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BRIEF REPORT

Cryptococcal Disease in the Era of "Test and Treat": Is There Cause for Concern?

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Treatment of cryptococcosis requires deferred initiation of antiretroviral therapy (ART). Early ART initiation may be detrimental in the context of cryptococcal infection by increasing the risk of immune reconstitution inflammatory syndrome (IRIS). We present 3 cases where early ART initiation in the presence of unrecognized cryptococcal disease had fatal outcomes.

Keywords. cryptococcal immune reconstitution syndrome; HIV; test and treat.

In an effort to scale up responses to the HIV epidemic, the Joint United Nations Programme on HIV/AIDS [1] set an ambitious 90-90-90 treatment target aiming for 90% of all HIV-infected persons knowing their status, 90% of HIV-infected persons receiving antiretroviral therapy (ART), and 90% of individuals on ART achieving viral suppression [2]. The World Health Organization, citing evidence that earlier ART results in better long-term outcomes and reduced HIV transmission, updated HIV guidelines to recommend ART initiation in all persons regardless of CD4 counts [3].

The move toward HIV testing followed by immediate ART initiation ("test and treat") has become a recommended tool to help reach the 90-90-90 treatment target. In addition, early ART initiation after many opportunistic infections results in fewer deaths and less AIDS progression vs delayed ART initiation [4]. However, cryptococcosis provides a notable exception, where early ART initiation could lead to worse outcomes compared with delayed ART initiation [5]. We present 3 cases from Uganda where "test and treat" in the setting of undiagnosed cryptococcal disease had detrimental outcomes.

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Case 1

A 45-year-old, newly diagnosed HIV-seropositive, ART-naïve man presented to an urban HIV clinic with 5 months of recurrent fevers and 4 days of bloody diarrhea. He appeared markedly wasted, but otherwise had an unremarkable physical examination. He was started on ciprofloxacin and metronidazole for presumptive infectious colitis and given a 1-week follow-up date. Upon return to clinic, his laboratory test results were reviewed and found to be notable for a CD4 count of 20 cells/μL. He underwent ART counseling and was immediately initiated on tenofovir, lamivudine, and efavirenz (TDF/3TC/EFV). Given his low CD4 count, a serum cryptococcal antigen (CrAg) was requested to be run from the central laboratory. Ten days later, he returned to the clinic complaining of evening fevers, cough, anorexia, and malaise. The serum CrAg results were reviewed and were positive, with a titer of 1:80. Clinical evaluation and symptom assessment found him to be asymptomatic for cryptococcal meningitis, and he was prescribed fluconazole 800 mg/d for asymptomatic cryptococcal antigenemia. Four days later (2 weeks from ART initiation), he returned to the clinic in a wheelchair, unconscious. His caretaker stated that he deteriorated at home, having experienced several seizures, worsening anorexia, and generalized weakness. While in clinic triage, he experienced a tonic-clonic seizure, leaving him unresponsive, hypotensive, and hypoxic, with a Glasgow Coma Scale score of 6 out of 15. Despite resuscitation efforts, he died before he could be transferred to a hospital.

Case 2

A 35-year-old man was newly diagnosed HIV-seropositive at a rural HIV clinic 3 weeks prior to hospital admission. His baseline CD4 was noted to be 7 cells/μL. At the time of HIV diagnosis, he had been experiencing persistent headaches. However, CrAg testing was not performed, and he was initiated on TDF/3TC/EFV 9 days prior to hospital admission. At hospital presentation, examination was notable for visual and hearing impairment, but he was awake, alert, and oriented. Laboratory test results were positive for both serum and cerebrospinal fluid (CSF) CrAg. His intracranial pressure was markedly elevated, with an opening pressure of 50 cmH_2O, CSF WBC <5 cells/μL, and CSF culture of 630 000 colony forming units/mL of *Cryptococcus*. He was started on amphotericin B (50 mg IV daily) and fluconazole (800 mg/d) for the treatment of cryptococcal meningitis. He required 3 subsequent lumbar punctures on consecutive days for persistently elevated intracranial pressure. He deteriorated on the fifth day of hospitalization and died.

Case 3

A 35-year-old man newly diagnosed HIV-seropositive with a baseline CD4 of 28 cells/μL presented to the hospital with 4 weeks of a dry cough, 2 weeks of headaches, and 1 day of vomiting. One month prior to hospital admission, he was found to be HIV-seropositive at a local clinic and initiated on TDF/3TC/EFV. Two weeks prior to hospital admission, he was initiated on empiric antituberculosis therapy based on clinical symptoms and an abnormal chest radiograph. He had no known history of cryptococcal disease, and no prior CrAg testing was performed. At hospital admission, he was alert, awake, oriented, and clinically stable. Laboratory test results were positive for both serum and cerebrospinal fluid (CSF) CrAg. CSF white cells were <5 cells/μL, CSF opening pressure was 20 cmH_2O, and CSF cultures grew *Cryptococcus* with a low fungal burden (10 colony-forming units/mL). He was started on amphotericin B (50 mg IV daily) and fluconazole (800 mg/d) for the treatment of cryptococcal meningitis according to national guidelines. Four days following admission, he became confused, unresponsive, and developed respiratory failure. Vancomycin and piperacillin-tazobactam were administered for possible sepsis, and dexamethasone was administered for potential unmasking immune reconstitution inflammatory syndrome (IRIS). Despite these measures, he continued to deteriorate and died 13 days after hospital admission.

DISCUSSION

Cryptococcosis deaths are estimated to account for approximately 15% of AIDS-related mortality [6]. Estimates place the global prevalence of cryptococcal antigenemia at 6.0% among HIV-infected persons with CD4 <100 cells/μL, resulting in 278 000 (95% confidence interval, 195 500–340 600) people with cryptococcal infection annually; the majority of these cases occur in Sub-Saharan Africa [6]. In order to prevent new cases of cryptococcal meningitis, the 2017 World Health Organization (WHO) guidelines, including current Ugandan National guidelines [7], recommend CrAg screening of all HIV-seropositive adolescents and adults with CD4 <100 cell/μL, followed by preemptive therapy with fluconazole for asymptomatic cryptococcal antigenemia [8]. The WHO recommends consideration of delaying ART initiation for 2 weeks after starting antifungal therapy in persons with asymptomatic cryptococcal antigenemia, albeit with a low level of evidence. Current WHO guidelines for management of cryptococcosis are under review.

In Uganda, inadequate infrastructure, resources, and training have led to critical gaps in cryptococcal antigen screening. The cases presented here depict missed or delayed opportunities for early CrAg screening and treatment. In case 1, *Cryptococcus* was considered only after a CD4 <100 cell/μL was noted, and further CrAg testing was delayed by following routine laboratory testing practices, rather than using the CrAg lateral flow assay (LFA) as a point-of-care test. Effective CrAg screening programs largely depend on concurrent CD4 testing and reflex laboratory-based CrAg screening. As CrAg screening is often dependent on CD4 count testing, there can be a delay from HIV diagnosis to detection of cryptococcal antigenemia in an at-risk person. Cases 2 and 3 highlight the lack of CrAg screening in HIV clinics, both rural and urban, either because of a lack of CrAg LFA kits or training and awareness among health care workers. Case 3 also highlights the challenges faced in persons with cryptococcal disease who have been misdiagnosed as having tuberculosis, leading to missed opportunities and delays in CrAg screening and treatment. In all 3 cases, ART initiation prior to CrAg screening and preemptive fluconazole therapy likely contributed to rapid clinical deterioration and death. More streamlined approaches to cryptococcosis diagnosis are clearly needed with the paradigm shift to "test and treat."

Cryptococcal infection must be considered in any newly diagnosed HIV-seropositive persons with a headache, particularly when the CD4 count is low. Cases 2 and 3 suggest a missed opportunity for early diagnosis of cryptococcal meningitis at the time of ART initiation. ART initiation in the context of early signs of cryptococcal meningitis may lead to the development of overt meningitis, rapid clinical deterioration, and death, as these cases demonstrate. When symptoms suggestive of cryptococcal meningitis are present at the time of HIV diagnosis, a lumbar puncture should be performed to rule out cryptococcal meningitis prior to ART initiation. Where lumbar punctures are not possible, persons with CrAg antigenemia in the presence of symptoms should be emergently referred to centers for further evaluation, and ART should be delayed. Clinicians, in their commitment to comply with the new guidelines for "test and treat," should not lose sight of potentially serious complications associated with opportunistic infections and ART initiation, such as IRIS or unmasking disease, which can be fatal [9].

Unmasking cryptococcal-related immune reconstitution inflammatory syndrome can lead to severe and rapid clinical deterioration following the restoration of immune function after ART initiation (Box 1) [10]. Since the widespread rollout of ART, the "90-90-90" goals set forth by UNAIDS, and the recommendation by the WHO to "test and treat," an increasing percentage of people are receiving ART at the time of cryptococcal meningitis diagnosis. In 2017, a majority of persons with cryptococcosis are now receiving ART at the time of meningitis diagnosis [11, 12]. Persons receiving ART at cryptococcal diagnosis have higher mean CD4 counts and lower CSF fungal burden, yet similar acute mortality to ART-naïve persons [13]. However, we have observed that individuals who initiate ART within 14 days of developing cryptococcal meningitis are at higher risk of death than those

Box 1. Abbreviated Case Definition of Unmasking Cryptococcal Immune Reconstitution Inflammatory Syndrome

- Unrecognized cryptococcal disease at the initiation, reintroduction, or switch of antiretroviral therapy
- Exaggerated or heightened inflammatory response:
  - Markedly elevated cerebrospinal fluid leukocyte count (>50 cells/μL)
  - Elevated opening pressure refractory to therapy
  - Painful or suppurating lymphadenopathy
  - Rapidly expanding central nervous system lesions, cryptococcoma(s)
  - Unusual focal site (ie, not within the central nervous system, lung, skin, or lymph nodes)
  - Granulomatous inflammation on histology
- Pneumonitis
- Clinical deterioration occurring early after antiretroviral therapy initiation, within 3 months

receiving ART for >14 days [14]. ART-experienced persons with cryptococcal meningitis are not all the same, as the timing of ART is crucial, and those with unmasking IRIS vs virologic failure may differ vastly immunologically. While dexamethasone was administered in case 3, it is unclear whether this is an effective management strategy for the treatment of unmasking IRIS. While current evidence appears to support a short course of corticosteroids in cases of severe *paradoxical* cryptococcal meningitis IRIS [15], there are limited data to support corticosteroid use for *unmasking* IRIS. In a recent trial that included ART-experienced participants in Southeast Asia and Sub-Saharan Africa, universal adjunctive dexamethasone did not provide benefit when added to standard antifungal therapy and was associated with more adverse events [9].

Immune reconstitution in the presence of cryptococcal disease should be a concern in centers where baseline CD4 testing is unavailable and where routine CrAg screening has a delayed turnaround time or has not yet been implemented. In the absence of a more streamlined approach to diagnosis, however, further consideration may be given to the role of empiric fluconazole therapy pending results of CD4 and CrAg testing in cases where ART is initiated immediately after HIV diagnosis. Earlier studies have demonstrated that daily prophylaxis with fluconazole is effective in reducing the risk of invasive cryptococcosis [16]. Most recently, an enhanced prophylaxis regimen consisting of fluconazole, trimethoprim–sulfamethoxazole, isoniazid–pyridoxine, azithromycin, and a single dose of albendazole was shown to be effective in preventing mortality from cryptococcal meningitis [17]. It is unclear if the improved mortality in this study was the result of preventing new infections, preventing the evolution of meningitis in cases of unrecognized cryptococcal antigenemia, or the reduced risk of developing IRIS by treating other possible opportunistic infections and improving immune function. It is possible that some combination of empiric or prophylactic fluconazole together with serum CrAg testing could be effective in preventing cryptococcal disease and minimizing mortality using a "test and treat" strategy.

The contribution of health systems in failing to curtail the high incidence of cryptococcal deaths in Africa, despite widespread ART roll out, may require new tailored approaches, both human and financial, to improve outcomes in persons with cryptococcal disease. Measures should be taken to disseminate and implement guidelines for cryptococcal antigen screening, equip health care facilities with point-of-care diagnostic test kits, and ensure an adequate supply of antifungals. Failure to enhance screening for cryptococcal antigenemia or cryptococcal meningitis while scaling up ART availability and distribution will undoubtedly lead to increasing fatalities of unmasking IRIS in an already vulnerable and severely immunocompromised population.

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