HIV/AIDS Programme

RAPID ADVICE

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

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Rapid Advice

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
CM	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
TB	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 HIV-infected 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 mortality[1], accounting for between 13% and 44% of deaths in HIV-infected cohorts in resource-limited countries[2]. 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 tuberculosis[1].

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 pressure[4]. 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 antiretroviral-naive 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 Gavriilidis 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 children[5]. 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, GRADE[6] 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.

2. RECOMMENDATIONS AT A GLANCE

The recommendations contained in this Rapid Advice on diagnosis, prevention and management of cryptococcal disease (meningeal and non-meningeal) in adults, adolescents, and children are based on several guiding principles:

- Early diagnosis is key to improving mortality due to cryptococcal disease. Health care professionals need to have a low threshold for suspecting cryptococcal meningitis. Countries should prioritise reliable access to rapid diagnostic CrAg assays, either latex agglutination (LA) or lateral flow assay (LFA) for use in cerebrospinal fluid (CSF) and serum or plasma.
- Early ART initiation is the most important and cost-effective preventive strategy to reduce the incidence and high mortality associated with cryptococcal meningitis. Patients should ideally initiate ART at a CD4 count of 350 cells/mm^3, and definitely before a decline in the CD4 cell count to less than 200 cells/mm^3, or development of WHO stage 3 or 4 disease.
- To promote the use of optimal antifungal treatment regimens and approaches that improve survival, clinical and neurological outcomes, and rapid fungal clearance, while minimising drug related toxicities.
- Prompt referral for HIV testing and care should be undertaken as soon as appropriate following diagnosis of cryptococcal disease, to facilitate early HIV diagnosis, uptake of ART and retention in care.

The major recommendations for the six key areas covered in this Rapid Advice

I. Diagnosis of cryptococcal disease **(see page 16)**

- Prompt LP with measurement of CSF opening pressure and rapid CSF CrAg assay (either LA or LFA) or rapid serum CrAg (either LA or LFA) is the preferred diagnostic approach. Alternative recommended diagnostic approaches will depend on programmatic considerations (see page 16).

II. Prevention of cryptococcal disease (primary prophylaxis) **(see page 18)**

- The routine use of antifungal primary prophylaxis for cryptococcal disease in HIV-infected adults, adolescents and children with a CD4 count less than 100 cells/mm^3, and who are CrAg-negative or where CrAg status is unknown, is not recommended prior to ART initiation, unless a prolonged delay in ART initiation is likely.
- Routine serum or plasma CrAg screening in ART-naïve adults (but not adolescents or children), followed by pre-emptive anti-fungal therapy if CrAg-positive may be considered prior to ART initiation in patients with a CD4 count less than 100 cells/mm3, and where this population also has a high prevalence of cryptococcal antigenaemia.

III. Induction, consolidation and maintenance treatment regimens (see page 21)

- For the two-week induction treatment phase, a regimen containing amphotericin B combined with flucytosine or fluconazole is the recommended option.
- In settings where amphotericin B is not available, regimens containing fluconazole combined with flucytosine, or high-dose fluconazole monotherapy are alternative options.
- For the eight-week consolidation treatment phase, a regimen containing oral fluconazole is the recommended option.
- For the maintenance treatment phase, a regimen containing oral fluconazole is the recommended option.

IV. Prevention, monitoring and management of amphotericin B toxicity (see page 26)

- In HIV-infected patients receiving amphotericin B-containing induction treatment regimens, a minimal package of toxicity prevention, monitoring and management is recommended to minimize the serious amphotericin B-related toxicities of hypokalaemia and nephrotoxicity.

V. Timing of ART initiation (see page 28)

- In HIV-infected patients with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to anti-fungal therapy, and after 2-4 weeks of induction and consolidation treatment with amphotericin B-containing regimens combined with flucytosine or fluconazole, or after 4-6 weeks of treatment with a high-dose oral fluconazole induction and consolidation regimen.

VI. Discontinuation of treatment maintenance (secondary prophylaxis) (see page 30)

- In HIV-infected adults, adolescents and children above two years of age with successfully treated cryptococcal disease, discontinuation of anti-fungal maintenance treatment is recommended when patients are stable and adherent to ART and anti-fungal maintenance therapy for at least one year **and** show evidence of immune reconstitution.
- In children aged less than two years with successfully treated cryptococcal disease, anti-fungal maintenance treatment should NOT be discontinued.

3. THE GUIDELINE PROCESS

3.1 Retrieving, summarizing and presenting the evidence

1. The PICO[7] questions to be considered were agreed upon by the internal WHO Cryptococcal Guideline Working Group in consultation with an expert group in February 2011, and finalised in April 2011. A series of activities then were undertaken to prepare for the July 2011 Guideline Development Group meeting:
2. Evidence profiles based on the GRADE methodology[6] were prepared for the six PICO questions that are contained in the rapid advice. All relate to HIV-infected adults, adolescents and children in RLS:
    I. **Diagnosis:** What is the optimal assay or combination of assays for the diagnosis of cryptococcal meningitis and non-meningeal cryptococcal disease, and to screen for cryptococcal infection?
    II. **Primary prevention:** What is the most effective (and cost-effective) strategy for the prevention of cryptococcal disease?
    III. **Treatment:** What are the most effective induction, consolidation and maintenance treatments of cryptococcal meningitis and non-meningeal cryptococcal disease?
    IV. **Toxicity – prevention, monitoring, and management:**
        i. What is the most appropriate approach to prevent and manage key drug toxicities?
        ii. What is the most appropriate type and frequency of toxicity monitoring of patients on initial treatment regimens for cryptococcal disease?
    V. **Timing of ART initiation:** When is the optimal time to initiate ART after initial treatment of cryptococcal meningitis and non-meningeal cryptococcal disease?
    VI. **Discontinuation of maintenance treatment (secondary prophylaxis):** What is the optimal timing for discontinuing secondary azole prophylaxis for preventing relapse?

The final Guideline will cover the following additional PICO questions:

VII. What is the most appropriate type (routine or targeted) and frequency of monitoring to assess treatment response in patients on initial treatment regimens for cryptococcal disease?

7 PICO is an acronym that describes the elements of a well-formed clinical question. The structure includes: "P" for the patient or population; "I" for the intervention of interest; "C" for comparison; and "O" for outcome

VIII. What is the optimal approach to diagnosis and management of microbiological treatment failure or relapse in cryptococcal disease?

IX. What is the optimal management of the complications of raised intracranial pressure (ICP) and cryptococcoma in cryptococcal meningitis?

X. What is the optimal management of cryptococcal meningitis immune reconstitution inflammatory syndrome (IRIS)?

3. Based on the PICO questions, systematic reviews of the peer-reviewed literature and conference abstracts were conducted through a collaborative effort between WHO and the University of California at San Francisco (UCSF), using the HIV/AIDS Cochrane Collaborative Review Group search strategy.

4. A review was undertaken to study and compare current recommendations on management of cryptococcal disease in guidelines from 31 countries in RLS.

5. A country-level feasibility assessment was undertaken through a semi-structured telephone interview with 30 health care providers in 16 countries across Africa, Asia and Latin America to determine current availability of diagnostic tests and cryptococcal drugs, and barriers to access.

6. Costing information for the key cryptococcal drugs (amphotericin B, liposomal amphotericin, fluconazole and flucytosine) in different countries was prepared from pricing information contained in key databases[8]. Cost implications of the proposed recommendations were presented and discussed at the Guidelines Development meeting.

7. A report was produced on drug interactions between fluconazole, amphotericin B, and flucytosine, with antiretroviral drugs and anti-tuberculosis (TB) drugs.

8. Consultations were conducted with two organizations that had experience with drug donation programmes, and the findings summarized.

The GRADE evidence profiles, and the full set of supporting documentation is accessible from the Cryptococcal Guideline Working Group website[9], and will be included and referenced in the full Guideline.

3.2 Key principles

The Guideline Development Group meeting on *Diagnosis, Prevention and Management of Cryptococcal disease in HIV-infected adults, adolescents and children* was held in Geneva from July 21-22, 2011.

8 Global Price Reporting Mechanism (GPRM) (http://apps.who.int/hiv/amds/en/ and http://apps.who.int/hiv/omds/opic/) and International Drug Price Indicator (http://arc.msh.org/priceguide)

9 http://cryptococcus.pbworks.com

In considering the evidence and before making its recommendations, the Guideline Development Group discussed and agreed upon a set of principles that should be used by national advisory bodies in developing national treatment recommendations for cryptococcal disease. The key consideration was that the proposed interventions should secure the greatest likelihood of survival and quality of life for the greatest number of PLHIV.

The key principles guiding the development of these recommendations were as follows:

- to prioritize the best options for diagnosis, prevention and treatment of cryptococcal disease, and propose alternatives if the best option was not available;
- to be both realistic and aspirational, recognizing the need for progressive implementation of the recommendations of these guidelines;
- to be clear when high-quality evidence supports a strong recommendation;
- to be clear when low-quality evidence or an uncertain balance between risks and benefit supports a conditional recommendation.

3.3 Consensus, external review and updating

The Guideline Development Group meeting reviewed evidence around the six key PICO questions in different sessions. Each of the sessions included presentations on the GRADE analyses or other evidence, cost implications, and proposed recommendations.

Risk-benefit analysis tables were compiled for each question, covering the following domains:

- recommendations
- quality and grade of evidence for the outcomes deemed critical
- benefits and risks
- values and preferences
- costs and feasibility
- areas for advocacy
- research gaps

The proposed recommendations were reviewed and existing recommendations refined taking into consideration the quality of evidence and these other factors. If outcomes of the GRADE analyses were inconclusive, other factors as listed above were taken into consideration in making a recommendation.

Discussions were held in plenary sessions with all members present. Consensus was sought on each recommendation, and the ranking of both the strength of each recommendation, and the quality of evidence, as outlined below. Disagreements were debated during plenary and group sessions.

A **Strong recommendation:** the Guideline Development Group was confident that the desirable effects of the recommendation would outweigh any undesirable effects and that most individuals should receive the intervention.

A **Conditional recommendation:** the Guideline Development Group concluded that the desirable effects of the recommendation probably outweighed any undesirable effects, but the Guideline Development Group was not confident about these trade offs.

The **quality of evidence** describes the 'extent to which one can be confident that an estimate of effect or association is correct'. For the purposes of the GRADE process, evidence is categorized as high, moderate, low or very low. Low, or very low quality of evidence does not necessarily imply that the studies were conducted poorly, but that the data were not perhaps optimal for developing this recommendation.

The key recommendations, and risk-benefit tables with factors that were considered in making the recommendation, were sent to 20 independent peer reviewers. Each was asked to provide written feedback on whether they agreed with the recommendation or not, and whether there were any other key points that needed to be addressed. With representation from different regions, countries and perspectives, the peer-review process confirmed overall strong support for the proposed recommendations. Suggestions and comments were received from peer review, and the draft recommendations and risk benefit tables were reviewed and finalized.

The summary recommendations were finalized and approved by the WHO Guideline Review Committee in November 2011.

3.4 Publication and timing

This *Rapid Advice for Diagnosis, Prevention and Management of Cryptococcal disease in HIV-infected Adults, Adolescents and Children* will be posted online, with a limited print edition in English. However, requests from WHO Regional Offices for translation into other languages can be supported from WHO Headquarters.

It is expected that a draft of the full Guideline will be available in February 2012 for final clearance, with publication and dissemination anticipated in March 2012. The full guideline document will be reviewed again in 2015, unless significant new evidence warrants an earlier review process.

4. DISSEMINATION, ADAPTATION, IMPLEMENTATION AND EVALUATION

WHO will work closely with WHO Regional and Country Offices, UN and other implementing partners to plan for rapid dissemination, adaptation and implementation of the new recommendations. Much experience has been obtained from previous Guideline publications, and active support for Guideline revision at country-level is needed. Key steps in the dissemination include:

- Release of the Rapid Advice.
- Production and publication of the full Guideline, with translation into other languages.
- Rapid development of adaptation tools to assist countries prioritise limited resources to facilitate full implementation over time.
- Briefings and joint planning for dissemination with international and national implementing partners.
- Regional conferences and workshops, to support country adaptation.

5. DECLARATIONS OF INTEREST

Declaration of interest forms were collected from every member of the Guideline Development Group and peer reviewers. The WHO Secretariat considered that there were no declarations that represented a conflict of interest. Technical information was provided by Sean Bauman, Chief Executive of IMMY diagnostics, on the CrAg Lateral Flow Assay for cryptococcal antigen by way of a short presentation followed by questions from the Guideline Development Group. He was not present for any other part of the meeting, and was not involved in the decision-making process.

6. COLLABORATION WITH EXTERNAL PARTNERS

There were several external collaborators specific to this Rapid Advice. All collaborations will be detailed in the full Guideline.

Development of this Guideline was supported through PEPFAR (President's Emergency Plan for AIDS Relief) through the US Centers for Disease Control and Prevention (CDC) and The United States Agency for International Development (USAID).

7. KEY RECOMMENDATIONS

Diagnosis of first episode of cryptococcal disease

Guiding principles

- Early diagnosis and treatment are key to improving mortality from cryptococcal disease. Health care professionals need to have a low threshold for suspecting cryptococcal meningitis (CM). Countries should prioritise widespread and reliable access to rapid diagnostic CrAg assays, either latex agglutination (LA) or lateral flow assay (LFA) for use in cerebrospinal fluid (CSF), serum or plasma.
- Measurement of CSF opening pressure should be performed at the initial LP examination.
- Fungal culture remains the gold standard for confirmation of the diagnosis of initial cryptococcal disease, confirmation of relapses or cases refractory to treatment, and adequate response to treatment. Countries should strengthen their national laboratory capacity and access to fungal culture.

Recommendations

1. In HIV-infected adults, adolescents and children with suspected first episode of cryptococcal meningitis (CM), prompt lumbar puncture (LP) with measurement of CSF opening pressure and rapid CSF CrAg assay (either LA or LFA) or rapid serum or plasma CrAg (either LA or LFA) are recommended as the preferred diagnostic approach.

   [Strong recommendation, moderate quality of evidence]

   Depending on programmatic considerations, the following diagnostic approaches are recommended.

   A. In settings with ready access to and no contraindication for LP:
      a. If both access to CrAg assay (either LA or LFA), and rapid results (i.e. <24 hours) are assured:
         LP + rapid CSF CrAg assay.
         [Strong recommendation, moderate quality of evidence]
      b. If access to CrAg assay either not available and/or rapid results not assured:
         LP + CSF India ink test examination.
         [Strong recommendation, moderate quality of evidence]

   B. In settings without immediate access to LP, or when it is clinically contraindicated[10]:

10 Such as significant coagulopathy or suspected space occupying lesion based on focal neurological signs, recurrent seizures, or confirmed on CT scan. Raised intracranial pressure is not a contraindication to LP. Contraindication may include major spinal deformity and consistent patient refusal.

a. If both access to CrAg assay (either LA or LFA), and rapid results (i.e., less than 24 hours) are assured:
   Rapid serum or plasma CrAg. If CrAg is positive, initiate treatment for presumed cryptococcal meningitis, with immediate referral for further investigation and treatment as appropriate.

   [Strong recommendation, moderate quality of evidence]

b. If serum or plasma CrAg assay is either not available and/or rapid access to results is not assured:
   Rapid referral for further investigation and treatment as appropriate.

   [Strong recommendation, moderate quality of evidence]

2. In HIV-infected adults, adolescents and children with suspected non-meningeal cryptococcal disease, use of a serum or plasma CrAg assay is recommended, in conjunction with histopathological and/or culture examination of appropriate tissue or fluid samples where possible, and exclusion of other competing diagnoses. India ink microscopy examination or a CrAg assay in appropriate tissue or fluid samples may also be used.

   [Strong recommendation, low quality of evidence]

Remarks

In developing these recommendations, the Guideline Development Group placed very high value on early diagnosis of cryptococcal disease and, therefore, prompt antifungal therapy, to reduce the high pre and post ART early mortality and morbidity. There was high value placed on the use of simple low cost assays for RLS that are less labour intensive or laboratory dependent.

The Guideline Development Group recognised the importance of a high index of suspicion for CM among health care professionals, and the importance of LP to confirm CM, exclude other diagnoses, and both measure and manage intracranial pressure.

The conventional approach to diagnosis of CM requires LP with an India ink test, positive cryptococcal antigen test or culture. The Guideline Development Group reviewed GRADE evidence profiles based on pooled data from more than 30 observational studies on the performance (sensitivity, specificity and predictive value) of three types of CrAg assays in CSF and serum (LA, enzyme immunoassay (EIA) and LFA), as well as CSF India ink test, compared to CSF culture (in most cases) as the gold standard, in participants with either suspected or confirmed cryptococcal disease.

The Guideline Development Group's recommendations for the preferred use of a rapid CrAg assay (either LA or LFA) in CSF or serum (depending on access to lumbar puncture), was

based on the CrAg assays much higher sensitivity and specificity than the India ink test (especially in patients with low CSF fungal burden), and that it is easier to perform and less dependent on technician skill than the India ink test. The EIA assay was not included as a recommended CrAg assay because of its higher cost. The LFA has several advantages over the LA CrAg assay: it is less expensive, has a rapid 5-15 minute turnaround time, requires little training for its use and interpretation, can be performed with minimal laboratory infrastructure and without refrigeration since it is stable at room temperature, and satisfies most of the WHO ASSURED criteria for point-of-care tests (POCT)[11]. However, the Guideline Development Group recognized the more limited evaluation to date of the LFA, particularly regarding specificity, and so both the LA and LFA were included as recommended CrAg assays. There is currently a lack of data on CrAg assay performance in other relevant populations, such as children, patients with pulmonary disease, and in lower-prevalence settings.

A serum or plasma CrAg was recommended as an initial diagnostic option in settings where access to LP was limited or contraindicated, despite its slightly lower sensitivity, to expedite diagnosis and initiation of anti-fungal therapy. The Guideline Development Group emphasised that serum CrAg diagnosis should not replace the need for referral and CSF examination, which should be undertaken whenever it is feasible and clinically appropriate.

The Guideline Development Group recognised the need for cost reduction of CrAg assays to make them more widely available in RLS. Countries should develop plans to improve access to rapid CrAg assays, although the speed and completeness of access will be determined by each country's health system capacity, cryptococcal burden, ART coverage and available funding.

Prevention of cryptococcal disease

Guiding principles

- Early ART initiation is the most important and cost-effective preventive strategy to reduce the incidence and high mortality associated with cryptococcal meningitis in HIV-infected adults, adolescents and children in RLS. Although it is never too late to initiate ART, patients should ideally initiate ART at a CD4 count of 350 cells/mm^3, and definitely before a decline in the CD4 cell count to less than 200 cells/mm^3, consistent with WHO 2010 ART guidelines[12].
- Patients with a positive serum or plasma CrAg identified on screening, and with symptoms or signs suggestive of cryptococcal meningitis, should have an LP with CSF examination and India ink or CSF CrAg assay, to exclude active cryptococcal disease.

11 Affordable, Sensitive, Specific, User-Friendly, Rapid, Equipment-free, and Delivered to those who need it (ASSURED)

12 http://www.who.int/hiv/pub/arv/adult2010/en/index.html

Recommendations

1. The routine use of antifungal primary prophylaxis for cryptococcal disease in HIV-infected adults, adolescents and children with a CD4 count less than 100 cells/mm^3, **and** who are CrAg-negative or where CrAg status is unknown, is not recommended prior to ART initiation, unless a prolonged delay in ART initiation is likely.

   [Strong recommendation, high quality of evidence]

2. The use of routine serum or plasma CrAg screening in ART-naïve adults, followed by pre-emptive anti-fungal therapy if CrAg-positive, to reduce the development of cryptococcal disease, may be considered prior to ART initiation in:

   a. patients with a CD4 count less than 100 cells/mm^3, **and**

   b. where this population also has a high prevalence of cryptococcal antigenaemia[13].

   [Conditional recommendation, low quality of evidence]

3. The use of routine CrAg screening in ART-naïve adolescents and children with pre-emptive antifungal therapy if CrAg positive, prior to ART initiation is not recommended.

   [Conditional recommendation, low quality of evidence]

4. In settings where screening for unrecognised cryptococcal infection is currently undertaken or being considered, a serum or plasma CrAg assay (LA or LFA) is recommended.

   LA [Strong recommendation, moderate quality of evidence]

   LFA [Conditional recommendation, moderate quality of evidence]

Remarks

There is a high incidence of cryptococcal meningitis (CM) and mortality before ART initiation, and at least a third of all cases of CM now present after ART initiation. In developing these recommendations, the Guideline Development Group placed high value on prevention of cryptococcal disease, as well as early detection to prevent the development of severe disease and mortality before and after ART initiation.

The Guideline Development Group recognised that earlier initiation of ART at a CD4 cell count of 350 cells/mm^3 in accordance with 2010 WHO guidelines remains the most important preventive strategy to reduce the incidence of cryptococcal infection and associated high mortality.

13 At least >3%: From: Meya D, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cells count <100 cells/μL who start HIV therapy in resource-limited settings. Clin Infect Dis 2010; 51:448-55.

The Guideline Development Group recommended against the routine use of primary fluconazole prophylaxis to prevent cryptococcal disease in all patients with a low CD4 count prior to ART, unless a prolonged delay in ART initiation was likely. Five RCTs have shown that azole prophylaxis reduces the incidence of cryptococcal disease (most patients had a CD4 count less than 150 cells/mm^3), but there was no clear impact on overall survival, with the exception of one study from Thailand. A further trial of fluconazole prophylaxis in CrAg negative patients with a CD4 count less than 200 cells/mm^3 again showed a significant reduction in the risk of cryptococcal disease, but not on all-cause survival. The recommendation was therefore based on the lack of consistent survival benefit associated with routine prophylaxis; the observation that the majority of patients (greater than 90%) even with advanced immunodeficiency are CrAg-negative, and at low risk of developing cryptococcal meningitis unless ART is delayed; the large number of patients that would require prophylaxis and associated costs; the risk of prophylaxis providing inadequate therapy in patients who may have unrecognized active cryptococcal disease; and concerns regarding drug resistance, and the potential for drug interactions and teratogenicity with fluconazole.

The Guideline Development Group considered the alternative strategy of serum CrAg screening in ART-naïve patients with low CD4 counts, to identify early on persons at high risk of developing cryptococcal disease, with pre-emptive fluconazole therapy in those CrAg-positive, to prevent cryptococcal disease and associated mortality both before and after ART initiation (including cryptococcal IRIS). There have been three cost effectiveness studies of this "screen and treat" approach in patients with a CD4 count less than 100 cells/mm^3. The cost to prevent one death ranged from $77 to $266, and this approach was estimated to be cost-saving above a CrAg prevalence of 3% in one study against the cost of amphotericin induction therapy. However, further field studies are needed to establish: (i) the feasibility of this "screen and treat" approach and its impact on mortality; (ii) the most cost-effective threshold of prevalence above which a "screen and treatment" programme is cost-effective relative to routine azole prophylaxis in all patients; (iii) the optimal selection of serum CrAg-positive patients who require an LP to rule-out central nervous system (CNS) disease; and (iv) the optimal treatment regimen in those with isolated serum CrAg positivity. Therefore, the Guideline Development Group made only a conditional recommendation for programmes to consider the use of a "screen and treat" approach in patients with both a low CD4 count and a high prevalence of cryptococcal infection. Given the low incidence of cryptococcal infection in adolescents and children, a "screen and treat" approach is not recommended in these groups.

The use of the LFA CrAg point-of-care-test would further facilitate and reduce the costs of a "screen and treat" strategy, especially in settings lacking laboratory support, but only the LA CrAg assay has been evaluated in existing studies. There is a need for prompt evaluation of the utility of LFA as a screening tool in asymptomatic patients across a range of prevalence settings.

Induction, consolidation and maintenance treatment regimens

Guiding principle

- To promote the use of optimal antifungal treatment regimens and approaches that improve survival, clinical and neurological outcomes, and rapid fungal clearance, while minimising drug related toxicities.

Recommendations

Summary of induction, consolidation and maintenance treatment recommendations and dosage for HIV-infected adults, adolescents and children (See Table 1)

1. Induction phase treatment

For the induction phase of treatment in HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal), the following two-week anti-fungal regimens are recommended in order of preference.

a. Amphotericin B + flucytosine

   [Strong recommendation, high quality of evidence]

b. Amphotericin B + fluconazole

   [Strong recommendation, moderate quality of evidence]

c. Amphotericin B short course (5-7 days) + high-dose fluconazole (to complete two weeks of induction) when a minimum package of pre-emptive hydration and electrolyte replacement and toxicity monitoring and management cannot be provided for the full two week induction period.

   [Conditional recommendation, low quality of evidence]

d. Fluconazole high dose + flucytosine, when amphotericin B is not available

   [Conditional recommendation, low quality of evidence]

e. Fluconazole high dose alone, when amphotericin B is not available

   [Conditional recommendation, low quality of evidence]

2. Consolidation phase treatment

For the consolidation phase treatment of HIV-infected adults, adolescents and children with cryptococcal meningitis or disseminated non-meningeal disease, the following eight-week anti-fungal regimen is recommended:

a. Fluconazole 400-800 mg/day after a two-week induction with amphotericin B regimen (6-12 mg/kg/day up to 400-800 mg/day if below 19 years).

b. Fluconazole 800 mg/day after induction treatment with short course amphotericin B or a fluconazole based induction regimen (fluconazole 12 mg/kg/day up to 800 mg/day if below 19 years).

[Strong recommendation, low quality of evidence]

3. Maintenance treatment (or secondary prophylaxis)

For maintenance treatment of cryptococcal disease in HIV-infected adults, adolescents and children, oral fluconazole 200 mg daily (6 mg/kg/day up to 200 mg/day if below 19 years) is recommended.

[Strong recommendation, high quality of evidence]

4. Localized non-meningeal disease

For localized non-meningeal disease, or in patients with isolated serum CrAg positivity (where active cryptococcal meningitis has been excluded), fluconazole 800 mg/day (or 12 mg/kg/day up to 800 mg/day if below 19 years) for two weeks, then 400 mg/day (or 6 mg/kg/day up to 400-800 mg/day if below 19 years) for eight weeks, and continued maintenance with fluconazole 200 mg/day is recommended. The optimal antifungal regimen in this population remains to be determined.

[Conditional recommendation, low quality of evidence]

Remarks

In developing these recommendations, the Guideline Development Group placed high value on balancing the need for the best anti-fungal regimens to achieve optimal survival, neurological outcome, and fungal clearance, while minimizing drug related toxicities. The Guideline Development Group was concerned by the high incidence of serious amphotericin B-related toxicities, particularly hypokalaemia and nephrotoxicity, and the need to ensure its administration is always linked to a simple package of measures to prevent, monitor and manage these toxicities.

Induction regimens in adults

The recommended induction regimens are ranked in order of preference, based on the Guideline Development Group's review of the evidence of impact on survival, neurological morbidity and fungal clearance, and depending on local access to drugs and facilities for toxicity prevention, monitoring and management. The importance of rapid fungal clearance as an outcome is supported by studies that show an association between two-week culture status and 10-week clinical outcome.

A two-week regimen of amphotericin B plus flucytosine is the preferred option if resources are available for toxicity prevention, monitoring and management. There is high quality evidence from three trials that the addition of flucytosine to amphotericin B during induction therapy, compared to amphotericin B alone is associated with increased rates of CSF sterilisation, a reduced risk of relapse, and a non-significant reduction in mortality at two weeks and a significant reduction at 10 weeks in two trials. There is evidence from one RCT and an observational study of more rapid clearance of Cryptococcus from the CSF with amphotericin B plus flucytosine compared with amphotericin B plus fluconazole.

The combination of amphotericin B plus fluconazole 800 mg/day is the recommended regimen when flucytosine is not available, supported by evidence from one trial that this combination is associated with a marginally superior rate of CSF clearance compared to amphotericin B alone, and evidence from two trials for a non-significant decrease in mortality and neurological morbidity.

In settings where amphotericin B may be available, but a minimum package of pre-hydration, electrolyte replacement and laboratory monitoring is not reliable or sustainable for the full two-week period, there are data from observational studies to support the recommendation that patients should be given a short course of 5-7 days of amphotericin B, in combination with fluconazole for 14 days, based on more rapid fungal clearance. However, clinical trials are needed to assess the early fungicidal activity and clinical outcomes of short course amphotericin B relative to high dose oral fluconazole.

The Guideline Development Group recognized that many countries where CM is prevalent lack access to the preferred drugs (amphotericin B and flucytosine) or the required facilities and resources to provide the minimum appropriate toxicity monitoring and management. Therefore, the Guideline Development Group also reviewed the evidence for fluconazole-based regimens plus flucytosine or for high-dose fluconazole monotherapy, while recognising that fluconazole is less effective because it is fungistatic and may require longer administration to achieve a sterile CSF. There is evidence from two trials that the addition of flucytosine to fluconazole for at least two weeks was associated with a significant decrease in mortality compared to fluconazole monotherapy, and one of these trials evaluated the recommended dose of fluconazole (1200 mg) and flucytosine (100 mg/kg). If flucytosine is not available, fluconazole 1200 mg/day alone for at least two weeks is recommended based on one quasi-randomized trial that showed the rate of cryptococcal clearance was more rapid in adults receiving 1200 mg/day compared to 800 mg/day. However, the fungicidal activity with fluconazole 1200 mg/day is still below that for amphotericin B regimens, and further studies are needed to establish the optimal fluconazole dose in oral regimens.

Table 1: Summary of treatment recommendations and dosage for HIV-infected adults, adolescents and children with cryptococcal disease (meningeal and disseminated non-meningeal)

Target Population	Drugs available	Pre-hydration + electrolyte replacement + toxicity monitoring/ management	Induction phase options[14] (2 weeks)	Consolidation phase options (8 weeks)	Maintenance/ secondary prophylaxis options
Adults	Amphotericin B[15] ± flucytosine	Available	**a.** Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day **b.** Amphotericin 0.7-1 mg/kg/day + fluconazole 800 mg/day	Fluconazole 400-800 mg/day	Fluconazole 200 mg daily
	Amphotericin B[15]	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 800 mg/day (2 weeks)	Fluconazole 800 mg/day	
	Amphotericin B not available	Not available	**a.** Fluconazole 1200 mg/day ± flucytosine 100 mg/kg/day **b.** Fluconazole 1200 mg/day alone	Fluconazole 800 mg/day	

14 Route of administration: amphotericin B (IV); flucytosine (oral); fluconazole (oral and IV).

15 Liposomal amphotericin B (3 mg/kg/day) may be considered as an alternative to conventional amphotericin B, if available.

Target Population	Drugs available	Pre-hydration + electrolyte replacement + toxicity monitoring/ management	Induction phase options[14] (2 weeks)	Consolidation phase options (8 weeks)	Maintenance/ secondary prophylaxis options
Adolescents and Children[16]	Amphotericin B ± flucytosine	Available	**a.** Amphotericin 0.7-1 mg/kg/day + flucytosine 100 mg/kg/day **b.** Amphotericin 0.7-1 mg/kg/day + fluconazole 12 mg/kg/day up to 800 mg/day	Fluconazole 6-12 mg/kg/ day up to 400-800 mg/day	Fluconazole 6 mg/kg/day up to 200 mg/day
	Amphotericin B	Not available for full 2 week induction period	Amphotericin 0.7-1 mg/kg/day short course (5-7 days) + fluconazole 12 mg/kg/day up to 800 mg/day (2 weeks)	Fluconazole 12 mg/kg/day up to 800 mg/day	
	Amphotericin B not available	Not available	**a.** Fluconazole 12 mg/kg/day up to 1200 mg/day ± flucytosine 100 mg/kg/day **b.** Fluconazole 12 mg/kg/day up to 1200 mg/day alone		

** For localized non-meningeal disease, or patients with isolated serum CrAg positivity (after active cryptococcal meningitis excluded), fluconazole 800 mg/day for two weeks followed by fluconazole 400 mg/day for eight weeks*

The optimal anti-fungal regimen in patients with isolated serum CrAg positivity (where active cryptococcal meningitis has been excluded), as well as in those with localized non-meningeal disease remains to be determined, but the Guideline Development Group made a conditional recommendation of fluconazole 800 mg for two weeks followed by 400 mg for eight weeks in this situation.

16 Up to 19 years. Excludes first week of life.

The Guideline Development Group highlighted other considerations regarding cost and availability of the recommended drugs in RLS. Both amphotericin and flucytosine are expensive, and, in addition, flucytosine is currently not licensed nor available in most RLS. Fluconazole is well tolerated and cheap, and widely available through drug donation programmes. Liposomal amphotericin B (3 mg/kg/day) is associated with less toxicity and may be considered as an alternative to conventional amphotericin B, based on low quality evidence from two trials. However, liposomal formulations are much more costly, and for this reason should not be used as a preferred strategy.

Induction regimens in children

Regarding which induction regimen to use in children, there were no RCTs and only three small observational studies which compared amphotericin B with flucytosine to those treated with amphotericin B monotherapy. Pooled data from these studies found a non-significant decrease in mortality in children who received amphotericin B plus flucytosine compared to amphotericin B alone, similar to the results from the adult trials. Another study found a non-significant reduction in mortality in children who received amphotericin B plus flucytosine and amphotericin B monotherapy versus those receiving fluconazole monotherapy. Therefore, the hierarchy of regimens recommended was largely extrapolated from the adult trials, supported by data from these observational studies in children.

Consolidation regimens

Two trials have compared eight weeks of fluconazole 400 mg/day as consolidation therapy with itraconazole for outcomes of mortality, sterilization of CSF, and severe adverse events. The Guideline Development Group recommended fluconazole at a dose of 400-800 mg/day for eight weeks for those who received induction therapy with an amphotericin B-based regimen, and 800 mg/day if induction was conducted with short course amphotericin or a fluconazole-based induction regimen.

Maintenance treatment

In ART naïve patients, fluconazole was effective at preventing relapse in one RCT, with no relapses in the fluconazole arm. Fluconazole was also superior as a maintenance treatment to weekly amphotericin B and itraconazole.

Prevention, monitoring and management of amphotericin B toxicity

Recommendation

1. In HIV-infected adults receiving amphotericin B-containing regimens for treatment of cryptococcal disease, a minimal package of toxicity prevention, monitoring and

management is recommended to minimize the serious amphotericin B related toxicities, particularly hypokalaemia and nephrotoxicity (see Box 1).[17]

[Strong recommendation, moderate quality of evidence]

For patients receiving amphotericin B, the following minimum toxicity prevention, monitoring and management regimen is recommended.

Box 1: Minimum package for amphotericin B toxicity prevention, monitoring and management

Pre-emptive hydration and electrolyte supplementation[17]

- Adults:
  One litre of normal saline solution with one ampoule (20 mmol) of KCL over 2-4 hours before each controlled infusion of amphotericin B (with one litre of 5% dextrose) **and** one to two 8mEq KCL tablets orally twice daily. An additional one 8mEq KCL tablet twice daily may be added during the second week. If available, magnesium supplementation should also be provided (two 250mg tablets of magnesium trisilicate twice daily).
- Adolescents and Children:
  Up to one litre of normal saline solution with one ampoule (20 mmol) of KCL at 10-15 ml/kg over 2-4 hours before each controlled infusion of amphotericin B. If saline is unavailable, then other intravenous rehydration solutions that contain potassium can be used eg. Darrow's or Ringer's Lactate solutions.
- Potassium replacement should not be given patients with pre-existing renal impairment or hyperkalaemia.
- A test dose for amphotericin B is not recommended

Monitoring

- Serum potassium and creatinine (baseline and twice weekly), especially in the second week of amphotericin B administration.
- Haemoglobin (baseline and weekly)
- Careful attention to fluid monitoring of intake and output, and daily weight

Management

- If significant hypokalaemia (K $<$3.3mmol/l), increase potassium supplementation to two KCL ampoules (40 mmol), or one or two 8mEq KCL tablets three times daily. Monitor potassium daily.
- If hypokalaemia remains uncorrected, double magnesium oral supplementation
- If creatinine increases by $\geq$2 fold from baseline value, either temporary omission of an amphotericin B dose, or increase pre-hydration to one litre 8 hourly. Once improved, restart at 0.7 mg/kg/day and consider alternate day amphotericin B. If creatinine remains elevated, discontinue amphotericin and continue with fluconazole at 1200mg/day. Monitor creatinine daily.

17 Echevarria J, et al. Oral rehydration solution to prevent nephrotoxicity of Amphotericin B. Am. J. Trop. Med. Hyg., 2006: 75(6): 1108–1112; Thakur CP, et al. Improving outcome of treatment of Kala-Azar by supplementation of amphotericin B with physiologic saline and potassium chloride. Am. J. Trop. Med. Hyg., 2010; 83(5):1040–1043; Girmenia C, et al. Effects of hydration with salt repletion on renal toxicity of conventional amphotericin B empirical therapy: a prospective study in patients with haematological malignancies. Support Care Cancer 2005: 13:987-992; Bahr N, et al. The impact of routine electrolyte supplementation during amphotericin induction therapy in resource-limited settings. 8th International Conference on Cryptococcus and Cryptococcosis, Charleston, May 2011.

Remarks

In developing these recommendations, the Guideline Development Group placed a high priority on the avoidance of the serious and potentially life-threatening amphotericin B-related toxicities of hypokalaemia and nephrotoxicity, balanced against the need for a simplified approach to prevention, monitoring and management of drug toxicities, and and approach that is feasible in RLS.

The Guideline Development Group reviewed evidence on the significant risk of toxicity with amphotericin B-based regimens. Rates of hypokalaemia ranged from 11% to 33% in five RCTs and rates of nephrotoxicity from 1.3% to 14.8% in three RCTS. A protocol for twice-weekly monitoring of potassium and creatinine, particularly in the second week, and a haemoglobin weekly was based on evidence from all trials and observational studies that the highest incidence of toxicities occurred in the second week of therapy. The incidence of liver dysfunction with fluconazole remains low, therefore, routine monitoring of liver function was not recommended.

A simplified protocol for pre-hydration and electrolyte replacement prior to each amphotericin B infusion is a core recommendation, based on evidence from a pooled analysis of data from two RCTs and two observational studies that the incidence of these toxicities can be substantially reduced using this approach. In two RCTs of patients receiving amphotericin B for leishmaniasis, there was significant reduction in either the development of hypokalaemia or nephrotoxicity following pre-hydration with intravenous normal saline. In a further cohort of patients receiving pre-hydration with normal saline and potassium replacement prior to amphotericin B, 79% received a complete treatment course without major adverse events, and fewer than 8% or 20% respectively developed a significant rise in creatinine or had severe hypokalaemia. Finally, in a small sub-analysis of data on patients within an ongoing RCT of CM, there was a marked reduction in the incidence of grade 3 or higher hypokalaemia after universal electrolyte supplementation was introduced in addition to pre-hydration.

Timing of ART initiation

Guiding principle

- To facilitate early HIV diagnosis, uptake of ART and retention in care, provider-initiated HIV testing and counselling (PITC) and referral for HIV care services should be undertaken as soon as appropriate following diagnosis of cryptococcal disease, in accordance with existing WHO recommendations[12].

Recommendations

1. Immediate ART initiation is not recommended in HIV-infected patients with cryptococcal meningitis due to the high risk of IRIS, which may be life-threatening.

   [Conditional recommendation, low quality of evidence]

2. In HIV-infected adults, adolescents and children with a recent diagnosis of cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to anti-fungal therapy, **and**

   - after 2-4 weeks of induction and consolidation treatment with amphotericin B-containing regimens combined with flucytosine or fluconazole (after two weeks with non-meningeal disease); **or**
   - after 4-6 weeks of induction and consolidation treatment with high-dose oral fluconazole regimen (after four weeks with non-meningeal disease).

     [Conditional recommendation, low quality of evidence]

Remarks

In developing these recommendations, the Guideline Development Group placed high value on earlier initiation of ART to reduce the high HIV-related mortality in the months prior to ART initiation, particularly in sub-Saharan Africa, balanced against the more frequent (estimated 15% to 30% of patients with CM) and life-threatening risk of intracranial cryptococcal IRIS. Other considerations with earlier initiation of ART are the higher pill burden, and potential drug interactions with high-dose fluconazole.

There is a high rate of loss to follow up in patients with cryptococcal disease discharged from hospital, and poor linkages with outpatient ART services. Therefore, PITC and referral for HIV care services should be undertaken as soon as appropriate following diagnosis of cryptococcal disease, and at least before hospital discharge.

The optimal timing of ART after cryptococcal meningitis is unclear, with conflicting evidence from two two RCTs with very different study designs. In one trial, there was a reduction in AIDS progression or deaths when ART was initiated at 14 days versus a median of 45 days following an OI. Although it was not powered to examine the impact of ART timing in specific OIs, a non-significant trend favoured earlier ART in patients with CM who were treated with amphotericin B. In a second small trial, there was increased mortality in adult patients given very early (less than 72 hours) versus delayed (10 weeks) ART following fluconazole induction therapy, but this trial stopped prematurely and had several methodological limitations. Therefore, in contrast to the strong evidence for a mortality reduction with early ART initiation in patients with TB and a CD4 count less than 50 cells/mm^3, immediate ART initiation is not recommended in patients with CM because

of the potentially high risk of life-threatening intracranial IRIS, especially with fluconazole-based regimens. The Guideline Development Group made a conditional recommendation to defer ART initiation for 2-4 weeks (following an amphotericin B-based induction regimen), or longer at 4-6 weeks (following a fluconazole-based induction regimen), based on a lower rate and longer time to achieve CSF fungal clearance with fluconazole compared to amphotericin B in two observational studies.

In patients with non-meningeal cryptococcal disease, where the risk of life-threatening IRIS is low, the Guideline Development Group recommended even earlier initiation of ART therapy (after two weeks of amphotericin B-based induction, or 4 weeks of high-dose oral fluconazole). A large RCT on the optimal timing of ART initiation in CM is ongoing in Uganda and South Africa, with results expected in 2014.

Discontinuation of maintenance treatment (secondary prophylaxis)

Recommendations

1. In HIV-infected adults and adolescents with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of anti-fungal maintenance treatment is recommended based on the following criteria.

   a. If HIV viral load monitoring is not available

      When patients are stable and adherent to ART and anti-fungal maintenance treatment for at least one year **and** have a CD4 cell count of greater than or equal to 200 cells/mm^3 (two measurements six months apart).

      [Strong recommendation, low quality of evidence]

   b. If HIV viral load monitoring is available

      Patient stable and adherent to ART and anti-fungal maintenance treatment for at least one year **and** with a CD4 cell count of greater than or equal to 100 cells/mm^3 (two measurements six months apart) **and** a suppressed viral load.

      [Conditional recommendation, low quality of evidence]

2. In HIV-infected children aged between two and 5 years, with successfully treated cryptococcal disease (meningeal and non-meningeal), discontinuation of anti-fungal treatment maintenance is recommended if the child is stable and adherent to ART and anti-fungal maintenance treatment for at least one year **and** with a CD4 cell count percentage greater than 25% or absolute count greater than 750 cells/mm^3 (two measurements six months apart).

   [Strong recommendation, low quality of evidence]

3. Maintenance treatment for cryptococcal disease should NOT be discontinued in children less than two years.

   [Strong recommendation, low quality of evidence]

4. Maintenance treatment for cryptococcal disease should be restarted if CD4 count drops to 100 cells/mm^3 or below in HIV-infected adults and adolescents (or CD4 cell count less than or equal to 25% or 750 cells/mm^3 in children aged between two and five years), or if a WHO stage 4 clinical event occurs, irrespective of patient age.

   [Strong recommendation, low quality of evidence]

Remarks:

In developing these recommendations, the Guideline Development Group placed high value on the avoidance of recurrent disease, but balanced against the increased cost and potential for drug interactions with prolonged fluconazole maintenance treatment.

The number of patients who have been evaluated for recurrent disease following discontinuation of maintenance treatment remains limited, particularly in RLS. Based on a GRADE profile of five single-arm trials and one observational study, only four out of 185 adults who discontinued maintenance treatment at a CD4 count greater than 100 cells/mm^3 relapsed or experienced recurrent disease, and there were no deaths after discontinuation in 106 adults. In the only data from a RLS - an RCT in Thailand, there were no cases of recurrent disease in 20 patients, 48 weeks after discontinuation at a CD4 count greater than 100 cells/mm^3 and an undetectable HIV viral load for three months. Therefore, the recommendations for discontinuation of prophylaxis are based on the very low risk of recurrence when patients have successfully completed initial induction and consolidation antifungal therapy, and have had a sustained increase in their CD4 count to greater than 200 cells/mm^3. This higher threshold takes into account the greater use of fungistatic fluconazole induction treatment and less frequent CD4 monitoring in RLS. The Guideline Development Group recommended discontinuation at a lower threshold of greater than 100 CD4 cells/mm^3, if viral load monitoring is available and confirms a suppressed viral load.

World Health Organization

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