) attributed to central nervous system

infections [9]. Eleven people died of known CM, and all were CRAG+ at baseline (7 incident CM and 4 prior CM). Among people without prior CM with a positive CRAG and a CD4⁺ cell count \leq 100 cells/ μ L, the mortality rate was 42% (11/26; 95% CI, 23%–63%). Of 21 persons who received fluconazole therapy, 6 (29%) died during follow-up (Figure 1). Causes of death were CM ($n = 3$), d4T-related lactic acidosis ($n = 1$), putative toxoplasmosis ($n = 1$), or unknown ($n = 1$). Of these 6 persons who died, 2 received fluconazole 400 mg for 2 weeks, and 4 received fluconazole 200 mg for 2 weeks.

For 5 persons with a CD4⁺ cell count \leq 100 cells/ μ L who were treated with ART only (ie, without fluconazole), putative causes of death were CM ($n = 2$), lymphoma ($n = 1$), toxoplasmosis ($n = 1$), or unknown ($n = 1$), all occurring within 2 months of starting ART. Retrospectively, in the absence of imaging studies and biopsy diagnoses, the toxoplasmosis and lymphoma may have been inflammatory intraparenchymal masses due to cryptococcal immune reconstitution inflammatory syndrome; however, consent for postmortem examinations were not given.

Among persons with a CD4⁺ cell count >100 cells/ μ L, the CRAG+ incidence was 2.3% (7/298), excluding 1 person with known prior CM. Of the 7 CRAG+ persons, 6 (86%) survived.

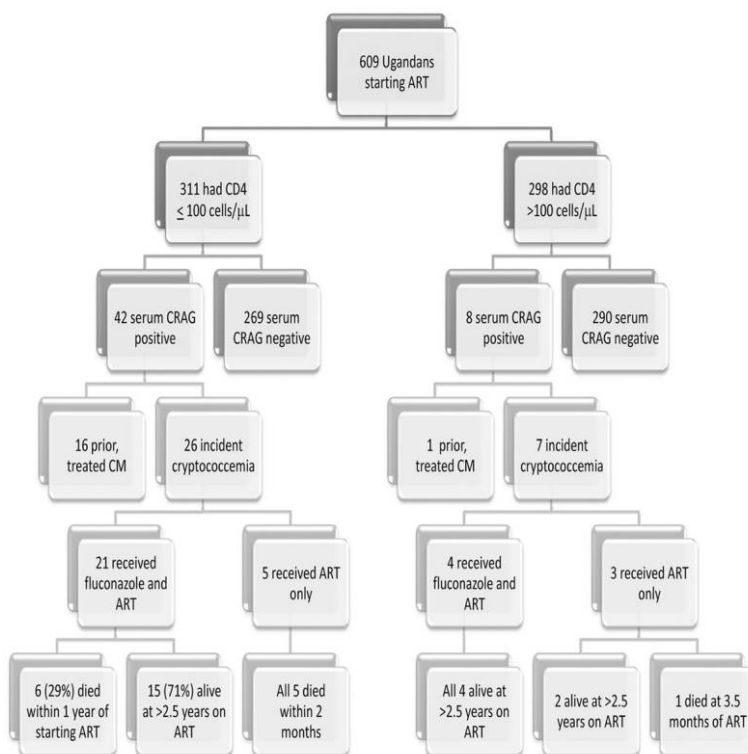


Figure 1. Study profile of HIV-infected persons in a resource-limited setting in Uganda to determine the cost-effectiveness of serum cryptococcal antigen (CRAG) screening to prevent deaths. Of 295 people with a CD4⁺ cell count \leq 100 cells/ μ L without cryptococcal meningitis (CM), 26 (8.8%; 95% confidence interval, 5.8%–12.6%) were positive for serum CRAG prior to initiating antiretroviral therapy (ART).

Of the 6 survivors, 4 received fluconazole, and 2 remained asymptomatic without fluconazole. The 1 person who died did not receive fluconazole. For all people with incident cryptococcal antigenemia, fluconazole use was associated with survival (odds ratio [OR] 9.5; 95% CI, 1.5–60; $P = .017$). The percentage of persons who survived for 3 years without fluconazole therapy was 25% among all incident CRAG+ subjects and 0% among those with a CD4⁺ cell count ≤ 100 cells/ μ L (Figure 2). In a multivariate logistic regression model, fluconazole remained independently associated with survival (OR, 34.6; 95% CI, 1.7–703; $P = .021$) among all 33 subjects with incident CRAG+. Baseline CD4⁺ cell count was loosely associated with >30-month survival with increasing odds for each pre-ART CD4⁺ cell count increase of 25 cells/ μ L above zero (OR, 1.9; 95% CI, 0.96–3.8; $P = .064$). Baseline viral load was associated with mortality in a univariate model ($P = .013$); however, in multivariate regression models, viral load, CD4%, weight, height, body mass index, age, sex, and/or hemoglobin were not predictive of 30-month survival whenever fluconazole use was included in the model.

Cost-effectiveness. Using these outcomes, we performed a cost-effectiveness analysis, excluding the 17 persons with prior known history of cryptococcosis. The analysis determined the number needed to CRAG test and treat with fluconazole to prevent CM and CM-related death. To detect 1 person who was CRAG+, the number needed to test was 11.3 (95% CI, 7.9–17.1) in those with a CD4⁺ cell count ≤ 100 cells/ μ L. To

prevent 1 death, 15.9 people (95% CI, 11.1–24.0 people) would need to be screened and treated to increase survival for 1 person for >30 months on ART.

On the basis of the CRAG cost at a CAP-certified clinical laboratory (\$16.75/test), this translates into \$190 (95% CI, \$132–\$286) to detect 1 asymptomatic person. To save 1 person's life by preemptive fluconazole therapy, the cost is \$266 (95% CI, \$185–\$402) to prevent 1 fatal CM case occurring within 30 months of ART initiation. Assuming an average increase in life expectancy of 12.5 years with ART in Africa [16], we found that this equates to \$21 (95% CI, \$15–\$32) per disability-adjusted life year (DALY) saved. The functional quality of life was normal in survivors with a median Karnofsky performance status of 100 at last follow-up (mean, 96; minimum, 90).

In the absence of CD4⁺ cell count testing, using WHO clinical stage criteria of screening all people with stage III/IV disease or a CD4⁺ cell count <200 cells/ μ L, we found that the cost-benefit ratio was less favorable. For the total cohort, the asymptomatic CRAG positivity was 5.6% (95% CI, 3.9%–7.7%). The number needed to test and treat for CRAG screening to prevent 1 death was 31.5 (95% CI, 22.7–45.4) with a cost of \$527 (95% CI, \$380–\$760) assuming mean fluconazole efficacy (76%) and mean survival without preemptive therapy (25%) among the total cohort. Using WHO clinical stage criteria, we found the cost per DALY saved to be \$42 (95% CI, \$30–\$61). Specifically, the incremental cost of screening persons with a CD4⁺ cell count 101–200 cells/ μ L is associated with a number needed to

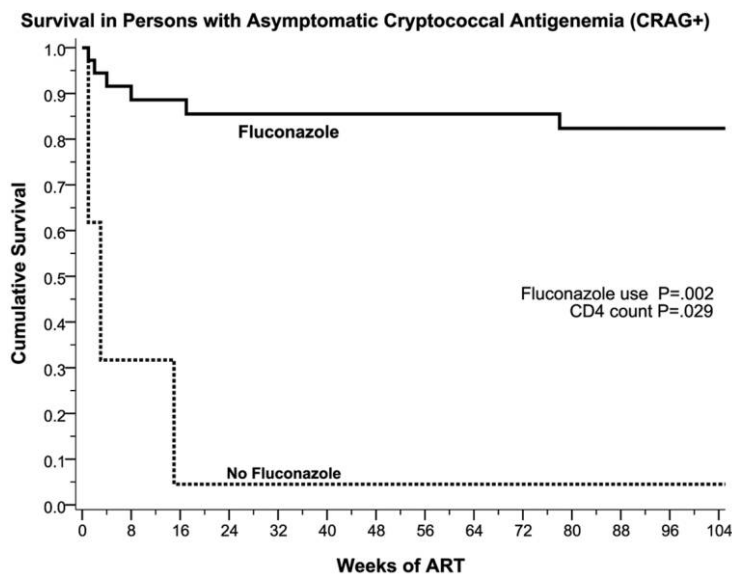


Figure 2. Survival rate of people with asymptomatic cryptococcal antigenemia starting HIV therapy. The Kaplan-Meier curve displays the 2-year survival rates with and without preemptive fluconazole use in 33 asymptomatic people starting HIV antiretroviral therapy (ART) who have tested positive for cryptococcal antigen (CRAG+). Survival curves are adjusted for pre-ART CD4⁺ cell count as a covariate by use of Cox regression. Without the adjustment, the survival rate without fluconazole therapy is 25% in all people and 0% in persons with a CD4⁺ cell count <100 cells/ μ L. No deaths occurred after 2 years, with a median follow-up of 3.9 years on ART. Follow-up was complete, and no persons were right-hand censored.

test and treat of 148 (95% CI, 69–401), with estimated costs of \$2479 (95% CI, \$1153–\$6723) to prevent 1 death.

These estimates do not include the avoidable costs of hospitalization for clinical CM and amphotericin costs (~\$245 for 14 days of amphotericin deoxycholate). Above a CRAG+ prevalence of ~3%, the amphotericin deoxycholate cost for CM treatment becomes exponentially greater than the CRAG screening cost. This does not include the costs of hospitalization and supportive care, which are highly variable by region.

Using mean estimates for survival and effectiveness of fluconazole therapy, we present cost-threshold estimates for screen-

ing in populations with different CRAG+ prevalence (Figure 3). For example, in populations with a CRAG prevalence of $\geq 4.7\%$, the cost of CRAG screening when starting ART is $\leq \$500$ to prevent 1 death and is \$40 per DALY. Conversely, in this scenario, if health systems chose not to implement CRAG screening, ~\$1150 in amphotericin costs would accrue with worse survival outcomes.

Economies of scale for CRAG testing. Our 2010 CRAG testing cost was \$16.75; however, this is based on the actual volume of 3–5 CRAG tests per day at the MU-JHU laboratory in Uganda. A previously published Centers for Disease Control

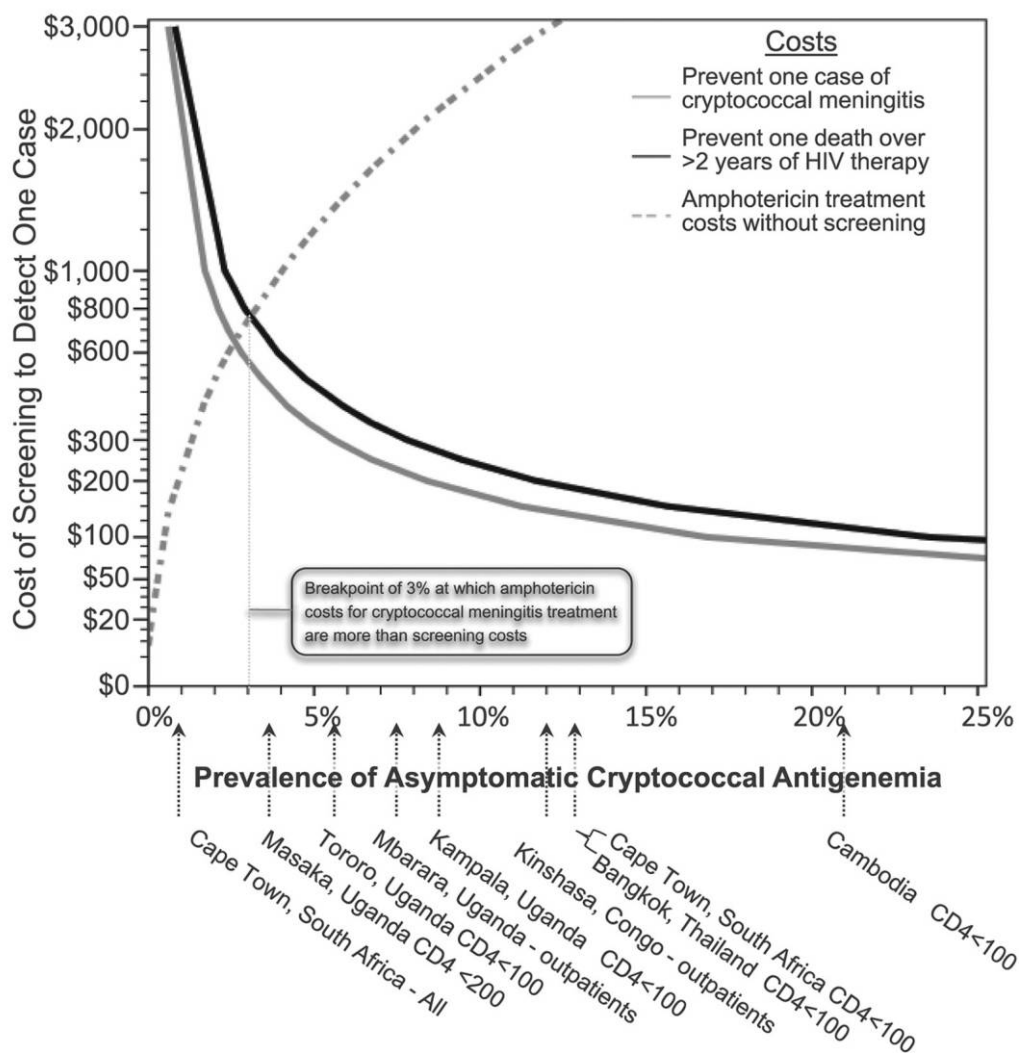


Figure 3. Cost of serum cryptococcal antigen (CRAG) screening based on asymptomatic prevalence. The relative cost-effectiveness of CRAG screening and preemptive fluconazole therapy, based on the prevalence of antigenemia within a given population and outcomes from Kampala, Uganda, is shown. The cost to prevent 1 case of clinical cryptococcal meningitis (*black line*) and to prevent 1 death from cryptococcal meningitis (*gray line*) are presented, with survivors living for >2.5 years on ART. Below the x-axis, the reported cross-sectional prevalence rates of asymptomatic antigenemia in various outpatient clinic populations of HIV-infected people without a prior history of cryptococcal meningitis are displayed [10, 12, 14, 15, 17–19]. Above a prevalence of ~3%, the cost of amphotericin deoxycholate for treatment of people unmasking ART-associated cryptococcal meningitis (\$245 per person) is greater than the costs of screening and treating with preemptive fluconazole, not including the additional hospitalization costs. CRAG screening costs are based on \$16.75/test, and different implementation costs would affect the cost-benefit curves proportionally.

and Prevention–Uganda cost estimate was \$3.97 per sample for CRAG testing with bulk purchase of reagents only [15]. The CRAG testing cost is highly dependent on the testing volume, because there are fixed costs, such as laboratory overhead, external quality assurance, and daily quality control, which do not increase with additional testing. The quality-control cost per test is highly dependent on volume, whereby, for each batch of samples tested, 1 positive control and 1 negative control are used.

There are additional efficiencies in batch testing. By incorporating a simple model based on increased testing volume, we found that the price per test decreases dramatically. For example, if CRAG testing increased from 3–5 tests to 16–20 tests per day, then the CRAG cost would decline by 45% (\$9.29/test), because of a decrease in reagent costs by bulk purchasing (\$3.97/test) [15], a decrease in the distribution of the daily quality control (\$0.15/test), and a decrease in annual external quality assurance costs (\$0.15/test), which are all fixed costs. Also, there would be a moderate reduction in the cost of disposable supplies (\$0.72/test) and labor costs (\$2.10/test), because the laboratory preparation time and effort are applied for the whole run. Finally, the overhead (\$1.77/test) and margin (\$.044/test) are affected accordingly, on the basis of the distribution of these costs on increased volume.

Using these estimates for increased CRAG testing, we found the overall cost-effectiveness to be even more beneficial. Incorporating these economies of scale to save 1 person's life by preemptive fluconazole therapy, we found the cost to be \$148 (95% CI, \$103–\$223) to prevent 1 fatal CM case; the cost is \$12 (95% CI, \$8–\$18) per DALY saved. Using the list cost in the South African National Health Laboratory System (ie, one-third the estimate used here), we found the cost of screening to be \$7 (95% CI, \$5–\$11) per DALY saved, under the same conditions. We believe that pre-ART screening in persons with a CD4⁺ cell count \leq 100 cells/ μ L is highly beneficial.

DISCUSSION

We report a prevalence of new cryptococcal antigenemia of 8.8% among patients with a CD4⁺ T cell count \leq 100 cells/ μ L at this urban health facility in Kampala, Uganda, with an overall prevalence of 13.5% including those with prior CM. In this representative prospective sub-Saharan African cohort, we have shown that initial CRAG screening prior to starting ART in patients with a CD4⁺ T cell count \leq 100 cells/ μ L can prevent disease and death in 8% of patients started on ART. These prevalence rates are comparable to those from Cambodia (21%), South Africa (13%), Bangkok (12.9%), and Tororo, Uganda (5.8%), among patients with a CD4⁺ cell count \leq 100 cells/ μ L [10, 14, 15, 17]. CRAG+ prevalence in outpatients has also been reported from Masaka, Uganda (3.8%), Mbarara, Uganda (7.5%), and Kinshasa, Congo (12.2%) [12, 18, 19]. In

the absence of ART, occult cryptococcal antigenemia precedes clinical CM symptoms by a median of 22 days [7]. Unfortunately, the attributable mortality rate for CRAG+ persons is 17%–18% in rural community cohorts from Uganda [7, 15], and asymptomatic, untreated cryptococcal antigenemia is an independently predictor of death during the first 12 weeks of ART [1, 20, 21]. The unmasking of clinical CM after initiating ART is relatively common, accounting for 30% of cases of CM diagnosed in 2 African cohorts in 2006, and the proportion is likely to increase [7, 15]. These data reiterate the importance of screening for opportunistic infections prior to initiating ART [20, 21].

The 2009 US Department of Health and Human Services guidelines for managing opportunistic infections unequivocally state that “[b]ecause the incidence of cryptococcal disease is low, routine testing of asymptomatic people for serum cryptococcal antigen is not recommended (DIII)” [22, p. 48], nor is primary prophylaxis recommended in the United States [22]. Yet, we strongly advocate that a different standard is necessary in resource-limited settings where the prevalence of asymptomatic antigenemia is high and where persons starting ART with AIDS is also still alarmingly commonplace. In Africa, fluconazole as primary prophylaxis is effective and safe in improving survival for people with a CD4⁺ cell count $<$ 200 cells/ μ L [12]. We would extend this finding further to say that those with a CD4⁺ cell count $<$ 100 cells/ μ L who are not receiving fluconazole prophylaxis should receive CRAG screening prior to ART initiation.

One necessity for a good screening test is an effective intervention. In our experience, untreated patients had a 75% mortality rate overall, and 100% of those with a CD4⁺ cell count \leq 100 cells/ μ L died. With use of fluconazole, 71% survived for $>$ 2.5 years. The 75% mortality rate is unfortunately similar to the published CM-related, 12-week mortality rate in Africa [1, 5, 8, 23]. The untreated CRAG+ survival rate (25%) in Uganda was lower than that seen in a prior cohort that reported a 56% survival rate in Cape Town, South Africa [14]. Although Uganda is a resource-limited region, the differences in survival are likely partially related to the degree of immunosuppression of the Uganda cohort. In CRAG+ persons, the median CD4⁺ cell count was 15 cells/ μ L in Uganda and 46 cells/ μ L in South Africa [14]. We previously reported that Ugandan patients with a CD4⁺ cell count $<$ 25 cells/ μ L have a 2.5-fold higher odds of mortality after starting ART [9].

To our knowledge, no previous studies have investigated the cost-benefit ratio of CRAG screening in HIV-infected persons to identify those with cryptococcosis in sub-Saharan Africa, and no studies have determined the optimal treatment strategy. Our prospective observational experience strongly favors fluconazole therapy for asymptomatic cryptococcal antigenemia; ART alone is insufficient. This type of therapy differs from the

types of therapy used for other opportunistic infections, such as Kaposi sarcoma, for which ART alone can be curative in localized disease [24, 25]. The optimal dose and duration of fluconazole is unknown. The majority of people in this study received 2–4 weeks of fluconazole at doses of 200–400 mg. Higher doses of fluconazole are likely to be more effective, because 800 mg of fluconazole is fungicidal, whereas dosing at ≤ 400 mg is fungistatic [23]. On the basis of available data, we would recommend 800 mg fluconazole for at least a 4-week course in combination with ART for CRAG+ asymptomatic persons without CM. Prospective trials of the optimal preemptive therapy in these patients are warranted. Limitations of the study include its observational nature; a randomized trial would have been more ideal. Our cost-effectiveness analysis was conservative and did not include further savings from reduced antifungal use or from avoidance of hospitalizations. All of these would enhance the cost-effectiveness of the CRAG screening, as would economies of scale. The moderate size of the cohort allows for an approximate but imprecise estimate. The magnitude of the benefit of CRAG screening is overwhelming, such that the degree of precision should not cast doubt on the efficacy of CRAG screening and treatment. The local prevalence of CRAG antigenemia and the degree of immunosuppression will affect the absolute benefit.

We demonstrate that CRAG testing for persons with a CD4⁺ cell count ≤ 100 cells/ μ L who are initiating ART is cost-effective in resource-limited settings and that ART alone is insufficient. We believe serum CRAG screening should be integrated into national ART treatment programs in sub-Saharan Africa, specifically targeting patients with severe immunosuppression (CD4⁺ cell count ≤ 100 cells/ μ L), because CRAG screening to reduce early mortality of patients on ART is both cost-effective and affordable.

Acknowledgments

We thank all the medical officers and nursing staff at the Infectious Disease Institute who managed the patients and Ms Agnes Kiragga for assisting with data extraction.

Financial support. The Infectious Disease Institute is supported in part by a philanthropic grant from Pfizer pharmaceuticals (to B.C., A.K., and M.K.), and this research was supported by the University of Minnesota Academic Health Center (P.R.B. and D.B.M.) and the National Institutes of Health (grant K23AI073192-01A2 to D.R.B. and grant R34 AI081554 to D.R.B., D.B.M., and P.R.B.).

Potential conflicts of interest. All authors: no conflicts.

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