RAPID ADVICE

DIAGNOSIS, PREVENTION AND MANAGEMENT OF CRYPTOCOCCAL DISEASE IN HIV-INFECTED ADULTS, ADOLESCENTS AND CHILDREN

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Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-infected Adults, Adolescents and Children

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ACRONYMS AND ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
ASSURED	affordable, sensitive, specific, user-friendly, rapid, equipment-free, and delivered to those who need it
CDC	US Centers for Disease Control and Prevention
СМ	cryptococcal meningitis
CNS	central nervous system
CrAg	cryptococcal antigen
CSF	cerebrospinal fluid
EIA	enzyme immunoassay
GPRM	Global Price Reporting Mechanism
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HIV	human immunodeficiency virus
ICP	intracranial pressure
IRIS	immune reconstitution inflammatory syndrome
LA	latex agglutination
LFA	lateral flow assay
LP	lumbar puncture
OI	opportunistic infection
PEPFAR	President's Emergency Plan for AIDS Relief
PICO	patient or population, intervention, comparison, outcome
PITC	provider-initiated HIV testing and counselling
PLHIV	people living with HIV
POC	point-of-care
POCT	point-of-care testing
RCT	randomized, controlled trial
RLS	resource-limited settings
ТВ	tuberculosis
UCSF	University of California at San Francisco
UN	United Nations
USAID	The US Agency for International Development
WHO	World Health Organization

1. OVERVIEW

1.1 Background and Executive Summary

Increasing access to antiretroviral therapy (ART) has transformed the prognosis of HIVinfected patients in resource-limited settings (RLS). However, treatment coverage remains relatively low, and HIV diagnosis occurs at a late stage. As a result, many patients continue to die of HIV-related opportunistic infections (OIs) in the weeks prior to, and months following initiation of ART. Cryptococcal disease is one of the most important OIs, and a major contributor to this early mortality¹, accounting for between 13% and 44% of deaths in HIV-infected cohorts in resource-limited countries². In sub-Saharan Africa alone, there are more than 500,000 deaths each year due to cryptococcal meningitis (CM), which may exceed those attributed to tuberculosis¹.

The case fatality rate in patients with cryptococcal meningitis, the commonest presentation of HIV-related cryptococcal disease in adults, remains unacceptably high, particularly in sub-Saharan Africa, at between 35%-65%³. This compares with 10%-20% in most developed countries. The main reason for this is a delay in presentation with diagnosis only when meningitis is advanced and treatment is less effective, mainly as a result of limited access to lumbar puncture (LP) and rapid diagnostic assays. A further contributing factor is the poor availability and high cost of the first-line anti-fungal induction treatment – intravenous amphotericin B, and the ability to monitor and manage its treatment-limiting toxicities, as well as the frequent complication of raised intracranial pressure. A recent WHO review of national guidelines from RLS on management of cryptococcal disease also highlighted variations in recommendations for induction and consolidation regimens and doses, as well as gaps in guidance on important aspects of management, such as the optimal timing of ART initiation, the monitoring and management of amphotericin B toxicity, and the frequent complication of raised intracranial pressure⁴. An approach leading to earlier diagnosis, and improved treatment of cryptococcal disease and its complications, therefore, is urgently needed to reduce the incidence and associated high mortality in RLS.

¹ Park BJ et al. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS 2009;23 (4):525-30.

² French N, et al. Cryptococcal infection in a cohort of HIV-I infected Ugandan adults. AIDS 2002; 16(7):1031-8; Okongo M, et al. Causes of death in a rural, population-based human immunodeficiency virus type 1 (HIV-1) natural history cohort in Uganda. Int J Epidemiol 1998;27: 698-702; Churchyard GJ, et al. Factors associated with an increased case-fatality rate in HIV-infected and non-infected South African gold miners with pulmonary tuberculosis. Int J Tuberc Lung Dis 2000:4:705-712.

³ Lessells RJ, et al. Poor long-term outcomes for cryptococcal meningitis in rural South Africa. S Afr Med J. 2011; 101(4): 251-2; Bicanic T, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviralnaive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. Clin Infect Dis 2007; 45:76-80; Kambugu A, et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. Clin Infect Dis 2008; 1694-701.

⁴ Gavrillidis G, et al. Cryptococcal Meningitis (CM): Review of Induction Treatment Guidance in Resource-Limited Settings (RLS). ICASA December 2011, Addis Ababa. (TUAB0505)

During 2011, the WHO Department of HIV/AIDS in collaboration with the Department of Maternal, Child and Adolescent Health has worked to develop recommendations on diagnosis, prevention and management of cryptococcal disease in adults, adolescents and children⁵. The evidence to support these recommendations has been assembled through a series of coordinated activities to review and synthesize existing and emerging evidence using systematic reviews, GRADE⁶ profile preparation and analysis, evaluation of recommendations in current national guidelines, survey of costs of diagnostics and drugs, and a country-level feasibility assessment.

The key recommendations contained here are released as Rapid Advice because several countries are in the process of updating their national guidelines for HIV care and OI management. There is also important new evidence in the diagnosis and management of cryptococcal disease of relevance to RLS, that needs to be incorporated into guidance, including:

- i. a new point-of-care (POC) assay for detection of cryptococcal antigen lateral flow assay (LFA) for use in diagnosis and screening of infection;
- ii. data about the use and cost-effectiveness of cryptococcal antigen screening prior to ART initiation, to identify persons for targeted pre-emptive fluconazole therapy and prevention of disease;
- iii. recent clinical trial data on the most effective first-line treatments for cryptococcal meningitis, and experience supporting the value of a more affordable and available high-dose oral therapy regimen;
- iv. evidence that a simplified protocol of pre-hydration and electrolyte replacement before administering amphotericin B substantially reduces associated toxicities.

This Rapid Advice focuses on six key areas out of the ten planned for the full Guideline:-

- Diagnosis of cryptococcal disease
- Screening and prevention of cryptococcal disease
- Induction, consolidation and maintenance antifungal treatments
- Prevention, monitoring and management of drug toxicities
- Timing of ART initiation
- Timing of discontinuation of fluconazole maintenance treatment (secondary prophylaxis).

The recommendations encourage earlier diagnosis using rapid cryptococcal antigen (CrAg) assays, consideration of CrAg screening and pre-emptive therapy in high-

⁵ WHO definition of adolescent (10 to 19 years) and children (up to 10 years)

⁶ http://www.gradeworkinggroup.org/index.htm

burden cryptococcal populations, early treatment with amphotericin B-based regimens and a minimum package of toxicity prevention, monitoring and management, and guidance on timing of ART initiation, and discontinuation of azole maintenance treatment.

1.2 Objectives

- To provide both a summary of the key evidence and its assessment using the GRADE process, and recommendations on the prevention, diagnosis and management of cryptococcal disease in HIV-infected adults, adolescents (10-19 years) and children (up to 10 years), with a focus on settings with limited health systems capacity and resources, and a high burden of cryptococcal disease.
- To outline standards for high quality care of persons living with HIV infection (PLHIV) and patients with cryptococcal disease, by providing evidence-based recommendations that consider the risks and benefits, acceptability, feasibility, cost and other resource implications.
- To identify gaps and prioritize areas where further clinical and operational research are required.

1.3 Target audience

The recommendations are aimed at policy makers, national treatment advisory boards, and HIV programme managers, as well as health-care professionals providing care for HIV-infected adults, adolescents, and children in both outpatient and inpatient settings. In addition, these recommendations are intended for partners supporting implementation of HIV care and treatment services, and organizations providing technical and financial support to HIV care and treatment programmes in resource-limited settings.

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