Institution: St George's, University of London

Unit of Assessment: A1 Clinical Medicine

Title of case study:

Optimising the Prevention and management of HIV associated *cryptococcal meningitis*

1. Summary of the impact (indicative maximum 100 words)

Researchers from St Georges have evaluated and optimised anti-fungal therapy for cryptococcal meningitis, the commonest cause of adult meningitis in sub-Saharan Africa. They have developed a "screen-and-treat" strategy to prevent the development of clinical disease in HIV-positive patients, and with collaborators developed and tested a novel point-of-care diagnostic test. These advances have led to changes in and development of a series of international guidelines and application of these new strategies in parts of Africa. A case for reduced costs of amphotericin was advanced by the group who were instrumental in reducing these costs in South Africa, allowing wider drug provision.

2. Underpinning research (indicative maximum 500 words)

Cryptococcal meningitis is the commonest cause of meningitis in most of Africa, and a major cause of death in HIV-infected individuals globally. It accounts for up to 0.5 million deaths per year.

Harrison, Bicanic and colleagues at St George's conducted a series of randomised controlled phase II studies in Asia and Africa [1-4], to optimise antifungal dosages and combinations for the treatment of cryptococcal meningitis. Specifically, to obtain evidence of improved efficacy the group looked for increased rates of clearance of the infection, a metric of efficacy that they developed for this purpose. They studied:

1. Amphotericin B compared to fluconazole [4]
2. Higher doses of amphotericin B'
3. Amphotericin B plus flucytosine compared to amphotericin B alone [1],
4. Increased doses of fluconazole up to 1200 mg/d [2], and
5. Addition of flucytosine to high dose fluconazole [3].

Fluconazole, which unlike flucytosine is widely and often freely available in the developing world, was shown to be as rapidly effective as flucytosine as a second drug to prescribe in combination with amphotercin B. Furthermore, a one week course of amphotericin B was shown to be much better tolerated than the standard 2 week course, with no decrease in the rate of clearance of infection. This work underpinned the analysis of drug costs for this indication [5].

Prevention and early diagnosis:

Cryptococcal meningitis is a major cause of mortality in HIV-positive patients in Africa. The team provided the rationale for a pre-emptive treatment strategy that has the potential to prevent over half of all cases presenting after a diagnosis of HIV has been made [6]. 5-10% of HIV-infected patients with a low CD4 cell count (<100 cells/mm^3) were found to test positive for cryptococcal antigen in plasma (indicative of early sub-clinical infection) prior to initiation of antiretroviral therapy (ART). One third of antigen positive patients developed clinical cryptococcal disease in the first year of antiretroviral therapy, while none of over 660 patients testing antigen negative developed clinical cryptococcosis. This would give a 100% negative predictive value for the test if it were used to screen patients prior to ART [6].

The team, with collaborators from University of Nevada and Immuno-Mycologics, developed and tested a novel point-of-care diagnostic test for early infection that would make "screen-and-treat" feasible, and enable earlier, primary care-based diagnosis of cases presenting with symptomatic disease [7]. The novel test was shown to have excellent sensitivity in both blood and urine, making routine screening for antigen practicable in resource-limited settings [6].

3. References to the research (indicative maximum of six references)

1. A.E. Brouwer, A. Rajanuwong, W. Chierakul, G.E. Griffin, R.A. Larsen, N.J. White, T.S. Harrison. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomized trial. The Lancet 2004; 363:1764-67. No DOI available.

2. N. Longley, C. Muzoora, K. Taseera, J Mwesigye, J. Rwebembera, A. Chakera, E. Wall, I. Andia, S. Jaffar, T.S Harrison. Dose-Response Effect of high dose fluconazole for HIV-associated cryptococcal meningitis in Southwest Uganda. Clinical Infectious Diseases 2008; 47:1556-61. doi: 10.1086/593194.

3. Nussbaum JC, Jackson A, Namarika D, Phulusa J, Kenala J, Kanyemba C, Jarvis JN, Jaffar S, Hosseinipour MC, Kamwendo D, van der Horst CM, Harrison TS. Combination flucytosine and high dose fluconazole is superior to fluconazole monotherapy for cryptococcal meningitis: a randomized trial in Malawi. Clinical Infectious Diseases 2010; *50:338-44* (plus accompanying Editorial). doi: 10.1086/649861.

4. T. Bicanic, C. Muzoora, A.E. Brouwer, G. Meintjes, N. Longley, K. Taseera, K. Rebe, A. Loyse, J. Jarvis, L. G.Bekker, R. Wood, D. Limmathurotsakul, W. Chierakul, K. Stepniewska, N.J. White, S. Jaffar, and T.S. Harrison. Independent Association between Rate of Clearance of Infection and Clinical Outcome of HIV- Associated Cryptococcal Meningitis: Analysis of a Combined Cohort of 262 Patients. Clinical Infectious Diseases 2009; 49:702-9. doi: 10.1086/604716.

5. Bicanic T, Wood R, Bekker LG, Darder M, Meintjes G, Harrison TS. Antiretroviral roll-out, antifungal roll-back: access to treatment for cryptococcal meningitis. *Lancet Infect Dis 2005; 5:530-1*. No DOI available.

6. Jarvis JN , Lawn SD , Vogt M, Bangani N , Wood R , Harrison TS. Screening for cryptococcal antigenemia in patients accessing an antiretroviral treatment program in South Africa. Clinical Infectious Diseases 2009; 48:856-62. doi: 10.1086/597262.

7. Jarvis JN, Percival A, Bauman S, Pelfrey J, Meintjes G, Williams GN, Longley N, Harrison TS, Kozel TR. Evaluation of a Novel Point of Care Cryptococcal Antigen (CRAG) Test on Serum, Plasma and Urine from Patients with HIV-associated Cryptococcal Meningitis. Clin Infect Dis 2011; 53:1019-23. doi: 10.1093/cid/cir613.

4. Details of the impact (indicative maximum 750 words)

The major impacts of the work can be summarised:

International guidelines for the management of cryptococcal meningitis:

The results of the research outlined above have been central to the development of the Infectious Disease Society of America (IDSA) guidelines for management of Cryptococcal meningitis (2010) [A], the "*WHO Rapid Advice: Diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents, and children"* published in 2011 [B], and the Southern African guidelines published in 2007 [C] and updated in 2013 [D]. Specifically, these guidelines endorse findings from the underpinning research outlined above, and advise:

1. Superiority of amphotericin B over fluconazole – and preference for use of amphotericin B wherever it is possible to use it safely.
2. Addition of flucytosine (when available) to amphotericin B supported by demonstration of the added fungicidal activity resulting from the combination.
3. High dose amphotericin B based on superior sterilizing activity.
4. At least 1200 mg/d as the preferred initial fluconazole dose, and high dose fluconazole plus flucytosine as preferred oral treatment option.
5. Adoption of a short, one week, course of amphotericin B where resources do not allow safe, sustainable use of standard 2 weeks courses.

Mortality:
The impact of adopting these recommendations in resource-limited settings, which previously used ineffective fluconazole monotherapy, is a reduction in the the 10-week mortality from over 50% to 25-35% when amphoteracin B based treatments are used (see Research References 1 & 4 above). This is achieved through wider use of standard amphotericin B induction, and of effective but also affordable and sustainable alternatives (short course amphotericin B, and combination oral therapy with high dose fluconazole).

Economic benefits:
The cost comparisons, lobbying and advocacy initiated by the study team [E,F] caused the pharmaceutical company Bristol Myers Squibb to reduce the price of amphotericin B in South Africa by 80% (146 to 26 ZAR/50mg vial). This has resulted in the use of amphotericin B (as opposed to fluconazole) for induction therapy being increased from an estimated 34% of patients in 2005 to 83% in 2010 [F,G]. Based on the work of the group, and in line with the international guidelines, an increasing number of Sub-Saharan Africa countries have adopted 1200 mg/d as the standard fluconazole dose, with the effect that this dose is now routinely used in initial therapy throughout those countries [H].

Adoption of the screen and pre-emptive treatment strategy after HIV diagnosis.
Following the evidence produced by the St George's group The Department of Health in South Africa has agreed to a phased implementation of the introduction of a screen and pre-emptive treatment strategy for cryptococcal meningitis in newly diagnosed HIV patients. In many African centres this now represents over half of all cases. This was incorporated into the 2012 Department of Health strategic plan [I] following meetings in Pretoria in February 2011 with CDC, PEPFAR representatives and Harrison. Of note is that a cost-effectiveness analysis demonstrated that screening has become the optimal standard of care – i.e. it both saves lives and saves money (through a reduction in costs associated with caring for patients) [J]. Screening is now in routine use in South Africa's Western Cape and Gauteng provinces; further projects based on this strategy are being implemented in Uganda, Kenya, Zambia, and Tanzania. Screening, using the new point-of-care diagnostic test, was endorsed by the 2011 WHO guidelines for areas of high prevalence [B] and recommended in the updated 2013 Southern African Clinicians Society guidelines [D]. Effective screening with subsequent treatment substantially reduces the number of cases of cryptococcal meningitis presenting after a diagnosis of HIV has been made and anti-retroviral therapy started, demonstrating the extensive reach and significance of this research.

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Disease Society of America. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, **Harrison TS**, Larsen RA, Lortholary O, Nguyen MH, Pappas PG, Powderly WG, Singh N, Sobel JD, Sorrell TC. Clinical Infectious Diseases 2010; *50:291-322.* doi: 10.1086/649858.

B. *"WHO Rapid Advice: Diagnosis, prevention, and management of cryptococcal disease in HIV-infected adults, adolescents, and children",* December 2011. **Harrison TS** expert panel member; **T Bicanic,** J Jarvis Peer Review Panel
http://whqlibdoc.who.int/publications/2011/9789241502979_eng.pdf

C. Southern African HIV Clinicians' Society Guidelines for the prevention, diagnosis and management of cryptococcal meningitis and disseminated cryptococcosis in HIV-infected patients. Conveners McCarthy K, Meintjes G. Writing committee: Arthington-Skaggs B, Bicanic T, Cotton M, Chiller T, Govender N, **Harrison T**, Karstaedt A, Maartens G, Varavia E, Venter F, Vismer H. Southern African J HIV Med Sept 2007; 25-35. No DOI available.

D. Southern African HIV Clinicians' Society Guidelines for the Prevention, Diagnosis and Management of Cryptococcal Meningitis among HIV-infected Persons. Update – 2013. Conveners: Govender N, Meintjes G. Expert Panel members: **Bicanic T**, Dawood H, **Harrison T**, Jarvis J,

Karstaedt A, Maartens G, McCarthy K, Rabie H, Varavia E, Venter F. Southern African J HIV Med 2013 in press. No DOI available.

E. **Bicanic T**, Wood R, Bekker L-G, Darder M, Meintjes G, **Harrison TS**. Antiretroviral roll-out, antifungal roll-back: access to amphotericin B and flucytosine for the treatment of cryptococcal meningitis. Lancet Infectious Diseases 2005; 5:530-1. DOI: http://dx.doi.org/10.1016/S1473-3099(05)70197-3.

F. **Loyse A,** Thangaraj H, Easterbrook P, Ford N, Roy M, Chiller T, Govender N, **Harrison TS, Bicanic T**. Cryptococcal meningitis: improving access to essential antifungal medicines in resource poor countries. Lancet Infectious Diseases 2013; May 31st doi: 10.1016/S1473-3099(13)70078-1

G. Personal communication: Nelesh Govender, Head Mycology Laboratory service, National Health Laboratory Service, South Africa

H. Ministry of Health 2011. Clinical Management of HIV in children and adults. Malawi Integrated guidelines. First Edition, Malawi Ministry of Health.

I. South African DoH – have adopted the screen-and treat prevention strategy in the National Strategic Plan on HIV, STIs, and TB 2012-16; dated 15th Feb 2012, accessed at http://www.doh.gov.za/docs/stratdocs/2012/NSPfull.pdf
see intervention 3.19 page 49; and reference to cost effectiveness analysis in South Africa: ref 34 p 76.

J. Jarvis JN, **Harrison TS**, Lawn SD, Meintjes G, Wood R, Cleary S. Cost-Effectiveness of Cryptococcal Antigen Screening as a Strategy to Prevent HIV-associated Cryptococcal Meningitis in South Africa. PLoS One 2013; 8(7): e69288. DOI: 10.1371/journal.pone.0069288