BOTSWANA
HARVARD AIDS INSTITUTE
PARTNERSHIP
FOR HIV RESEARCH AND EDUCATION

July 23, 2021

PRESS RELEASE

Positive AMBITION-cm Study Findings on the Treatment of HIV-Associated Cryptococcal Meningitis (CM).

The AMBIsome Therapy Induction OptimisatioN (AMBITION-cm) trial announced the study results at the 11th International AIDS Society (IAS) Conference on HIV Science on Wednesday the 21st of July 2021. The AMBITION-cm trial investigated whether a single high dose of liposomal amphotericin-B (L-AmB, Ambisome) paired with two oral antifungals, fluconazole and flucytosine, was as effective as 7-day amphotericin-B based therapy in reducing deaths.

Botswana Harvard AIDS Institute (BHP) was a collaborating partner in this trial, which was coordinated by the London School of Hygiene & Tropical Medicine (LSHTM). Prof. Joe Jarvis (LSHTM) and BHP Research Associate , with Prof. Tom Harrison of St George's University of London (SGUL) were Principle Investigators while Prof. Mosepele Mosepele Chair of the Department of Medicine at the University of Botswana and BHP Research Associate, was the local Principal Investigator.

Background of the Study

Cryptococcal meningitis is a fungal infection that affects tissues of the brain and spinal cord. The infection is caused by the fungus *Cryptococcus,* found in certain trees, and pigeon droppings and soil. CM is a major – and neglected – opportunistic infection amongst immunosuppressed HIV positive individuals across the globe.

Cryptococcal meningitis is the most common type of adult meningitis in much of Africa, and without effective treatment, infection progresses quickly. Globally, there are roughly 230,000 cases of cryptococcal meningitis and 180,000 cryptococcal meningitis-related deaths each year, the majority of which occur in sub-Saharan Africa. Tackling the high mortality rate remains challenging.

The current treatments for cryptococcal meningitis in sub-Saharan Africa are either (a) a 7-14-day course of amphotericin-B combined with oral antifungal tablets or (b) oral fluconazole. 10-week mortality with fluconazole treatment remains at

Private Bag BO 320
Gaborone, Botswana
Phone: +267 267 3902671
Fax: +267 3901284
Website: wwww.bhp.org.bw

approximately 60%, and standard treatment with amphotericin-B also has major drawbacks:

- Amphotericin-B is not widely available across Africa
- Amphotericin-B can cause kidney impairment and reduced blood counts
- Prolonged hospitalisation requires intensive nursing care and expensive laboratory monitoring which can be expensive for the healthcare system and the patient

Sustainable, cost-effective and easily administered treatments are urgently needed. A liposomal formulation of amphotericin B called AmBisome may be well suited to treat cryptococcal meningitis as it is less toxic and can be given in large doses that remain in the brain for some time. Professor Joe Jarvis (LSHTM) and Professor Tom Harrison's (SGUL) research groups have previously found that a single, high-dose of AmBisome was effective at clearing *Cryptococcus* from around the brain. We needed to test the impact of this approach on deaths from cryptococcal meningitis in a large number of participants.

This therefore trial investigated whether a single high dose of liposomal amphotericin-B (L-AmB, Ambisome) paired with two oral antifungals, fluconazole and flucytosine, was as effective as 7-day amphotericin-B based therapy in reducing deaths.

What the research entailed

The trial recruited individuals from 8 hospitals across 7 cities in 5 countries in southern and eastern Africa (Botswana, Zimbabwe, South Africa, Malawi, Uganda). We recruited adult patients with a first episode of HIV-associated cryptococcal meningitis. We enrolled 844 individuals with the Botswana site contributing 85 study participants. After late exclusions there were 407 participants in each arm who were included in the main analysis. No participants were lost to follow up.

Study Results/Findings

The trial found that a single, high-dose of liposomal amphotericin B was as good as ("non-inferior") to the current WHO recommended standard of care for HIV-associated cryptococcal meningitis and much easier to give, requiring just one intravenous infusion compared to 7 days with standard therapy. The liposomal amphotericin B regimen was also associated with significantly fewer drug related effects such as anaemia, electrolyte abnormalities and intravenous line site infections

The two arms were well matched at baseline and represented the general population of patients presenting with cryptococcal meningitis. 60% were male, the median age was 37 years, and the majority had previously been prescribed antiretroviral therapy.

Private Bag BO 320
Gaborone, Botswana
Phone: +267 267 3902671
Fax: +267 3901284
Website: wwww.bhp.org.bw

The proportions of participants with confusion or reduced consciousness were similar as was the quantity of *Cryptococcus* around the brain.

There were 407 participants in each arm. At 10 weeks the mortality was 24.8% (101/407) in the AmBisome arm and 28.7% (117/407) in the control arm. The difference in the AmBisome arm compared to the control arm was -3.9% and it can be concluded that the AmBisome treatment was "non-inferior" to the control treatment. At the 10 week time point, when we made adjustments for differences between the two groups we found the AmBisome treatment may even be statistically superior to the control treatment. The rate of clearance of *Cryptococcus* from the cerebrospinal fluid of both arms was similar.

Drug related toxicity was more common in the control arm. Anaemia occurred in 13% of AmBisome participants compared to 41% in the control arm. The average drop in haemoglobin over the first week was 0.3g/dL in the AmBisome arm and 1.9g/dL in the control arm and as a result more participants in the control arm needed blood transfusions. There was also a difference in the impact on kidney function with an average increase in creatinine over the first week of 20.2% in the Ambisome arm and 49.7% in the control arm. Electrolyte abnormalities and infections around intravenous lines were also more common in the control arm.

Take home messages/impact

This was the largest cryptococcal meningitis trial conducted to date and has demonstrated that single, high-dose AmBisome given with flucytosine and fluconazole was as good as ("non-inferior") to the current WHO recommended standard of care in avoiding mortality. The AmBisome regimen effectively cleared cryptococcus from around the brain and was associated with a significant reduction in adverse events. This regimen offers a practical, easier-to-administer and better-tolerated treatment for HIV-associated cryptococcal meningitis in Africa with the potential to reduce the length and cost of hospital admissions. There is now an urgent need to broaden access to AmBisome and flucytosine.

For more information, contact:

Nabila Youssouf, PhD
AMBITION Trial Manager
Tel: +267 390 8169
Mobile; +257 7591482
Email: nabila.youssouf@lshtm.ac.uk

Dr David Lawrence
Ambition Study Lead Clinician
Tel: +267 724 64 834
Email: david.s.lawrence@lshtm.ac.uk

Private Bag BO 320
Gaborone, Botswana
Phone: +267 267 3902671
Fax: +267 3901284
Website: wwww.bhp.org.bw