Asymptomatic cryptococcal antigenemia in HIV-infected patients: a review of recent studies

Xiao-Lei Xu1, Ting Zhao2, Vijay Harypursat1, Yan-Qiu Lu1, Yan Li3, Yao-Kai Chen1

1Division of Infectious Diseases, Chongqing Public Health Medical Center, Chongqing 400036, China; 2Division of Science and Education, Chongqing Public Health Medical Center, Chongqing 400036, China; 3Public Health College, Zunyi Medical University, Zunyi, Guizhou 563000, China.

Abstract
The prevalence of asymptomatic cryptococcal antigenemia (ACA) in human immunodeficiency virus (HIV) infected individuals has been observed to be elevated. The prevalence of ACA ranges from 1.3% to 13%, with different rates of prevalence in various regions of the world. We reviewed studies conducted internationally, and also referred to two established expert consensus guideline documents published in China, and we have concluded that Chinese HIV-infected patients should undergo cryptococcal antigen screening when CD4+ T-cell counts fall below 200 cells/μL and that the recommended treatment regimen for these patients follow current World Health Organization guidelines, although it is likely that this recommendation may change in the future. Early screening and optimized preemptive treatment for ACA is likely to help decrease the incidence of cryptococcosis, and is lifesaving. Further studies are warranted to explore issues related to the optimal management of ACA.

Keywords: Cryptococcal antigenemia; HIV; Prevalence; Screening; Treatment

Introduction
Cryptococcal infection can cause severe and often fatal cryptococcal meningitis (CM) in individuals living with human immunodeficiency virus (HIV), accounting for 70% of CM-related deaths in low-income countries,[1] and inflicting an onerous burden on healthcare resources. Among the different varieties of cryptococcal infection, asymptomatic cryptococcal antigenemia (ACA) is not unusual and has been observed to be elevated among HIV-infected individuals with severe immunosuppression, with prevalence ranging between 5% and 9% among antiretroviral therapy (ART)-naive populations in low- and middle-income countries,[2] with some regional variations in prevalence.[1] ACA generally refers to the presence of cryptococcal antigen (CrAg) in the serum without overt signs or symptoms of meningitis or sepsis. It is regarded as an early biologic marker of disseminated cryptococcal infection,[3] and the presence of ACA is highly prognostic for the development of CM within a year.[4] Thus, the critical importance of screening and preemptive intervention for ACA is being increasingly recognized.

A few recent studies regarding ACA have been conducted and published. These studies have been conducted in different populations, and concern different aspects of ACA. The present review is a synthesis of these current studies with an aim to gathering data on prevalence, indications for preemptive treatment, and refinements to recommended regimens, striving to distill a comprehensive summary to give clinicians robust, evidence-based, and contemporary recommendations regarding the clinical management of ACA in China.

Definition
ACA is defined as the presence of CrAg in serum or plasma while cerebrospinal fluid (CSF) CrAg tests, CSF pathogenic detection, and blood cultures are negative, in the absence of any history of cryptococcosis during the previous two years, and without the presence of any other clinical symptoms, signs, or imaging manifestations of cryptococcal infection.[5,6] It is worth noting that cryptococcal antigenemia may sometimes be symptomatic, and patients with symptomatic cryptococcal antigenemia (SCA) may have mild symptoms such as fever, headache, stiff neck,
cough, rash, or abnormal imaging results. In one particular study, the individuals with neurologic SCA had relatively milder symptoms at baseline, normal CSF opening pressures, and slightly higher CD4+ T-cell counts. [7] Compared with ACA, SCA has a higher probability of progression to life-threatening cryptococcosis. [8,9] Moreover, Kenneth and colleagues found that most (56%) SCA patients had confirmed CSF CrAg positive and that the inhospital mortality was similar between SCA and CM, indicating that SCA may be classified as a form of early cryptococcal meningoencephalitis. [7] Therefore, the management of individuals with SCA should be approached similarly to overt cryptococcal central nervous system infection, with consideration for more aggressive management with amphotericin-based therapy, or a combination of fluconazole and flucytosine. [10] Due to the substantial differences between ACA and SCA in definition and their natural history, discussion of SCA is beyond the scope of this review.

Prevalence

The prevalence of ACA has been found to vary depending on the geographical area. As an example, in sub-Saharan African, and Southeast Asian countries, the prevalence of ACA in patients presenting with advanced HIV infection has been reported to be between 1% and 16%, [11] whereas in the United States the prevalence of ACA among such patients was observed to be around 3%. [12,13] The reported prevalence of ACA among HIV-infected persons varies from 3.5% in Argentina, [14] to 8.8% in Uganda, [15] and 13% in South Africa. [16] Cryptococcal antigenemia has been found in 3.1% of asymptomatic hospitalized patients admitted to a referral center in Brazil [16,14] with CD4+ T-cell counts <200 cells/μL, irrespective of ART status. In studies from Asia, the prevalence of ACA among HIV-infected patients is about 7.1% in Indonesia and 1.3% in Chinese hospital inpatients. [17,18]

As expected, CrAg positivity is associated with a greater degree of systemic immunosuppression. Globally, the average prevalence of ACA in ART-naïve patients with CD4+ T-cell counts <100 cells/μL is estimated at 6.0%, corresponding, in 2014, to 278,000 people globally. [20] In the systematic review by Awoke et al., [19] the overall prevalence of cryptococcal antigenemia ranged between 1.7% and 33%, and pooled prevalence was 8%, with mean CD4+ T-cell counts approaching 100 cells/μL. Among HIV-infected patients with CD4+ T-cell counts between 101 and 200 cells/μL, the pooled prevalence of ACA is approximately 2%. [20] One study from Ethiopia reported an estimated serum CrAg positivity prevalence of 5.8% among HIV-infected adults with CD4+ T-cell counts between 201 and 350 cells/μL. [21]

In addition to ART-naïve patients, an increasing proportion of ART-experienced patients have also been observed to be positive for CrAg. For Ugandan adult patients with virologic failure (≥1000 ribonucleic acid [RNA] copies/mL), the prevalence of CrAg positivity was 4.2% among those with viral loads ≥5000 RNA copies/mL, and 0.7% among those with viral loads <5000 RNA copies/mL. [22]

Outcomes

ACA independently predicts mortality in patients initiating ART, and asymptomatic CrAg-positive HIV-infected adults have a 20% higher mortality than CrAg-negative adults. [23] One reason for this is that ACA has the potential to eventually develop into CM if untreated, and the mortality for CM is dramatically high in resource-limited settings. CM is reported to account for 15% of acquired immune deficiency syndrome (AIDS)-related deaths globally, [17] and has an in-hospital mortality of 30% to 60% in resource-limited settings. [24] In sub-Saharan Africa, the mortality for CM ranges between 37% and 58% in clinical trial settings, [25] and 30% and 59% in tertiary care settings, [26] even with ART and antifungal therapy. Incident CM occurs in 14% and 100% of patients, and death in 10% and 100% of patients in the absence of ART. [27]

Nevertheless, not all individuals with ACA go on to develop CM. [28] It is estimated that approximately 56% to 84% of individuals with ACA will progress to develop CM or succumb without a diagnosis unless treated with ART and/or preemptive fluconazole. [23] However, a South African study reported that ACA at baseline was 100% sensitive for predicting the development of CM during the first year of ART. [29] A Ugandan study of patients initiating ART reported a population attributable risk for mortality of 18%, compared with that associated with active tuberculosis. [29] Those who were positive for CrAg had a higher chance of early loss to follow-up (44.8% vs. 28.9%), and higher one-year mortality (22.4% vs. 11.6%) as compared to those who had a negative CrAg result, in a large cohort study conducted in Indonesia. After correction for other factors, such as ART administration, low CD4+ T-cell count, body mass index (BMI) <18.5 kg/m2, high plasma HIV RNA, and oral candidiasis, ACA remained significantly associated with one-year survival and the combined endpoint of death or loss to follow-up. [17]

The preceding evidence emphasizes the importance of screening patients with low CD4+ T-cell counts for CrAg, and has been advocated by experts in this field, and also has been recently recommended by World Health Organization (WHO). In addition, the value of screening programs is undermined when those who are screened positive do not receive appropriate treatment. A recently published study from Tanzania showed that even short-course intensive fluconazole may reduce mortality in patients with ACA. [23] Thus, early diagnosis, and targeted preemptive antifungal treatment for ACA, is crucial to reducing CM-related mortality in individuals living with HIV. [10]

Screening strategies

Detectable CrAg in peripheral blood precedes the onset of clinical symptoms by weeks to months, providing a window of opportunity for preemptive therapeutic intervention. [12,31] Therefore, early identification of cryptococcal antigenemia is crucial to improving patient outcomes. CrAg screening and preemptive treatment is now recommended by WHO and is also advocated by numerous national HIV guidelines.
Current evidence suggests that CrAg screening in the blood of HIV-positive patients with advanced immunodeficiency can identify those at risk of developing CM before the onset of clinically evident disease.[9] Screening for cryptococcal antigenemia is now considered the optimal approach for guiding resources in a national public health approach and is the preferred approach for identifying the risk of progression of disease when managing people presenting with advanced HIV disease.

**CD4+ T-cell count threshold for CrAg screening among HIV-infected patients**

An increasing number of researchers have recently focused their attention on the screening for ACA, and its predisposing factors. Among the studied risk factors, a low CD4+ T-cell count is the most important and most common risk factor for the identification of ACA in HIV-infected patients.

Ethiopia has adopted a cut-off screening level of <150 cells/µL, whereas in Rwanda CrAg screening is conducted at a CD4+ T-cell count of <200 cells/µL.[20] South Africa now includes universal reflex CrAg screening, where a CrAg test is performed on remnant blood samples from CD4+ T-cell count testing, in its national HIV guidelines for people with CD4+ T-cell counts <100 cells/µL.[11] However, the latest data from sub-Saharan Africa indicates that individuals with CD4+ T-cell counts >100 cells/µL also develop cryptococcal meningitis associated with HIV infection.[32] Moreover, a study in rural Tanzania used the presence of cryptococcal antigenemia to predict mortality or loss to follow-up among HIV-infected people with CD4+ T-cell counts >100 cells/µL and found that a CrAg screening threshold of CD4 <100 cells/µL missed 18% of CrAg-positive patients, suggesting that guidelines should consider a higher CrAg screening cut-off threshold.[31] Another retrospective, cross-sectional study in Nigeria also noted a high prevalence of ACA in patients with CD4+ T-cell counts between 100 and 200 cells/µL.[34] For people in high-income settings, like the United States, guidelines state that screening should be considered in patients with CD4+ T-cell counts <100 cells/µL (and especially in those with a CD4+ T-cell counts <50 cells/µL).[12,28] A study in Cotonou, Benin, suggests that routine screening for cryptococcal antigenemia should be conducted in profoundly immunodeficient patients with CD4+ T-cell counts <50 cells/µL.[15]

Current WHO and Infectious Disease Society of America guidelines, recommend CrAg screening in blood among those HIV-infected individuals who are ART-naive, with CD4+ T-cell count <100 cells/µL, and to consider testing those not on ART with CD4+ T-cell counts between 100 and 200 cells/µL.[36] This recommendation is based on past studies demonstrating that a “screen-and-treat” program identifying CrAg-positive individuals, and prescribing preemptive fluconazole therapy, in combination with an ART-adherence intervention, prevents invasive cryptococcal disease and death.[47] The WHO guidelines also state that CrAg screening may be considered at a higher CD4+ T-cell threshold of <200 cells/µL, but does not describe the precise circumstances in which to increase the threshold for CrAg screening.[38]

**Screening indications in both ART-naive and ART-experienced HIV-infected patients**

Since the “90–90–90” target for HIV/AIDS was proposed by The Joint United Nations Programme on HIV and AIDS in 2014, global ART coverage has increased significantly.[19] As a result of this strategic goal, the total number of individuals with very low CD4+ T-cell counts has declined, while the proportion of these individuals who are ART-experienced (i.e., currently taking ART, or who have previously taken ART but have interrupted therapy) has increased. Accumulating evidence strongly indicates the need to develop CrAg-screening approaches that cater for ART-naive individuals, and also to include ART-experienced individuals who present after disengagement from care, or individuals on ART with persistently low CD4+ T-cell counts.

As previously mentioned, it is universally accepted that a low CD4+ T-cell count is a significant risk factor for ART-naive patients. A lower CD4+ T-cell count is a surrogate for severe immune depletion; therefore, this subgroup of patients will inherently have a higher risk of cryptococcal infection.[19] Besides, HIV-infected patients with exposure to soil contaminated with avian droppings,[30] patients with low BMI,[19] males,[19] older people,[19] and patients living in high prevalence regions[41] are all associated with an increased risk for the development of cryptococcal antigenemia. It is interesting to note that a statistically significant difference in prevalence related to gender has been observed in some studies on ART-naive patients. This is likely due to poor health-seeking behavior in men, who tend to present later to care,[41,43] and the interaction of Cryptococcus with testosterone, which results in increased capsular polysaccharide release, and Cryptococcus-mediated macrophage death.[44]

The prevalence of cryptococcal antigenemia among the ART-experienced population has been observed at 3.0% in Uganda,[12,13] 2.8% in South Africa,[45] 3.1% in Brazil,[23] and 4.1% in Ethiopia.[21] Other studies in this population in Nigeria and Ethiopia have observed a higher CrAg prevalence of 8.9% and 8.4%,[21,46] respectively. All of these studies included participants who responded to ART or did not report a viral load. A significant proportion of ART-experienced patients with virologic failure present with fulminant cryptococcosis.[47] ART-experienced individuals with virologic failure are at high risk of developing CM, and/or death, despite receiving ART,[15,21] yet this subgroup of patients is not currently included in the WHO CrAg screening guidelines high-risk category. In Uganda during 2013–2017, nearly half of the patients presenting with CM were ART-experienced.[67] This implies that ART alone may be an insufficient therapeutic option for CrAg-positive HIV-infected individuals and that the high likelihood of death in CrAg-positive individuals is not completely abrogated by effective ART.[4,58] Because of this, it is necessary to perform new viral load-based CrAg screening in ART-experienced HIV positive patients.
Studies evaluating the value of CrAg screening in this ART-experienced population were identified as a research priority in recent WHO cryptococcal management guidelines. The prevalence of ACA depending on ART-status does not seem significantly different, with similar rates occurring in both ART-experienced and in ART-naïve individuals. The findings are consistent with a recent systematic review that found similar CrAg prevalence rates among cohorts including only ART-naïve individuals, and cohorts including both ART-naïve and ART-experienced patients. CrAg positivity was shown to significantly increase with higher viral loads, indicating a higher risk for cryptococcosis in people with more fulminant virologic failure. As national regulations and policies strengthen HIV detection and treatment as well as virological surveillance, increasing proportions of individuals with CM have been observed among ART-experienced individuals with undetected virologic failure. WHO guidelines recommend CrAg screening for individuals with CD4+ T-cell counts <100 cells/μL prior to initiating ART; however, no such guidelines exist for ART-experienced individuals. Given that viral load, monitoring is emphasized more than CD4+ T-cell count monitoring in this population, using viral load thresholds to identify who may require CrAg screening becomes more pertinent. We would, therefore, recommend CrAg screening among persons with virologic failure (>5000 RNA copies/mL), as this threshold is where a CrAg prevalence of 4.2% is observed based on current findings, irrespective of CD4+ T-cell count. In addition, academic investigative areas, including the optimal viral load threshold for CrAg testing, optimal timing of ART changes, effective implementation of cryptococcal management strategies, and the potential benefits of CrAg screening in ART-experienced individuals should be explored, in order to prevent the development of cryptococcosis among individuals with virologic failure.

Quantification of CrAg titers

Higher CrAg titers have also been positively associated with the development of meningitis and death. Accumulating evidence indicates that it may be possible to risk-stratify CrAg-positive individuals using CrAg titers, identifying those at the highest risk of cryptococcus-related mortality for more intensive antifungal treatment. Thus, performing a quantitative CrAg test for those who are CrAg positive is important to stratify risk. However, the putative etiological relationship between higher blood CrAg titers and the subsequent development of CM and/or mortality in CrAg-positive patients needs systematic investigation and elucidation. It’s been reported that asymptomatic CrAg positive individuals with a CrAg titer >1:160 are nine times more likely to develop meningitis compared to those with a titer <1:160. Patients with ACA and baseline serum/plasma titers of ≥1:160 experience worse outcomes, and titers ≥1:160 conferred a 2.6-fold higher risk of 6-month mortality in 151 CrAg-positive subjects in a Ugandan trial. CrAg titers >1:80 were found to be strongly associated with CM at baseline in a cohort of South African outpatients. According to other studies, CrAg titers ≥1:80 provided optimal discrimination between patients who survived or died within 6 months, with similar mortality rates in those with titers <1:80 and CrAg-negative individuals. Those with baseline serum/plasma titers of ≤1:80 have an 80% chance of survival to 6 months, and those with titers of 1:512 are closely associated with progression to disseminated cryptococcosis, and have a 66% survival rate, whereas those with titers of ≥1:2560 only have a 45% survival rate. While national and international guidelines do not make recommendations concerning CrAg titers, customizing antifungal therapy according to CrAg titer, whereby more intensive therapy is given for those with high CrAg titers, is a potential treatment strategy worth exploring.

Intervention strategies

Patients who test negative for blood CrAg do not require antifungal therapy and should initiate ART immediately. However, HIV-infected individuals who are negative for cryptococcal antigenemia are also at risk of cryptococcal infection. The CM incidence in people with a CD4+ T-cell count of <200 cells/μL who were initially negative for cryptococcal antigenemia before initiating ART, is 5.14 per 100 person-years. Additionally, studies have shown that preemptive fluconazole for ART-naïve CrAg-positive patients is beneficial for clinical prognosis, and is highly cost-effective. The above results suggest that this group of patients still requires follow-up and investigation, and appropriate testing for cryptococcal antigenemia at regular intervals.

Antifungal treatment

For patients with ACA, a preemptive course of fluconazole is recommended: 800 mg/day orally for 2 weeks, followed by 400 mg/day for 8 weeks, and then 200 mg/day pending immune reconstitution with ART. In addition, to decrease mortality among asymptomatic CrAg-positive persons, antifungal therapy should be started as soon as possible. This strategy is included in WHO management guidelines for patients with advanced HIV infection, and has been adopted as recommended clinical practice in several countries. Yet even with preemptive fluconazole therapy, approximately 25% of patients fail preemptive treatment and go on to develop meningitis or death, suggesting that existing antifungal regimens require further improvement and refinement. The optimal treatment of ACA patients is yet to be determined. Data in recent years suggests that the specific intervention strategy appropriate for this subgroup of patients is determined by the patient’s blood CrAg titer. In asymptomatic patients with a high CrAg titer >1:512, preemptive antifungal therapy is recommended to be consistent with CM regardless of CD4+ T-cell count. In patients with low CrAg antigen titers (<1:512), oral fluconazole alone may be used as the intervention strategy. Fluconazole has been the antifungal drug of choice, and studies have proven that it did reduce mortality in certain populations. However, some studies have found that fluconazole on its own may not be adequate to effectively
treat cryptococcal disease in HIV-infected patients with low CD4+ T-cell counts.

A recently advocated option is to extend the induction period of fluconazole to 10 weeks, followed by consolidation and maintenance treatment. An alternative induction regimen is to use fluconazole combined with 5-flucytosine for eight weeks. Another therapeutic induction regimen based on amphotericin B, accompanied by fluconazole and/or flucytosine has been advocated by some investigators, although actual drug dosages and therapeutic durations were not specified by the authors. These three enhanced interventions require further validation in large-scale clinical studies. Thus, enhanced antifungal therapy for cryptococcal antigenemia in HIV-infected patients seems to be the direction that contemporary research is focused on.

**Timing for ART**

ART is usually initiated two to six weeks after antifungal therapy in cryptococcal diseases, due to the potential for the development of paradoxical immune reconstitution inflammatory syndrome (IRIS), which is associated with the very early initiation of ART in patients with cryptococcal diseases. In 2014, the Cryptococcal Optimal ART Timing group conducted investigations to elucidate the optimal timing for ART initiation and concluded that deferring ART for 5 weeks after the diagnosis of cryptococcal meningitis was associated with significantly improved survival in these patients, as compared with initiating ART at 1 to 2 weeks. A retrospective study also found that early ART (initiated at <4 weeks) may increase all-cause mortality in patients compared to deferred ART (initiated at >4 weeks). Unfortunately, studies specifically addressing the issue of the optimal timing of ART initiation in patients with ACA are rare. Some researchers suggest that ART should be initiated two weeks after antifungal preemptive therapy to prevent ACA-IRIS. On the other hand, Rajasingham et al suggests that initiation of ART should perhaps be delayed beyond 2 weeks among individuals with low antigen burden.

**Management practice of ACA in China**

In China, data regarding ACA is scarce. A study conducted in China found that the prevalence of cryptococcal antigenemia was 10.3% in hospitalized HIV-infected patients, 87.6% of which have cryptococcal antigenemia together with clinical cryptococcosis, and ACA accounted for only 1.3% of the total population. In the preceding study, 90% of HIV-infected individuals with CrAg titers ≥ 1:640 developed CM, whereas patients with CrAg titers ≤ 1:5 were unlikely to progress to CM or cryptococcal septicemia. Obviously, the preceding study is not representative of ACA prevalence in all of China, and more studies need to be designed and conducted within China to clarify this point.

A meta-analysis conducted by Li et al found that the pooled prevalence of CrAg positivity in HIV-infected persons with CD4+ T-cell counts <200 cells/µL was 5%, which is similar to the prevalence of 6% found among HIV-infected persons with CD4+ T-cell counts <100 cells/µL in the Temfack et al meta-analysis, and 6.5% among HIV-infected persons with CD4+ T-cell counts <100 cells/µL in Ford’s meta-analysis, indicating that antifungal treatment seems imperative for HIV-infected persons with cryptococcal antigenemia who have CD4+ T-cell counts <200 cells/µL. Li et al also found that the incidence of CM was significantly reduced by preemptive antifungal therapy in CrAg+ HIV-infected persons with CD4+ T-cell counts <200 cells/µL. Based on the above study results, and considering the resource-constrained settings in most parts of China, a newly published expert consensus document formulated by 36 HIV clinical experts from around China published in 2020 recommends that the CD4+ T-cell count threshold for routine CrAg screening be raised from 100 CD4+ T-cells/µL to 200 CD4+ T-cells/µL in HIV-infected patients, in order to avoid missed detection as far as possible. Another consensus document formulated by HIV experts from China’s Zhejiang province has also recommended that HIV-infected patients with CD4+ T-cell counts <200 cells/µL should be screened for CrAg.

There is, as yet, no evidence indicating how frequently HIV-infected patients with CD4+ T-cell counts <200 cells/µL should be screened for CrAg. In clinical practice in mainland China, HIV-infected patients usually visit healthcare clinics every three months to refill prescriptions for free government-provided ART drugs, and to receive a routine clinical assessment. Thus, the newly published Chinese consensus document from 2020 recommends integrating CrAg screening with routine clinic visits for HIV-infected patients with CD4+ T-cell counts <200 cells/µL and testing these patients for CrAg every 3 to 6 months until their CD4+ T-cell counts are above 200 cells/µL for at least 3 months.

Antifungal therapy varies depending on CrAg titers. If serum CrAg titers are more than 1:512, prescribed antifungal regimens should be consistent with those for CM patients. However, if serum CrAg titers are less than 1:512, the WHO guidelines recommended fluconazole therapy as the preferred regimen, that is, 800 mg/day orally for two weeks, followed by 400 mg/day for eight weeks, and then 200 mg/day pending immune reconstitution with ART. Alternative antifungal regimens are also recommended in the 2020 Chinese expert consensus document. The detailed treatment plans are shown in Table 1.

**Conclusion and prospects**

ACA is an important disease process that adversely affects morbidity and mortality of cryptococcosis in HIV positive individuals. Thus, early screening and appropriate preemptive antifungal treatment for patients afflicted with ACA is likely to help decrease the incidence of progression to overt cryptococcosis, especially CM.

However, some pertinent questions remain. Although there have been some large studies concerning ACA globally, no large-scale studies investigating the existing situation about ACA in China have been conducted. Thus,
there is a dire need to accumulate integrated data, and subsequently reveal the real incidence of ACA in China. Thus far, all analyses in the literature regarding CrAg screening rely on CD4+ T-cell counts. In order to decrease the missed diagnosis rates for ACA, further research is needed, to compare non-CD4+ T-cell-based ACA screening strategies. The question remains as to how best to perform a specific screening plan in a given environment. The most important step is to conduct hierarchical screening stratified by different CD4+ T-cell thresholds, different ages, different ART states, etc. The second key step is to provide care and regular follow-up to high-risk groups. Compared to no screening, previous studies have shown that CrAg screening prior to the initiation of ART for patients with baseline CD4+ T-cell counts <100 cells/μL is a relatively low cost/ cost-saving policy, that also saves lives. However, in China, there has been no corresponding research to assess the cost-effectiveness of serum CrAg screening to prevent death among this group of patients. In HIV-infected patients with ACA, although higher titers herald worse outcomes, the relationship between CrAg titers and prognosis has not been thoroughly explored. Moreover, the value of monitoring sequential serum/plasma CrAg titers in ACA patients is not clear. Currently recommended antifungal treatment regimens for the treatment of ACA comprise mainly fluconazole by itself, and the optimal antifungal therapeutic regimen remains to be determined. Other medications, including drugs in current clinical use other than fluconazole, new drugs, and repurposed drugs should be considered for use to treat ACA. Moreover, clarity regarding precisely when to initiate ART could further decrease the mortality of ACA, but this remains unclear at present. For HIV-infected individuals testing positive for CrAg in pregnancy and the postpartum period, relevant criteria for CrAg screening and appropriately tailored antifungal drugs are conjectural and unverified at present and warrants further exploration.

**Funding**

This work was supported by the National Science and Technology Major Project of China During the 13th Five-year Plan Period (No.2018ZX10302014); the Joint Medical Research Project of Chongqing Science and Technology Commission (No.2019ZDXM012); the Youth Scientific Research and Innovation Fund Project of Chongqing Public Health Medical Center (No.2019QNKYXM05); and the Capacity Improvement Plan Project of Units appointed by the Chongqing Municipal Health Commission (No.2019NLYT003).

**Conflicts of interest**

None.

**References**


