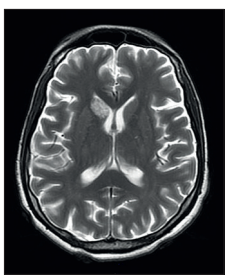
HIV-associated cryptococcal meningitis: ongoing challenges and new opportunities



Living Art Enterprises, LLC/Science Photo Library

See **Articles** page 843

In *The Lancet Infectious Diseases*, Joshua Rhein and colleagues[1] present findings from their phase 3 trial evaluating the efficacy of adjunctive sertraline in induction therapy for HIV-associated cryptococcal meningitis in Uganda. Disappointingly, the study of over 450 patients showed no mortality benefit of adding sertraline to amphotericin B and fluconazole, with 52% 18-week mortality in the sertraline group, compared with 46% in the control group. Although these results almost certainly mark the end of the road for sertraline as an adjunct in the treatment of cryptococcal meningitis, seeing the publication of another well conducted, large phase 3 clinical trial aimed at reducing mortality from HIV-associated cryptococcal meningitis—a disease that causes an estimated 181 100 deaths annually, three-quarters of which occur in sub-Saharan Africa—is extremely encouraging.[2]

Given the marked shortcomings of available treatments for cryptococcal meningitis (at present limited to amphotericin B and fluconazole in most low-income and middle-income countries because flucytosine remains unavailable),[3,4] and the absence of an extensive antifungal drug development pipeline, repurposing existing drugs with anti-cryptococcal activity is a pragmatic approach to delivering new treatments. In vitro and animal model data showing the anti-cryptococcal activity of sertraline provided justification for Rhein and colleagues' trial,[5] as did data from a phase 2 study appearing to show improved fungal clearance when adjunctive sertraline was added to amphotericin B and fluconazole in comparison to a historical cohort.[6] In their phase 3 trial, with use of a contemporaneous control group, Rhein and colleagues have now conclusively shown that adjunctive sertraline has no effect on the rate of cerebrospinal fluid cryptococcus clearance, or mortality. The authors speculate that the lack of antifungal activity might be due to inadequate sertraline concentrations in the brain,[1] potentially because of drug–drug interactions with antiretroviral therapy (ART). However, even in participants not receiving ART, most of whom would be expected to have brain sertraline concentrations above the minimum inhibitory concentrations of Ugandan cryptococcus isolates (on the basis of extrapolation from measured plasma levels), sertraline had no effect on fungal clearance or mortality. A second possible explanation is the time taken to reach therapeutic concentrations in the brain, which might only be achieved by the second week of treatment—perhaps too late to influence acute treatment outcomes.

The conclusive explanation for the absence of positive effects of sertraline is unknown, and other strategies are needed to improve treatment outcomes in HIV-associated cryptococcal meningitis. Several phase 3 trials are ongoing or have been reported over the past 3 years in Africa and Asia.[3,4] The CryptoDex trial[3] ruled out use of corticosteroids during induction therapy for HIV-associated cryptococcal meningitis; and the landmark ACTA trial,[4] based on a series of carefully done phase 2 studies, showed that a 1-week course of amphotericin B and flucytosine improves survival and reduces toxicity compared with traditional 2-week amphotericin B regimens, leading to adoption of this regimen as recommended first-line treatment in updated WHO guidelines.[7] The phase 3 Ambition-CM study (ISRCTN 72509687) is evaluating a single, high dose of liposomal amphotericin B with oral flucytosine and fluconazole, offering the potential to further simplify treatment.

Ensuring that patients in low-income and middle-income countries have access to effective treatments is essential to enable advances made in clinical trials to be translated into practice. Advocacy efforts led by the CryptoMAG consortium, Médecins Sans Frontières, and others, are aiming to improve access to flucytosine in these settings,[8,9] shown in the ACTA trial to be an essential component of shortened treatment courses.[4] These advocacy efforts have already led to several notable successes including the WHO prequalification of liposomal amphotericin B (AmBisome) in June, 2018; the addition of cryptococcal meningitis to the US Food and Drug Administration's priority review voucher scheme in August, 2018; the expansion of Gilead's preferential AmBisome pricing programme for visceral leishmaniasis to include cryptococcal meningitis in September, 2018; and the announcement of substantial

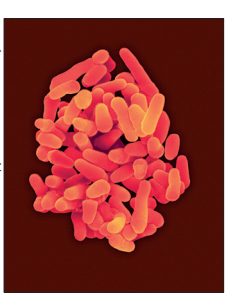
UNITAID funding for cryptococcal meningitis treatment in high-burden African countries in January, 2019. Coupled with continuing efforts to repurpose older drugs with antifungal activity (such as tamoxifen),[10] and develop new antifungal agents,[11,12] these advances, in addition to the dedicated work of clinical investigators such as Rhein and colleagues, offer a real hope that the unacceptably high mortality from HIV-associated crypotococcal meningitis can be substantially reduced in the near future.

Mark W Tenforde, Joseph N Jarvis
Division of Allergy and Infectious Diseases, University of Washington School of Medicine, Seattle, WA 98195, USA (MWT); Department of Epidemiology, University of Washington School of Public Health, Seattle, WA, USA (MWT); Botswana Harvard AIDS Institute Partnership, Gaborone, Botswana (JNJ); and Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK (JNJ)
mark.tenforde@gmail.com

MWT reports grant support from US National Institutes of Health, outside of the submitted work. JNJ reports grants from National Institute for Health Research and EDCTP outside of the submitted work; and is Principle Investigator for the phase 3 Ambition-cryptococcal meningitis study.

1 Rhein J, Hullsiek KH, Tugume L, et al. Adjunctive sertraline in HIV-associated cryptococcal meningitis: a randomised, placebo-controlled, double-blind phase 3 trial. *Lancet Infect Dis* 2019; **19:** 843–51.
2 Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* 2017; **17:** 873–81.
3 Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *New Engl J Med* 2016; **374:** 542–54.
4 Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *New Engl J Med* 2018; **378:** 1004–17.
5 Zhai B, Wu C, Wang L, Sachs MS, Lin X. The antidepressant sertraline provides a promising therapeutic option for neurotropic cryptococcal infections. *Antimicrob Agents Chemother* 2012; **56:** 3758–66.
6 Rhein J, Morawski BM, Hullsiek KH, et al. Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis: an open-label dose-ranging study. *Lancet Infect Dis* 2016; **16:** 809–18.
7 WHO. Guidelines for the diagnosis, management and prevention of cryptococcal disease. 2018.https://apps.who.int/iris/bitstream/handle/10665/260399/9789241550277-eng.pdf?sequence=1 (accessed June 26, 2019).
8 Médecins Sans Frontières. MSF calls on Mylan to urgently make its life-saving cryptococcal meningitis treatment more accessible and affordable. 2018. https://msfaccess.org/msf-calls-mylan-urgently-make-its-life-saving-cryptococcal-meningitis-treatment-more-accessible-and (accessed Mar 31, 2019).
9 Loyse A, Burry J, Cohn J, et al. Leave no one behind: response to new evidence and guidelines for the management of cryptococcal meningitis in low-income and middle-income countries. *Lancet Infect Dis* 2019; **19:** 143–47.
10 Ngan NTT, Mai NTH, Tung NLN, et al. A randomized open label trial of tamoxifen combined with amphotericin B and fluconazole for cryptococcal meningitis. *Wellcome Open Res* 2019; **4**: 8.
11 Lockhart SR, Fothergill AW, Iqbal N, et al. The investigational fungal Cyp51 inhibitor VT-1129 demonstrates potent in vitro activity against *Cryptococcus neoformans and Cryptococcus gattii. Antimicrob Agents Chemother* 2016; **60:** 2528–31.
12 Amplyx. FDA grants orphan drug designation to Amplyx Pharmaceuticals for APX001 for treatment of cryptococcosis. https://amplyx.com/fda-grants-orphan-drug-designation-to-amplyx-pharmaceuticals-for-apx001-for-treatment-of-cryptococcosis/ (accessed March 31, 2019).

A new point-of-care test to diagnose tuberculosis


Dennis Kunkel Microscopy/Science Photo Library

Published Online
May 30, 2019
http://dx.doi.org/10.1016/S1473-3099(19)30053-2

See Articles page 852

In 2017, tuberculosis caused an estimated 1·6 million deaths, including 300 000 deaths among people with HIV, and surpassed HIV/AIDS to become the leading infectious cause of mortality worldwide.[1] Approximately 36% of tuberculosis cases each year (around 3·5 million cases) are not diagnosed or reported, which might have contributed to the increase in tuberculosis prevalence.[2] Current diagnostic tools in routine clinical use, including the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), rely on sputum-based testing, which has consistently demonstrated suboptimal diagnostic sensitivity, especially in immunocompromised people with HIV who are unable to produce sputum when admitted to hospital or at increased risk of extrapulmonary disease. Research and development of new tuberculosis diagnostics has been lagging behind knowledge of tuberculosis pathogenesis, which includes incipient and subclinical tuberculosis.[3] As a result, WHO has prioritised a biomarker-based non-sputum test that could be used at the clinical point of care to rapidly diagnose all forms of tuberculosis (including extrapulmonary tuberculosis) for individuals of all ages, including children.[4]

In *The Lancet Infectious Diseases*, Tobias Broger and colleagues[5] evaluated a new urine-based point-of-care test for detecting urine lipoarabinomannan. The first commercial lipoarabinomannan assay, the Alere Determine TB LAM Ag (AlereLAM; Abbott, Chicago, IL, USA), has shown that lipoarabinomannan concentrations correlate with clinical disease severity and risk of mortality,[6] and the use of this assay has been shown to improve outcomes for hospital inpatients with HIV in a randomised trial,[7] but the assay has only moderate diagnostic sensitivity.[8] Broger and colleagues compared the diagnostic accuracy of the new Fujifilm SILVAMP TB LAM assay (FujiLAM;