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Asymptomatic Cryptococcemia in Resource-Limited Settings

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Abstract

Despite increasing availability of anti-retroviral therapy, invasive cryptococcal disease continues to be a leading cause of death among HIV-infected individuals in resource-limited settings. Screening asymptomatic HIV-infected individuals with advanced immunosuppression for serum cryptococcal antigen clearly identifies a population at high risk of cryptococcal meningitis and death. However, screening with serum cryptococcal antigen alone identifies a heterogeneous clinical population, many of whom have mild clinical symptoms, sub-clinical meningeal infection, or fungemia. Currently, there is wide variation in practice and little evidence to guide the use of anti-fungal and anti-retroviral treatment for asymptomatic cryptococcal antigenemia (ACA). Furthermore, implementing a targeted screening and treatment intervention for ACA presents numerous operational challenges for already overburdened health care systems in resource-limited settings. While such an intervention shows promise, there are critical gaps in our understanding of ACA and its implications in the outpatient setting and an urgent need for additional research in this area.

Keywords

cryptococcus; HIV/AIDS; meningitis; asymptomatic cryptococcal antigenemia; resource-limited settings; co-infections

Introduction

Invasive cryptococcal disease remains an important disorder in resource-limited settings with a high prevalence of HIV infection despite increasing access to anti-retroviral therapy (ART). In sub-Saharan Africa and southeast Asia, invasive cryptococcal disease is the second most common life-threatening HIV-associated opportunistic infection after tuberculosis and is responsible for up to 20% of deaths(1–4). One study estimates that cryptococcal meningitis (CM) may even be surpassing tuberculosis as the leading cause of

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

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death among individuals with HIV infection in sub-Saharan Africa(5). In contrast, in resource-rich settings, low case fatality rates and decreasing incidence of invasive cryptococcal disease have been observed since ART has become widely available (6, 7).

The prevalence of invasive cryptococcal disease is higher in sub-Saharan Africa and southeast Asia than in resource-rich settings(1–3, 8). This may be because cryptococcus is more prevalent in the environment (9, 10). Alternatively, invasive cryptococcal disease primarily affects individuals with advanced immunosuppression(11), and HIV-infected individuals present for care at lower absolute CD4+ T-cell counts in resource-limited settings(12).

Furthermore, case fatality rates for CM are dramatically higher in resource-limited settings. In resource-rich settings with ART and effective anti-fungal treatments, case fatality rates are between 9–38%(6, 7, 13, 14). In sub-Saharan Africa with ART and anti-fungal therapy, CM has a mortality of 37–58% in clinical trial settings(15–17) and 30–59% in tertiary care settings(18). Without ART and antifungal therapy, the mortality is 100%(19). However, the two medications considered the standard of care for CM are not readily available in most resource-limited settings; flucytosine is not commercially available in many countries and amphotericin is available only in referral centers(20). Thus, in some resource-limited settings CM is often treated only with oral fluconazole(21).

Invasive cryptococcal disease, especially CM, continues to have a high burden in resource-limited settings despite the existence of efficacious treatments. Thus, in resource-limited settings, effective prevention interventions are potentially a vital strategy to decrease the burden of disease and mortality due to invasive cryptococcal disease among HIV-infected individuals with advanced immunosuppression.

Potential approaches to preventing cryptococcal meningitis

Initial efforts to prevent CM focused on primary prophylaxis of HIV-infected individuals with low CD4+ T-cell counts with anti-fungal medications such as itraconazole and fluconazole. A meta-analysis demonstrated that this approach reduced the incidence of cryptococcal disease, but did not reduce mortality(22). A more recent study in Uganda of individuals who did not have cryptococcal antigenemia similarly demonstrated reduced incidence of cryptococcal disease but did not reduce mortality(23). Primary prophylaxis was not recommended in the most recent guidelines primarily because studies have not demonstrated a consistent survival benefit and because a majority of individuals would have a low risk of CM(20). However, other reasons included the cost of the intervention, the implications of treating individuals with unrecognized active disease, teratogenicity of fluconazole, and potential drug interactions(20).

Several developments have led to a growing interest in creating new approaches for the prevention of CM in resource-limited settings. Both ART and fluconazole are increasingly available in sub-Saharan Africa(12, 24). In addition, there is a well-established and highly sensitive and specific assay for invasive cryptococcal disease, the serum cryptococcal antigen (CrAg) assay(25). Thus, one proposed strategy to prevent CM is to screen asymptomatic individuals with advanced HIV-related immunosuppression for serum CrAg as they enter outpatient HIV care and treatment programs in resource-limited settings(26).

Rationale for targeted screening

Asymptomatic cryptococcal antigenemia (ACA) is generally defined as presence of CrAg in the serum without overt signs or symptoms of meningitis or sepsis. Several recent observational cohort studies from Uganda, South Africa, and Thailand revealed ACA in 6–

13% of asymptomatic ART-naïve individuals entering HIV outpatient care with a CD4+ cell count ≤100 cells/μl and no history of cryptococcal infection (Table 1)(27–30). A series of similar studies from outpatient HIV care settings demonstrated ACA in 2–21% (the wider range of prevalence estimates is likely due to the inclusion of individuals on ART, with symptoms of meningitis, and with a history of cryptococcal disease)(31–35). The prevalence of ACA was lower in populations with higher CD4+ cell counts(23, 27, 29, 30, 33, 34). ACA prevalence estimates from inpatient series from sub-Saharan Africa and Southeast Asia range from 5–19%(36–42). However, many of these studies included individuals with signs or symptoms of meningitis or sepsis, were either from the pre-ART era or included a substantial proportion on ART, or used higher CD4+ T-cell counts as a threshold for screening. In contrast, a study from the pre-ART era from the United Kingdom demonstrated a prevalence of 0.1%(43) while a more recent study demonstrated a prevalence of 5% though nearly all of these individuals were presenting for inpatient evaluation of meningitis(44).

There are few studies which describe the clinical implications of untreated ACA in HIV-infected individuals with CD4+ T-cell counts ≤100 cells/μl and most measured serum CrAg retrospectively in stored serum samples (Table 2). Without anti-fungal therapy, incident cryptococcal meningitis occurred in 14–100%(27, 28, 45, 46) and death in 10–100%(27, 28, 30, 47). A South African study reported that ACA at baseline was 100% sensitive for the development of CM during the first year of ART(27). A Ugandan study of patients initiating ART reported a population attributable risk for mortality of 18%, comparable to that associated with active tuberculosis(28). Thus, despite treatment with ART, ACA in individuals with low CD4+ T-cell counts is predictive of CM and death. Some studies have suggested screening for ACA could potentially be applicable to resource-rich settings(48), subpopulations in resource-rich settings(44), or have employed a higher CD4+ T-cell count threshold for screening(33, 34, 40). However, clinical outcomes have not been defined for these populations.

Most studies of ACA to date have used latex agglutination tests to identify individuals with serum CrAg. Enzyme Immunoassay (EIA) assays for CrAg have also been developed which have even higher sensitivity and specificity than latex agglutination assays and avoid false negatives in cases of extremely high antigen titers (i.e. the prozone phenomenon) to which the latex agglutination assay is vulnerable(11, 49, 50). However, EIA CrAg assays are more costly and take longer to perform than latex agglutination. Recently, a simpler and less expensive test has been developed—the lateral flow assay (LFA). Serum LFA has demonstrated high sensitivity and good agreement with EIA, latex agglutination, and culture in different populations with invasive cryptococcal infection(51–54). Discordant results between LFA and EIA have been reported but clinical outcomes for individuals with discordant test results have not been described(51, 52). Understanding the performance of LFA in a population of individuals with ACA as identified by latex agglutination or EIA is an important area for study.

Pathophysiology of asymptomatic cryptococcal antigenemia

Humans are thought to acquire cryptococcal infection by inhalation of airborne fungi early in life, which develops into clinical disease in the setting of advanced immunosuppression(55). Clinical disease can manifest as sepsis, subacute meningitis, pulmonary, prostate, skin or eye disease(11). In symptomatic patients, cryptococcal antigenemia is highly sensitive and specific for CM(25). In asymptomatic patients, cryptococcal antigenemia predicts mortality and incident CM but whether ACA represents an early stage of invasive cryptococcal infection is not entirely clear.

In two small studies from the US in the pre-ART era, serum CrAg was associated with disseminated disease in the blood, CSF or lungs, though a minority of patients had no other evidence of disseminated disease at the time of serum CrAg testing(45, 46). In a Thai cohort of asymptomatic outpatients presenting for HIV care and ART, 3 of 12 patients with ACA were found to have sub-clinical meningeal infection (defined as cryptococcal antigen present in the cerebrospinal fluid (CSF) or cryptococcus identified on India Ink smear or in culture of the CSF)(29). In a Cambodian cohort, 7 of 17 individuals with ACA had evidence of sub-clinical meningeal infection(39). Similar studies of mixed populations with and without symptoms of meningitis demonstrate that 66%–88% of individuals with advanced immunosuppression and serum CrAg have sub-clinical meningeal infection or fungemia(36, 37). One important observation from a Ugandan study from the pre-ART era demonstrated that serum CrAg positivity preceded the onset of clinical symptoms by a median of 22 days, although 11% of the patients had demonstrable serum CrAg for greater than 100 days(3).

Thus, the ideal approach would be to perform a full diagnostic evaluation on every individual with ACA to look for sub-clinical infection. Such an evaluation ideally would include lumbar puncture with cerebrospinal fluid CrAg and India Ink stain, chest radiograph and broncho-alveolar lavage, and fungal cultures of the cerebrospinal fluid, bronchoalveolar washings, blood and urine(46). However, most of these additional diagnostic tests are not available in or near most resource-limited HIV outpatient care settings(56). Furthermore, in many resource-limited settings, lumbar punctures are traditionally done in the inpatient setting, and the patient must assume financial responsibility for the costs of inpatient hospitalization and additional diagnostic tests(21). In contrast, in most HIV outpatient care settings, patients are not charged for their care. Thus, there is a substantial disincentive for patients to obtain additional testing. Finally, in many resource-limited settings, patients are reluctant to obtain lumbar punctures even for cryptococcal meningitis; in one study nearly 24% (36/151) of individuals with suspected cryptococcal meningitis refused diagnostic lumbar puncture and 94% of those with increased intracranial pressure refused subsequent therapeutic lumbar punctures(57).

In an ART-naïve population with advanced immunosuppression, ACA likely represents a heterogeneous clinical population in which a substantial proportion of individuals already have sub-clinical meningeal infection or fungemia, and only a small minority have isolated cryptococcal antigenemia. Furthermore, two recent studies in outpatient settings report that individuals with ACA often report mild symptoms(32, 33). Thus, this population could be more accurately described as having early cryptococcal infection rather than ACA. There are significant operational, financial and cultural barriers to performing additional diagnostic evaluations among individuals with ACA, particularly in performing lumbar puncture. A fuller understanding of the clinical significance of ACA in outpatient settings is essential to guide future research on treatment.

Treatment of asymptomatic cryptococcal antigenemia

Anti-retroviral medications

Timing of ART has been demonstrated to be important in the treatment of cryptococcal meningitis in two trials where early initiation of ART was shown to have higher mortality than delayed initiation of ART(58, 59). Research to determine the optimal timing of ART initiation for ACA is urgently needed.

Anti-fungal medications

As described previously, without anti-fungal therapy, ACA even in cohorts receiving ART leads to high mortality rates and high rates of incident cryptococcal meningitis. There are no clinical trials of anti-fungal medications for ACA. The most recent treatment guidelines do

not recommend a specific treatment strategy(20). Nonetheless, primary prophylaxis with low doses of fluconazole has demonstrated efficacy in decreasing the incidence of CM(22, 23).

Similarly, two studies from the U.S. reported no incident cryptococcal meningitis cases among HIV-infected individuals with ACA but no other evidence of cryptococcal disease who were treated with low-dose fluconazole(Table 2)(45, 46). However, in Cambodia, 10 patients with ACA and normal CSF were treated with 200mg fluconazole and ART and 2 (20%) died by 12 weeks(39).

In contrast, high mortality rates were observed using low and high dose fluconazole for ACA without additional diagnostic evaluation. In Uganda, 21 patients with ACA who were immediately treated with low dose short term fluconazole (200–400mg for 2–4 weeks) and ART had 29% mortality after a median 30 months of follow-up(30). Five-year follow-up of an expanded cohort including the previously described patients demonstrated 24% mortality (60). In Kenya, among 59 individuals with ACA who received high-dose fluconazole the mortality rate was 39%, with 27% mortality within 3 months(32). The mortality in individuals without ACA was 24%(32).

The standard of care for CM is amphotericin B with flucytosine(20). A recent trial among individuals with CM in Vietnam demonstrated that the combination of Amphotericin B with flucytosine resulted in a significant increase in survival at 70 and 182 days as compared to Amphotericin B alone(61). This study also demonstrated that Amphotericin B in combination with flucytosine led to significantly higher rates of fungal clearance as compared to either Amphotericin B alone or in combination with fluconazole(61). However, amphotericin B must be administered intravenously in an inpatient setting, which makes its use challenging for treatment of a relatively asymptomatic population. Fluconazole monotherapy, an oral alternative, is only recommended for the treatment of CM in the absence of more efficacious medications such as amphotericin B(20, 62). Low doses of fluconazole (400mg) have mortality rates of up to 75%(15) while higher doses of fluconazole (800mg–1200mg) have somewhat improved outcomes with mortality rates of approximately 30%(17).

Thus, there is urgent need for an efficacious oral therapy for ACA which is feasible to administer to a largely asymptomatic outpatient population in resource limited settings where additional diagnostic evaluation is not available. Fluconazole in combination with other oral anti-fungal treatments may be a potential alternative to fluconazole monotherapy or treatment with intravenous medications. Several recent clinical trials of CM have noted good tolerability and safety of high-dose fluconazole alone and in combination with either flucytosine, amphotericin B or both(63–65). Furthermore, combination therapy with high-dose fluconazole and flucytosine has shown promise in small clinical trials for the treatment of CM in the ART era. In a recent study from Malawi, high dose fluconazole (1200mg × 2wks, then 800mg × 8wks, then 200mg) in combination with flucytosine (100/mg/kg × 2wks) was superior to fluconazole alone for the treatment of CM(16). Similar trials in the pre-ART era with varying doses or durations of fluconazole and flucytosine also showed significant benefits(66–68). However, there are significant safety concerns since treatment related deaths have been reported in several trials(16, 66, 67).

A Phase IIb randomized, controlled, open-label trial comparing induction therapy for ACA with combination high-dose fluconazole and flucytosine to fluconazole alone is scheduled to begin enrolling in Kenya soon (http://clinicaltrials.gov, NCT01562132). However, there will be significant challenges to conducting Phase III clinical trials for the treatment of ACA. First and foremost, there is no intermediate biomarker of treatment efficacy in early

cryptococcal infection—early fungicidal activity is not useful because only a small proportion of patients have positive cultures(29, 39) and serum CrAg is not useful to monitor the course of cryptococcal disease(25). Therefore, the only remaining option is to use mortality as the primary outcome which requires costly large sample sizes to establish a favorable benefit-to-risk ratio.

Implementation Challenges and Cost-Effectiveness

Recently, an algorithm for implementation of a targeted CrAg screening and ACA treatment intervention for resource-limited settings was proposed(56). To date, there has been one published outcome evaluation of the impact of such an intervention in a resource-limited HIV outpatient care setting (32). This study was conducted in Kenya at Family AIDS Care and Education Services (FACES) and did not demonstrate a significant decrease in mortality among all individuals with CD4+ T-cell counts ≤100 cells/μl though it was underpowered to detect clinically important differences. In addition, this study highlights some of the challenges to be expected in implementing such an intervention across a wide geographic area in rural and urban sub-Saharan Africa.

For example, uptake of the intervention was fair (52%), with the greatest drop-off at the time of sCrAg testing. Only 66% of eligible individuals had sCrAg testing performed(32). This may have been due to reagent stock-outs, lack of a serum sample obtained at the same time as the baseline CD4+ T-cell count, or low uptake within the laboratory. Furthermore, at the clinic level, documentation of drug dosing and duration was poor, limiting our ability to interpret conclusively the results of the intervention. Additional operational research to evaluate the impact of these interventions is ongoing (http://clinicaltrials.gov, NCT01535469), including one national initiative in South Africa(69). Ultimately, implementation across decentralized clinics in resource-limited settings will be challenging, and a critical area for future research will be how to develop, monitor and strengthen this intervention and its supporting health systems.

Three cost-effectiveness estimates have been published and all suggest that a targeted screening and treatment intervention will be cost-effective. In a careful and thorough modeling study based on Cambodian data, the incremental cost-effectiveness ratio of screening vs. no intervention was US$ 180/life year gained (LYG) and of prophylaxis vs. screening was $ 511/LYG(70). Sensitivity analyses to account for differences in the patient population and in the cost of various components of the intervention led to variations in the costs, but in nearly all analyses, targeted screening and treatment was more cost-effective than primary prophylaxis.

Two additional estimates based on Ugandan data report substantially lower costs. In a study assuming use of latex agglutination testing, the cost to save one life was estimated at $266, equating to $21 per disability-adjusted life year (DALY) saved(30). A similar analysis modeling use of the less expensive LFA estimates the cost to save one life is $39.73, equating to $2.21 per DALY saved(48).

The substantial differences between these cost estimates are likely due to assumptions around mortality rates. This is supported by the sensitivity analyses performed as part of the Cambodian study(70). In that analysis, reducing the mortality rate due to CM led to the most dramatic effects on the incremental cost-effectiveness ratio; with a 25% lower mortality rate, targeted screening and treatment led to an incremental cost of only $44 per life year gained, a cost comparable to that reported in the Ugandan estimates. Once the mortality rates for treated ACA are more accurately defined, the true cost of these interventions will be clearer.

Conclusion

Despite increasing availability of ART, invasive cryptococcal disease continues to be a leading cause of death among HIV-infected individuals in resource-limited settings. Screening asymptomatic HIV-infected individuals with advanced immunosuppression for serum CrAg clearly identifies a population at high risk of CM and death and is feasible in resource-limited settings. However, screening with serum CrAg alone without additional diagnostic studies identifies a heterogeneous clinical population, many of whom have mild clinical symptoms, sub-clinical meningeal infection, or fungemia. Thus, this population could be more accurately described as having early cryptococcal infection rather than ACA. In addition, there is wide variation in practice and little evidence to guide the use of anti-fungal and anti-retroviral treatment for ACA or early cryptococcal infection. Implementing a targeted screening and treatment intervention for ACA presents numerous operational challenges for already overburdened health care systems in resource-limited settings.

While a targeted screening and treatment intervention shows promise, there are critical gaps in our understanding of ACA and its implications in the outpatient setting and an urgent need for additional research in this area. What is the optimal CD4+ T-cell count threshold to trigger screening for ACA? How many individuals with advanced immunosuppression and ACA have sub-clinical meningeal infection or fungemia? Is asymptomatic equivalent to minimally symptomatic? How can we improve access to and acceptance of diagnostic lumbar punctures? Is it possible to design an effective intervention that does not include lumbar puncture and fungal cultures? What are the best anti-fungal regimens for ACA and early cryptococcal infection? What is the optimal timing of ART initiation in individuals with ACA and early cryptococcal infection? Does targeted screening and treatment reduce incident CM, overall mortality, or mortality from invasive cryptococcal disease? Furthermore, what support is necessary to implement this intervention in already overloaded health systems in resource-limited settings? What is the cost of this intervention and how can it be most efficiently implemented?

A targeted screening and treatment intervention for ACA should be one part of a comprehensive strategy to reduce mortality from invasive cryptococcal disease. Other critical components include improving access to the most efficacious treatments for CM in the inpatient setting. Ultimately, strengthening HIV education, counseling, testing, and linkages to care is vital so that individuals in resource-limited settings access HIV care and ART *before* they develop advanced immunosuppression.

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Table 1

Prevalence of serum Cryptococcal antigen among various cohorts of HIV-infected individuals.

Region	Country	Year	CD4+ T-cell count	Prevalence	(n/N)	No Hx Crypto	ASx	Other population information	Test Type	Titer	Citation
Outpatient											
CD4+T-Cell count≤100 cells/μL											
Capetown	South Africa	2002–5	≤100	6.7%	(21/312)	yes *	yes	ART naïve	LA	1:2	(27)
Tororo	Uganda	2003–4	≤100	5.8%	(22/377)	yes	yes	ART naïve	LA	1:2	(28)
Bangkok	Thailand	2003–7	≤100	12.9%	(11/85)	yes	yes	ART naïve	LA	1:1	(29)
Kampala	Uganda	2004–6	≤100	8.8%	(26/295)	yes	yes	ART naïve	LA	NS	(30)
Kumasi	Ghana	2008–9	≤100	2.2%	(2/92)	no	no	42% on ART; 80% of all enrolled during study period	LA	1:1	(31)
Kisumu & Rongo	Kenya	2010–1	≤100	11.5%	(59/514)	no	yes	ART naïve	LA	1:2	(32)
Addis Ababa	Ethiopia	2011	≤100	11.2%	(13/116)	yes	no	74% on ART	LA	1:2	(33)
Benin City	Nigeria	2011	≤100	21.0%	(17/81)	yes	NS	ART naïve	LA	NS	(34)
Gauteng	South Africa	2012–3	≤100	4.2%	(124/2969)	no	no	ART unknown	LFA	—	(35)
CD4+T-Cell count>100 cells/μL											
Capetown	South Africa	2002–5	101–200	1.1%	(4/371)	yes *	yes	ART naïve	LA	1:2	(27)
Bangkok	Thailand	2003–7	>100	2.2%	(1/46)	yes	yes	ART naïve	LA	1:1	(29)
Kampala	Uganda	2004–6	101–200	2.4%	(7/297)	yes	yes	ART naïve	LA	NS	(30)
Masaka & Kalangala	Uganda	2004–8	<200	3.7%	(59/1578) †	no	yes	ART naïve;	LA	1:8	(23)
Addis Ababa	Ethiopia	2011	100–150	8.8%	(10/113)	yes	no	74% on ART	LA	1:2	(33)
Addis Ababa	Ethiopia	2011	>151	5.7%	(8/140)	yes	no	74% on ART	LA	1:2	(33)
Benin City	Nigeria	2011	101–200	2.9%	(2/69)	yes	NS	ART naïve	LA	NS	(34)
Benin City	Nigeria	2011	>200	2.5%	(1/40)	yes	NS	ART naïve	LA	NS	(34)
Inpatient or mixed inpatient/outpatient											
London	UK	1985–8	NS	0.1%	(1/759)	no	yes *	ART naïve	LA	NS	(43)
Kinshasa	DRC	1988	NS	12.2%	(55/450)	no	no	ART naïve	LA	NS	(36)
Mbarara	Uganda	~2003	NS	10.7%	(21/197)	NS	no	ART naïve; 51% CD4<50;	LA	1:5	(37)
Nakhon Phanom & Sa Kaeo	Thailand	2003–7	NS	13.1%	(92/704)	no	no	ART unknown; admitted for pneumonia	EIA	NS	(38)

Region	Country	Year	CD4+ T-cell count	Prevalence	(n/N)	No Hx Crypto	ASx	Other population information	Test Type	Titer	Citation
Phnom Phenh	Cambodia	2004	≤200	20.6%	(32/295)	yes	yes	ART naïve	LA	1:8	(39)
London	UK	2004–10	≤100	5%	(8/157)	no	no	ART naïve; 7/8 had CM	LA	1:2	(44)
Mwanza	Tanzania	2009–10	NS	5.1%	(17/333)	yes	no	~50% ART; 15/17 had CM	LA	1:4	(40)
Kampala	Uganda	2009–10	≤100	18.8%	(69/367)	yes	no	ART naïve; in and outpatient	LA	NS	(41)
Kampala	Uganda	2009–10	NS	5.7%	(32/563)	no	no	admitted for pneumonia	LA	NS	(42)

*As calculated for this review;

†Denominator estimated for this review;

Abbrev: ART: Anti-retroviral therapy; Asx: Asymptomatic; Crypto: cryptococcal disease; DRC: Democratic Republic of Congo; CM: Cryptococcal meningitis; EIA: Enzyme Immunoassay; Hx: History; LA: Latex agglutination; LFA: Lateral Flow Assay; NS: Not specified; UK: United Kingdom.

Table 2

Outcomes of various cohorts of HIV-infected individuals with positive serum Cryptococcal antigen.

Region	Country	Year	CD4+ T-cell count	Prevalence	(n/N)	No Hx Crypto	ASx	Other population information	Test Type	Titer	Citation
Mortality											
Treated with anti-fungals											
Phnom Phenh	Cambodia	2004	≤200	20.0%	(2/10)	yes	no	ART naïve; negative workup; low dose fluconazole;	LA	1:8	(39)
Kampala	Uganda	2004–6	≤100	28.6%	(6/21)	yes	yes	ART naïve; fluconazole	LA	NS	(30)
Kampala	Uganda	2004–6	101–200	0.0%	(0/4)	yes	yes	ART naïve; fluconazole	LA	NS	(30)
Kisumu & Rongo	Kenya	2010–11	≤100	39.0%	(23/59)	no	yes	ART naïve; high-dose fluconazole documented in 59%; sCrAg negative mortality 24% (107/455)	LA	1:2	(32)
Not treated with anti-fungals											
Capetown	South Africa	2002–5	≤200	34.1%	(14/41)	yes*	yes	ART naïve; sCrAg negative mortality 11% (64/574)	LA	1:2	(27)
Tororo	Uganda	2003–4	≤100	22.7%	(5/22)	yes	yes	ART naïve; sCrAg negative mortality 5% (19/355)	LA	1:2	(28)
Kampala	Uganda	2004–6	≤100	100.0%	(5/5)	yes	yes	ART naïve	LA	NS	(30)
Kampala	Uganda	2004–6	101–200	33.3%	(1/3)	yes	yes	ART naïve	LA	NS	(30)
Addis Ababa	Ethiopia	2011	≤200	9.7%	(3/31)	yes	no	74% on ART; only 3 received antifungal; sCrAg negative dead or lost to follow up 12% (41/336)	LA	1:2	(47)
Incident Cryptococcal Meningitis											
Treated with anti-fungals											
Philadelphia	USA	~1994	≤200	0.0%	(0/10)	NS	NS	ART naïve; negative workup; −4 Rx amphotericin; −4 Rx low dose fluconazole; −4 Rx itraconazole and fluconazole	NS	1:8	(45)
Los Angeles	USA	~1996	NS	0.0%	(0/6)	no	no	ART naïve; negative workup; treated with fluconazole	LA+ EIA	1:4	(46)
Not treated with anti-fungals											
Philadelphia	USA	~1994	≤200	66.7%	(2/3)	NS	NS	ART naïve; negative workup	NS	1:8	(45)
Los Angeles	USA	~1996	NS	100.0%	(1/1)	no	no	ART naïve; negative workup	LA+ EIA	1:4	(46)
Capetown	South Africa	2002–5	≤100	28.6%	(6/21)	yes*	yes	ART naïve	LA	1:2	(27)
Tororo	Uganda	2003–4	≤100	13.6%	(3/22)	yes	yes	ART naïve; 1%(4/355) sCrAg neg incident meningitis	LA	1:2	(28)

Abbrev: ART: Anti-retroviral therapy; Asx: Asymptomatic; Crypto: cryptococcal disease; EIA: Enzyme Immunoassay; Hx: History; LA: Latex agglutination; LFA: Lateral Flow Assay; NS: Not specified; sCrAg: serum cryptococcal antigen; USA: United States of America.

Note: inpatient studies of cryptococcal antigenemia were not included in this table unless they specified ACA with negative diagnostic evaluation (negative workup).