Institution: St George's, University of London

Unit of Assessment: 1 Clinical Medicine

Title of case study: Transforming the treatment and prevention of HIV-associated cryptococcal meningitis

Period when the underpinning research was undertaken: 2002 to 2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Harrison TS	Senior Lecturer, then Reader, Professor	1998 – 2020 (present)
Brouwer, A	Lancet Fellow, Wellcome Trust Clinical Researcher	2003 – 2006
Bicanic, TA	Clinical Research Fellow, Clinical Lecturer, Wellcome Inter Clinical Fellow, BIA Clinical Research Fellow, then Senior Lecturer, then Reader	2006 – 2020 (present)
Jarvis, JN	Clinical Lecturer, Wellcome Trust Clinical Researcher, then Clinical Lecturer	2006 – 2011
Loyse, A	Clinical Research Fellow, then Clinical Lecturer, then Senior Lecturer	2006 – 2020 (present)
Longley, N	Wellcome Trust Clinical Research Fellow	2011 – 2016
Molloy, S	Trial Manager, then Lecturer in Epidemiology	2012 – 2020 (present)
Wake, R	Meningitis Res. Found'n, Clinical PhD Fellow, then NIHR Clinical Lecturer and Honorary Research Fellow	2017– 2020 (present)

Period when the claimed impact occurred: 2013 to present

Is this case study continued from a case study submitted in 2014? Yes

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

Researchers from St George's have led international efforts to reduce the high burden of HIV-associated cryptococcal meningitis, developing new treatment regimens that significantly reduce mortality rates, and reduce costs.

The researchers conducted the largest phase 3 trial to date, evaluating new treatment regimens. The findings led to endorsement of a new regimen by WHO, and major investment from UNITAID that is making the diagnostic tests and drugs required more widely available. In-hospital mortality rate has since decreased by more than 30% in routine care in South Africa, from 36% to 24%. Another successful phase 2 trial has led to a second phase 3 trial of a further new regimen, possibly promising an even safer, more effective option. The group's screening and pre-emptive treatment strategy has been strongly recommended in WHO guidelines for advanced HIV disease after demonstrating a reduced mortality rate.

2. Underpinning research (indicative maximum 500 words)

Cryptococcal meningitis is the commonest cause of meningitis in most of Africa, and accounts for 15-20% of all HIV-related deaths and more than 180,000 deaths per year. The incidence is

not decreasing in most African countries despite access to antiretroviral therapy. The group have coordinated critical research in improving the treatment and prevention of this disease, realising a step change in both research and impact since the last REF.

Identifying new treatment regimens

A series of phase 2 studies carried out between 2007 and 2012, using a novel marker of treatment response developed by the group (the early fungicidal activity, or EFA [1]), defined two highly promising novel and sustainable approaches to treatment: oral combination treatment with high dose fluconazole plus flucytosine, and short, 1-week amphotericin B-based therapy [REF2014]. These treatments were found to be much more effective than the commonly used treatment in Sub-Saharan Africa of fluconazole monotherapy.

A subsequent landmark MRC-funded phase 3 trial (ACTA) is the largest to date conducted in the condition [2]. Compared with the international gold standard of 2 weeks amphotericin B plus flucytosine, 1 week of amphotericin B plus flucytosine was found to be much more effective (24% vs 38% mortality rate) and less costly (saving USD424 (2015) per patient treated), and the oral combination of fluconazole plus flucytosine was as effective and much less costly (saving USD843 (2015) per patient) [2, 3]. The oral combination was associated with a decrease of 35% in mortality rate compared with fluconazole alone [4]. Flucytosine was also shown to be superior to fluconazole as the partner drug given with amphotericin B (absolute decrease of 14% in mortality rate) [2].

Furthermore, a single high dose (10mg/kg) of liposomal amphotericin on day 1 was shown in a randomized phase 2 trial to be as effective as standard daily dosing of liposomal amphotericin over 14 days, and to be associated with far fewer side effects than conventional amphotericin deoxycholate [5]. A large phase 3 trial is ongoing (AMBITION, ISRCTN72509687), comparing single high dose liposomal amphotericin plus fluconazole and flucytosine, against the new (based on ACTA) WHO standard of one-week amphotericin B plus flucytosine.

Demonstrating the value of screening to identify at-risk patients

A pivotal early study conducted by the research group demonstrated the value of cryptococcal antigen (CrAg) detection in blood as a very sensitive and specific screening tool to identify those HIV-infected patients at risk of developing clinical cryptococcal meningitis [Clin Infect Dis 2009;48:865, REF2014].

A point of care test to enable screening was then jointly developed and tested by the group with collaborators from University of Nevada and Immuno-Mycologics [Clin Infect Dis 2011;53:1019,REF2014], and screening protocols developed. This test and pre-emptive treatment strategy was shown, together with antiretroviral therapy (ART) adherence support, to lead to a decrease of 28% in one year mortality rate in a phase 3 trial (REMSTART) in patients presenting with late stage HIV infection [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, Harrison TS. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. The Lancet 2004; 363:1764-67. doi: 10.1016/S0140-6736(04)16301-0. Journal article cited 296 times (WOS 03.03.2021).

2. Molloy SF, C. Kanyama, R.S. Heyderman, A. Loyse, MD, C. Kouanfack, D. Chanda, S. Mfinanga, E. Temfack, S. Lakhi, S. Lesikari, A.K. Chan, N. Stone, N. Kalata, N. Karunaharan, K. Gaskell, M. Peirse, J. Ellis, C. Chawinga, S. Lontsi, J.G. Ndong, P. Bright, D. Lupiya, T. Chen, J. Bradley, J. Adams, C. van der Horst, J.J. van Oosterhout, V. Sini, Y.N. Mapoure, P. Mwaba, T. Bicanic, D.G. Lalloo, D. Wang, M.C. Hosseinipour, O. Lortholary, S. Jaffar, Harrison TS, for the ACTA Trial Study Team. Antifungal Combinations for treatment of Cryptococcal Meningitis in Africa. New Engl J Med 2018 378:1004-17. doi: 10.1056/NEJMoa1710922. Journal article cited 97 times (WOS 03.03.2021).

3. Chen T, Mwenge L, Lakhi S, Chanda D, Mwaba P, Molloy SF, Gheorghe A, Griffiths UK, Heyderman RS, Kanyama C, Kouanfack C, Mfinanga S, Chan AK, Temfack E, Kivuyo S, Hosseinipour MC, Lortholary O, Loyse A, Jaffar S*, Harrison TS*, Niessen LW*; ACTA Trial Team. Healthcare Costs and Life-years Gained From Treatments Within the Advancing Cryptococcal Meningitis Treatment for Africa (ACTA) Trial on Cryptococcal Meningitis: A Comparison of Antifungal Induction Strategies in Sub-Saharan Africa.Clin Infect Dis. 69(4) 2019 Mar 13. pii: ciy971. doi: 10.1093/cid/ciy971. [Epub ahead of print] PMID:30863852 * equal contribution. Published in journal 3rd of 93 journals in infectious diseases.

4. Shiri T, LoyseA, MwengeL, Chen T, Lakhi S, Chanda D Mwaba P, Molloy SF, Heyderman R,Kanyama C, Hosseinipour MC, Kouanfack C, Temfack E, Mfinanga S,Kivuyo S,Chan AK, Jarvis JN, Lortholary O, Jaffar S, Niessen LW, Harrison TS. Addition of flucytosine to fluconazole for the treatment of cryptococcal meningitis in Africa: a multi-country cost-effectiveness analysis. Clin Infect Dis. Volume 70, Issue 1 2019 Feb 28. pii: ciz163. doi: 10.1093/cid/ciz163. [Epub ahead of print]. Journal article cited 4 times (WOS 03.03.2021).

5. Jarvis JN, Leeme TB, Molefi M, Chofle AA, Bidwell G, Tsholo K, Tlhako N,Mawoko N, Patel RKK, Tenforde MW, Muthoga C, Bisson GP, Kidola J, Changalucha J, Lawrence D, Jaffar S, Hope W, Molloy SF, Harrison TS. Short Course High-dose Liposomal Amphotericin B for HIV-associated Cryptococcal Meningitis: A phase-II Randomized Controlled Trial. Clin Infect Dis. 12(4). 2018 Jun 26. doi: 10.1093/cid/ciy515. [Epub ahead of print]. Journal article cited 23 times (WOS 05.03.2021.).

6. Mfinanga S, Chanda D, KivuyoSL, Guinness L,Bottomley C, Simms V, Chijoka C, Masasi A, Kimaro G, Ngowi B, KahwaA, Mwaba P, Harrison TS, Egwaga S, Jaffar S. Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial.. The Lancet 2015 385:2173-82. doi: 10.1016/S0140-6736(15)60164-7 (TSH designed the CrAg screening intervention, and trained teams in delivery, and helped interpret the data, and contributed to writing). Journal article cited 116 times (WOS 03.02.2021).

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

Influence on policy and guidelines

The results of the group's work have led to broad changes in clinical guidelines and practice for the treatment and prevention of HIV-associated cryptococcal meningitis. The ACTA trial results were shared confidentially with WHO prior to publication. They led to rapid revision in March 2018 of WHO guidance, recommending 1-week amphotericin B plus flucytosine as the preferred first-line treatment; and the oral combination as the second line option where amphotericin B is not available [A,B]. The Southern African HIV Clinicians Society Guidelines that drive practice in the region made the same recommendation based on the ACTA results in 2019 [C].

Pre-emptive therapy for asymptomatic people with positive CrAg screening results is now a key strategy to prevent cryptococcal meningitis in the 2017 WHO guidelines for the management of patients with advanced HIV infection [D]. Screening and pre-emptive therapy had been incorporated into WHO cryptococcal guidelines in 2011 as a conditional recommendation, but based largely on new prospective data from the REMSTART trial, the guidelines were updated, carrying a strong recommendation [D]. Such screening is now routine across South Africa, Botswana, and parts of Tanzania, and recommended in over 20 countries in Sub-Saharan Africa. The point-of-care CrAg test is now recommended and adopted world-wide as the diagnostic test of choice [A,C,D].

Widening global access to essential drugs and diagnostics

With Dr Loyse chairing the Cryptococcal Meningitis Action Group (CryptoMAG) coalition, with key partners including CDC, MSF, UNITAID and WHO representatives, the research group has been at the forefront of advocacy efforts to drive wide access to flucytosine, liposomal

amphotericin B, and the point of care tests needed to optimise treatment and screening strategies [E].

As a direct result of this effort, ACTA trial results, and the group's cost-effectiveness analyses, UNITAID initiated a USD20,000,000 (01-2019) programme (through Clinton Health Access Initiative, CHAI, with Loyse as chief consultant) to reduce HIV deaths through support for proven interventions for patients with advanced HIV disease. The programme includes support for CrAg testing, and wide access to liposomal amphotericin and, in particular, flucytosine. The announcement featured a survivor from the ACTA trial and Harrison as a key researcher driving the evidence base ["A plan to slash HIV deaths", please see F].

Following this, a call was made for generic manufacturers to supply WHO-pre-qualified flucytosine. Four manufacturers have committed to manufacture and costs are expected to halve from the best currently available (approximately USD1.20 per 500mg tablet). Mylan's first batch, produced in December 2019 in India, was more than the total prior annual supply [G]. After the UNITAID programme, continued access will be through country requests for flucytosine to the Global Fund.

Through continued advocacy, and the novel evidence for the efficacy and safety of single high dose liposomal amphotericin, the UNITAID programme also includes extension of the Gilead price reduction for liposomal amphotericin for treatment of leishmaniasis to the indication of cryptococcal meningitis [F].

Reducing mortality rates
According to the latest estimates, HIV-associated cryptococcal meningitis accounts for over 180,000 deaths per year, the vast majority in Sub-Saharan Africa. Implementation of the new ACTA regimens can reduce the case fatality rate for cryptococcal meningitis from the current mortality rate between 50% and 70% with fluconazole to a mortality rate between 25% and 35%. This translates to tens of thousands of lives saved each year.

Implementation in routine practice has started in South Africa and supports this assessment. MSF working with partner hospitals and the national surveillance network (GERMS-SA) are using the 1-week amphotericin B plus flucytosine treatment, and Western Cape province has purchased flucytosine for routine use [H]. The Department of Health in South Africa has granted a waiver for flucytosine use, while re-registration of flucytosine in the country moves forward (Mylan requested to use the ACTA data in their re-registration application). Flucytosine has also been added to the South African essential medicines list.

The mortality rate reductions seen in the ACTA trial have been realised in routine care in South Africa. 1-week amphotericin B plus flucytosine has been associated with more than 30% reduction in in-hospital mortality rate, decrease from 36% to 24% [Ia], in line with expectations based on ACTA. In Tanzania, using the new regimens, within the EDCTP-funded DREAMM project led by Loyse, has led to a reduction in 2-week, all cause HIV-related meningitis mortality rate, decrease from 59% to 29% [Ib].

Economic benefit of new regimens
The ACTA regimens dominate in health economic terms, saving lives and money compared to prior treatment regimens [ref 4 in research]. For example, based on 10-week outcomes [ref 4 in research] in South Africa, Zambia, and Botswana, switching to 1-week amphotericin B plus flucytosine, would save 17 lives per 100 patients treated and USD26,400 (2015) per 100 patients treated.

Accelerating treatment development.
The Early Fungicidal Activity endpoint developed by the St George's, University of London group has now been accepted and widely adopted in the field, greatly facilitating and accelerating the testing and understanding of new antifungal drugs and treatment strategies [J].

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

A. WHO. Guidelines for the Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. 2011, updated March 2018. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO. (Loyse A, Bicanic T, Harrison TS, involved as Members Guidelines Development Group and Expert Review Panel)

B. WHO letter corroborating role of group's work and ACTA trial in driving guidelines, implementation and benefit to patients

C. Govender NP, Meintjes G, Mangena P, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal diseases among HIV-infected persons: 2019 update. S Afr J HIV Med. 2019;20(1), a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030. https://sahivsoc.org/Files/crypto%20guidelines.pdf (TSH spoke on induction treatment options at the guidelines meeting Jan 18th 2019)

D. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. [see p5, Cryptococcal meningitis, p7 discussion REMSTART trial evidence (ref 46), p8 last paragraph, conclusions supporting REMSTART trial approach)]

E. 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. 2018 Oct 18. pii: S1473-3099

F. Unitaids invest to cut HIV-related deaths. (announcement January 28th 2019) https://unitaid.org/advanced-hiv-disease/?utm_source=English+list&utm_campaign=ca4e6db72a-News%2FRecap+June+2018_COPY_01&utm_medium=email&utm_term=0_72097710b3-ca4e6db72a-268309597#en [please see 'A plan to slash HIV deaths', featuring Patrick, a surviving participant from ACTA trial, and Harrison as key researcher driving evidence base]

G. Testimonial letter from Mylan regarding flucytosine programme. (Viatris is the new company name following a merger of Mylan with Upjohn, th off-patent division of Pfizer).

H. Western Cape Government Circular H66, May 2019 Confirming routine use of 1 week amphotericin plus flucytosine ACTA regimen and supply of flucytosine.

Ia. A Govender NP, Mathebula R, Shandu M, Meiring S, Quan V, Nel J, Variava E, Menezes C, Reddy D, Venter M, Tsitsi M, Stacey S, Madua M, Boretti L, Meintjes G, Shroufi A, van Cutsem G, Trivino-Duran L, Black J for GERMS-SA. Flucytosine-based combination treatment for cryptococcal meningitis in routine care, South Africa. Abstract number: 4441, International Conference on AIDS and STIs in Africa (ICASA) 2019 conference, Kigali, 3 December 2019.
b. Testimonial letter from Professor Mfinanga, Head NIMR, Dar Es Salaam, Tanzania.

J. Examples of other independent trials using Early Fungicidal Activity to evaluate novel treatments: Day et al NEJM 2013; 368:1291-302; Beardsley et al NEJM 2016; 374:542-54; Rhein et al. Lancet Infect Dis 2016; 16: 809–18; Ngan N et al Wellcome Open Res 2019 Jan 22;4:8. doi: 10.12688. https://clinicaltrials.gov/ct2/show/NCT04031833