Institution: Liverpool School of Tropical Medicine (LSTM)

Unit of Assessment: UOA1

Title of case study: Reducing HIV-associated mortality in sub Saharan Africa by improving the prevention and management of cryptococcal meningitis

Period when the underpinning research was undertaken: 2004 – 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:**
David Lalloo	Professor of Tropical Medicine	1999 -
Shabbar Jaffar	Professor of Epidemiology	2015 -
Louis Niessen	Professor of Health Economics	2013 -

Period when the claimed impact occurred: 2013 – 2020

Is this case study continued from a case study submitted in 2014? Y/**N NO**

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

Cryptococcal meningitis (CM) is an opportunistic fungal infection that is responsible for approximately 15-20% of deaths of people living with HIV-infection.

LSTM has played a leading role in pivotal trials that have evaluated novel approaches for the prevention and management of CM in low-resource settings. We have identified novel biomedical treatment and prevention strategies that are practical, low-cost and effective, which have been incorporated into World Health Organisation (WHO) guidelines and led to changes in clinical practice in Africa. Our research findings stimulated investment in a generic version of a key drug identified in our research (Flucytosine) to increase access for low-resource settings and also catalysed a USD20,000,000 investment from the global health organisation, UNITAID, enabling seven African countries to acquire the supported by the trials. These are being rolled out in the first quarter of 2021, combined with training of health care staff. Together, these improvements to CM management are saving tens of thousands of lives annually in Africa and other low-resource settings.

2. Underpinning research (indicative maximum 500 words)

Despite significant advances in the availability of HIV care and treatment, a large proportion of HIV positive (HIV+) patients in resource-poor settings will present with advanced disease and die from opportunistic infections. CM is the most common such infection. In 2014 there were 225,000 cases globally with 180,000 deaths. In low income countries (LICs), the 12-month mortality of cryptococcal meningitis is approximately 70%, compared to between 20% and 30% in high income countries (HICs). The main causes for this can be summarised as:

- Limited ability to detect cases early and prevent development of disease
- Limited availability of affordable and appropriate antifungals
- Uncertainty about the optimal antifungal regimen
- Limited ability of the healthcare system to monitor and manage treatment-limiting toxicities of the antifungal drugs.

Our research focussed on two approaches for reducing deaths from CM in HIV+ people:

Combination Treatment

Lalloo (Director, LSTM, in collaboration with Oxford University) conceived, gained initial funding and instigated a phase 3 trial in Vietnam (conducted between 2004 and 2010) which compared 4 week amphotericin B monotherapy with 2 weeks combination therapy of amphotericin B and

either flucytosine or fluconazole. A combination of intravenous amphotericin B combined with oral flucytosine led to a decrease of over 40% in all-cause mortality when compared with intravenous amphotericin B monotherapy. Combination therapy of amphotericin with fluconazole did not improve patient outcomes [1].

This finding clearly demonstrated the value of combination treatment with flucytosine for the first time, led to changes in WHO policy and changed clinical practice in South East Asia. However, a 2-week course of amphotericin B administered intravenously (i.v) requires regular toxicity monitoring and was prohibitively expensive in Africa, where the majority of CM cases occur. Furthermore, flucytosine was not registered anywhere in Africa and there were no generic formulations available. Instead in most of Africa, CM was routinely treated with 2 weeks of high dose oral fluconazole, which is associated with a high mortality rate (of approximately 70%).

The ACTA trial (Advancing Cryptococcal Meningitis Treatment for Africa 2015-2018; Jaffar, co-designed and co-supervised the trial and co-supervised the statistical analysis and dissemination; Lalloo: co-investigator, supported design and set up of Malawi sites) evaluated practical CM treatment regimens for Africa. It was the largest trial ever conducted in CM, with 9 sites in 5 countries, and compared three treatment strategies as well as the two alternative partner drugs for amphotericin B. The two new treatment strategies, consisting of either i) 1-week of i.v amphotericin B plus oral flucytosine or ii) an all oral combination of flucytosine plus fluconazole, were compared with a 2-week i.v. regime of amphotericin B combination-based treatment. One week of amphotericin B and flucytosine was associated with lower mortality, and 2 weeks of the oral drug combination was non-inferior to the 2 weeks of i.v amphotericin-based regimens. Both the novel 1-week i.v amphotericin B and all oral combination tested in ACTA had mortality rates between 2 and 3-fold lower than observed with previous standard treatment practice in Africa of fluconazole monotherapy [2]. Crucially, we also showed that the 1-week i.v amphotericin B was less costly as well as more effective when compared with the 2 weeks of i.v amphotericin-based regimens (reduction of USD500 per patient) [3]. The combination oral regimen was also highly cost-effective compared with fluconazole monotherapy, with an incremental cost-effectiveness ratio of between USD28 and USD44 per life-year saved (costs adjusted to 2015 USD prices) [4]. Thus, if flucytosine could be made available in Africa, then ACTA provides the evidence of regimens that could substantially reduce HIV-associated mortality in Africa at lower cost.

The potent steroid dexamethasone had commonly been used as an adjuvant in the treatment of CM to reduce brain swelling. However, Lalloo (in collaboration with Oxford University) co-designed and played a key part in running a phase 3 trial in 6 countries, between 2013 and 2014, which showed that dexamethasone did not reduce mortality in CM and was actually deleterious with more adverse events [5].

Detection and pre-emptive oral treatment

Once CM has developed (i.e. the infection has reached the brain), then treatment becomes hugely challenging. Screening for cryptococcal antigen (CrAg) in immunosuppressed patients, combined with pre-emptive antifungal treatment, can prevent many cases of CM as CrAg is detected in the blood weeks to months before symptoms of meningitis appear.

The REMSTART trial, between 2012 and 2015, led by Jaffar whilst at LSHTM, found that screening serum for CrAg combined with an adherence package led to a decrease of 28% (95% confidence intervals 10% - 43%) in all causes of mortality. After joining LSTM in 2015 Jaffar and Niessen led the health economics analysis of REMSTART, showing that the intervention was highly cost-effective with health service care cost per life-saved of USD70 (based on 2017 USD [6]). Jaffar was also a key investigator on a follow-on study, TRIP, funded by EDCTP (European and Developing Countries Clinical Trials Partnership) designed to facilitate the scale up of the approach tested in REMSTART. Working in 18 health facilities in Tanzania, TRIP demonstrated that the intervention could be scaled up in

low-resource settings in a cost-effective way, achieving similar efficacy as seen under trial conditions.

Furthermore, the CRYPTO-PRO trial (commenced 2004; Lalloo PI: conceived, designed and supervised trial) demonstrated that use of routine fluconazole prophylaxis prevented cryptococcal disease in patients who could not rapidly access antiretroviral therapy [7].

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

1. Day JN, Chau TTH, Wolbers M, Mai PP, Dung NT, Mai NH, Phu NH, Nghia HD, Phong ND, Thai CQ, Thai LH, Chuong LV, Sinh DX, Duong VA, Hoang TN, Diep PT, Campbell JI, Sieu TPM, Baker SG, Chau NVV, Hien TT, **Lalloo DG,** Farrar JJ. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med. 2013. DOI: 10.1056/NEJMoa1110404
2. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, Mfinanga S, Temfack E, Lakhi S, Lesikari S, Chan AK, Stone N, Kalata N, Karunaharan N, Gaskell K, Peirse M, Ellis J, Chawinga C, Lontsi S, Ndong JG, Bright P, Lupiya D, Chen T, Bradley J, Adams J, van der Horst C, van Oosterhout JJ, Sini V, Mapoure YN, Mwaba P, Bicanic T, **Lalloo DG**, Wang D, Hosseinipour MC, Lortholary O, Jaffar S, Harrison TS; ACTA Trial Study Team. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med. 2018. DOI: 10.1056/NEJMoa1710922
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. 2019. DOI: 10.1093/cid/ciy971
4. Shiri T, Loyse A, Mwenge L, Chen T, Lakhi S, Chanda D, Mwaba P, Molloy SF, Heyderman RS, 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 Multicountry Cost-effectiveness Analysis. Clin Infect Dis. 2020. DOI: 10.1093/cid/ciz163
5. Beardsley J, Wolbers M, Kibengo FM, Ggayi AB, Kamali A, Cuc NT, Binh TQ, Chau NV, Farrar J, Merson L, Phuong L, Thwaites G, Van Kinh N, Thuy PT, Chierakul W, Siriboon S, Thiansukhon E, Onsanit S, Supphamongkholchaikul W, Chan AK, Heyderman R, Mwinjiwa E, van Oosterhout JJ, Imran D, Basri H, Mayxay M, Dance D, Phimmasone P, Rattanavong S, **Lalloo DG**, Day JN; CryptoDex Investigators. Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. N Engl J Med. 2016. DOI: 10.1056/NEJMoa1509024
6. Kimaro GD, Guinness L, Shiri T, Kivuyo S, Chanda D, Bottomley C, Chen T, Kahwa A, Hawkins N, Mwaba P, Mfinanga SG, Harrison TS, **Jaffar S, Niessen LW**. Cryptococcal Meningitis Screening and Community-based Early Adherence Support in People With Advanced Human Immunodeficiency Virus Infection Starting Antiretroviral Therapy in Tanzania and Zambia: A Cost-effectiveness Analysis. Clin Infect Dis. 2020. DOI: 10.1093/cid/ciz453
7. Parkes-Ratanshi R, Wakeham K, Levin J, Namusoke D, Whitworth J, Coutinho A, Mugisha NK, Grosskurth H, Kamali A, **Lalloo DG**; Cryptococcal Trial Team. Primary prophylaxis of cryptococcal disease with fluconazole in HIV-positive Ugandan adults: a double-blind, randomised, placebo-controlled trial. Lancet Infect Dis. 2011. DOI: 10.1016/S1473-3099(11)70245-6

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

Our studies identified improved and cost-effective solutions to prevent and treat CM in low resource settings. The inclusion into WHO guidelines between 2013 and 2018 led to widespread adoption of these new approaches in most countries when practicable. This benefitted both individuals living with HIV and at risk of the opportunistic infection CM, and resource-poor

healthcare systems, particularly in Africa, by improving outcomes and reducing the costs associated with CM treatment.

Influence upon treatment guidelines and clinical practice.
The Vietnam trial demonstrating clear benefit from combination therapy with amphotericin and flucytosine in terms of survival rates, and showing that both drugs could be safely administered in settings where therapeutic drug monitoring is not available, informed policy and clinical practice in many countries (including Germany, USA, Australia and Indonesia) and has underpinned WHO recommendations for combination therapy since 2013 [1,2].
Although most countries in Africa typically follow WHO guidance, this new treatment regime was not widely adopted in this continent due to resource constraints. The ACTA trial evaluated practical comparatively low-cost interventions for Africa including a new, shorter treatment regime which proved to be highly cost effective. It led to an immediate change in WHO guidelines, published simultaneously alongside the paper in 2018 recommending this regimen as the gold standard for CM management [2]. The advice to change to the ACTA regimens was graded as “strong recommendation, moderate-certainty evidence”. The dexamethasone study demonstrating that use of corticosteroids was harmful in HIV-related CM was also cited as high-quality evidence against the use of dexamethasone in the 2018 WHO guidelines [2] and immediately influenced clinical practice in many countries, being adopted into US IDSA guidelines in the same year for example. The findings of all these trials are included in the on-line decision-making resource ‘UpToDate’ used by 1,900,000 doctors worldwide [3].

The WHO had been recommending CrAg screening and it changed its guidelines to “strong recommendation” following the REMSTART trial [4]. However, uptake of this recommendation has been very limited outside of South Africa (which has a well-funded health system), because the REMSTART package was a complex intervention involving both patient empowerment and CrAg screening and needed substantial infrastructure and resources to scale-up. The TRIP study adapted the REMSTART package and demonstrated that a) it can be scaled up in a low-resource setting and b) that in a real-life setting, the death rate is as low as observed under trial conditions in the REMSTART trial. Tanzania, with one of the weakest infrastructures for their HIV programmes, has used the evidence generated to scale up screening for CrAg in over 200 health facilities so far (over 1,000,000 people with HIV-infection in the country) and by the end of 2021 coverage is expected to cover the entire country.

The CRYPTO-PRO trial demonstrated the value of fluconazole prophylaxis in certain populations and was one of only two studies contributing to “high quality evidence” for recommendations in the 2017 WHO advanced HIV guidelines [4] and 2018 WHO Cryptococcal guidelines [2] recommending that fluconazole prophylaxis should be used in patients with advanced HIV that could not immediately access antiretroviral therapy.

Implementation of revised guidelines for CM treatment and diagnosis.
As a result of the ACTA trial findings and WHO recommendations that followed, in January 2019 UNITAID announced USD20,000,000 funding to support 7 African countries to scale the WHO recommendation on advanced HIV disease (which REMSTART and TRIP had informed) and scale up management of CM (which ACTA had informed) [5]. The African countries targeted by UNITAID were Tanzania, Nigeria, South Africa, Botswana, Malawi, Lesotho, and Uganda and they have used the funds to support training of health care staff and acquire commodities including CrAg tests and treatments (flucytosine and amphotericin). The US Centers for Disease Control has also invested in supporting governments to scale up CrAg screening in these countries and approximately 21 other countries in Africa, who are at varying levels of scale-up. On the basis of our research, it is evident that this rapid adoption of improved screening and treatment strategies has been key to saving tens of thousands of lives in the continent with the highest burden of CM.

Increased availability of treatment
Prior to the ACTA trial, flucytosine was not registered in Africa and no generic formulation existed. The results from this trial incentivised the pharmaceutical industry to manufacture

flucytosine and the WHO approved the first generic version of this drug, manufactured by Mylan, in 2018 [6]. Other pharmaceutical companies started working on generic flucytosine in 2019 including Lupin Pharmaceuticals (India), Strides Pharma (India), Macleods Pharmaceuticals (India). This will ensure, for the first time, that CM management will become widely available in many more centres. In those centres unable to provide the gold standard of i.v. amphotericin and flucytosine, an effective oral combination regimen of fluconazole and flucytosine can be used (this is far superior than using fluconazole alone, as was common practice prior to the ACTA trial).

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

Influence upon treatment guidelines and clinical practice.

1. Treatment guidelines
    a. 2019 Indonesian guidelines for the treatment of HIV: PEDOMAN NASIONAL PELAYANAN KEDOKTERAN TATA LAKSANA HIV http://siha.depkes.go.id/portal/files_upload/PNPK_HIV_Kop_Garuda__1_.pdf
    b. Australian Consensus guidelines for the treatment of yeast infections in the haematology, oncology and intensive care setting 2014. DOI: 10.1111/imj.12597
    c. German 2016: CNS infections in patients with hematological disorders (including allogeneic stem-cell transplantation)—Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). DOI: 10.1093/annonc/mdw155
    d. US department of Health and Human Services Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf]

2. World Health Organisation Guidelines For The Diagnosis, Prevention And Management Of Cryptococcal Disease In HIV-Infected Adults, Adolescents And Children March 2018. https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/

3. UpToDate Treatment of Cryptococcal Meningitis: https://www.uptodate.com/contents/cryptococcus-neoformans-treatment-of-meningoencephalitis-and-disseminated-infection-in-hiv-seronegative-patients?search=cryptococcus&source=search_result&selectedTitle=3~128&usage_type=default&display_rank=3#H3349804803

4. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017. Geneva: World Health Organization. https://www.who.int/hiv/pub/guidelines/advanced-HIV-disease/en/

Implementation of revised guidelines for CM diagnosis and treatment.

5. Information on UNITAID's investment is available here: https://unitaid.org/news-blog/targeting-opportunistic-infections-to-cut-hiv-related-deaths/#en

Increased availability of treatment

6. Prequalification of Flucytosine (https://extranet.who.int/prequal/medicine/3628)