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High dose AMBISOME on a fluconazole backbone for cryptococcal meningitis induction therapy in sub-Saharan Africa

Submission date
23/06/2017

Recruitment status
No longer recruiting

Registration date
13/07/2017

Overall study status
Completed

Last Edited
06/06/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Cryptococcal meningitis is a fungal infection of the tissues covering the brain and spinal cord. It is a leading cause of death in HIV-infected people in Africa. The current recommended treatment is a drug called amphotericin B deoxycholate (D-AmB). Treatment with amphotericin B deoxycholate requires 7 days of intravenous infusions (into a vein) given in hospital, making it difficult and costly to use. It also causes many side effects, including kidney impairment and anaemia (having too little haemoglobin and too few red blood cells), making close laboratory monitoring essential. The combination of the costs associated with prolonged hospital stays, the difficulties of use and the need for laboratory monitoring make amphotericin B deoxycholate treatment difficult in much of Africa. A modified form of amphotericin B is available called liposomal amphotericin B (Ambisome or L-AmB). This is considerably less toxic than standard amphotericin B deoxycholate, and is known to be effective in the treatment of cryptococcal meningitis. Its use has been limited by the high cost, but recent data suggest that much shorter courses of L-AmB may be effective in the treatment of cryptococcal meningitis. Due to its lower toxicity, higher doses of L-AmB can be given safely, and it also persists for a long time in the tissues, raising the possibility of delivering highly effective treatment with just a single dose. A large reduction in the number of doses and duration of hospitalisation, together with reduced pricing of L-AmB, may result in cryptococcal meningitis treatment costs that are not more than those with 7 days of conventional amphotericin B deoxycholate, and provide a convenient, safe and effective alternative to conventional amphotericin B treatment. The aim of this study is to find out whether a single high dose of L-AmB is as effective as the standard treatment in terms of preventing deaths from cryptococcal meningitis.

Who can participate?
Patients aged over 18 with cryptococcal meningitis and HIV positive

What does the study involve?
Participants remain in hospital and are randomly allocated to be treated with either a single high dose of L-AmB or the standard amphotericin-B treatment over 7 days. Participants are asked to return to hospital for four medical check-up at weeks 4, 6, 8 and 10. If they are in hospital for

less than 2 weeks they are also seen in clinic at 2 weeks. Each visit lasts about 60 minutes. The final follow-up is by telephone and takes place at week 16. This follow-up lasts about 5 minutes. Mortality (death rates) are compared between the two groups.

What are the possible benefits and risks of participating?
The evidence from previous studies suggests that Ambisome is likely to be better tolerated and cause fewer side effects than amphotericin B. Participants may also benefit from receiving a shorter course of treatment with fewer intravenous infusions if they are allocated to the Ambisome group. The results of this study might help improve the treatment of people with cryptococcal meningitis in the future. It is possible that short course of high dose Ambisome may not be enough for effective treatment, and that full 14-day courses may be required for effective clearance of infection. The trialists think that this is unlikely given the experience they have with using short course, high dose Ambisome in treating this same infection. To ensure all participants get effective treatment the clearance of infection is monitored very closely. If there is any evidence that the cryptococcal infection is not being cleared adequately participants are switched to standard courses of treatment. In the event of this happening, their hospital admission may be prolonged. It is also possible that high doses of Ambisome may be more toxic than standard doses. Ambisome can cause impairment to kidney function and anaemia. However, extensive experience, often in very sick patients on chemotherapy, suggests that high doses of Ambisome are well tolerated. To minimize any risk of toxicity participants are closely monitored for side effects in hospital and the drugs are stopped if required. Results from an earlier study suggest that high dose Ambisome is no more toxic than standard treatment, and may be less toxic. By taking part in the study participants probably receive more lumbar punctures than you would during routine treatment. Lumbar punctures are very safe procedures when performed correctly by experienced doctors. Serious complications are rare. Lumbar punctures can be painful, and soreness of the back and headaches may occur. Very rarely more serious complications such as bleeding, infection and leakages can occur. Great care is taken to ensure the risks are as low as possible, and that discomfort is minimised by using local anaesthetic. In many patients with cryptococcal meningitis, lumbar punctures relieve the associated headache. Great care is taken to ensure the risks are as low as possible. The trialists have experience of performing this schedule of lumbar punctures on over 500 patients, and have not had any serious complications. In fact, performing regular lumbar punctures appears to be associated with improved outcomes in patients with cryptococcal meningitis.

Where is the study run from?
1. Princess Marina Hospital (Botswana)
2. Mitchells Plain District Hospital (South Africa)
3. Parirenyatwa Central Hospital (Zimbabwe)
4. Queen Elizabeth Central Hospital (Malawi)
5. Kamuzu Central Hospital (Malawi)
6. Mulago Hospital, Infectious Disease Institute (Uganda)
7. Mbarara Hospital (Uganda)

When is the study starting and how long is it expected to run for?
January 2017 to December 2020

Who is funding the study?
1. European & Developing Countries Clinical Trials Partnership (EDCTP)
2. Wellcome Trust (UK)
3. Medical Research Council (UK)
4. Department for International Development Joint Global Health Trials (JGHT)

Who is the main contact?
Prof. Joe Jarvis

Contact information

Type(s)
Public

Contact name
Prof Joe Jarvis

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-

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Ambition P3

Study information

Scientific Title
High dose AMBISOME on a fluconazole backbone for cryptococcal meningitis induction therapy in sub-Saharan Africa: a Phase 3 randomised controlled non-Inferiority trial

Acronym
Ambition-cm

Study objectives
Current study hypothesis as of 01/08/2018:
Short-course high-dose L-AmB given with high dose fluconazole and flucytosine will be non-inferior to 7 days daily-dosed Amphotericin B based induction therapy with flucytosine for the treatment of HIV-associated cryptococcal meningitis in averting all-cause mortality.

Previous study hypothesis:
Short-course high-dose L-AmB given with high dose fluconazole and flucytosine will be non-inferior to 2 weeks daily-dosed Amphotericin B based induction therapy with flucytosine for the treatment of HIV-associated cryptococcal meningitis in averting all-cause mortality.

Ethics approval required
Old ethics approval format

Ethics approval(s)
LSHTM Interventional Committee Review Board, 09/06/2017, ref: 14322

Study design
Randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Cryptococcal meningitis in HIV patients

Interventions
Current interventions as of 01/08/2018:
850 patients will be enrolled and randomised 1:1 into two arms:
1. L-AmB 10 mg/kg day 1 (single dose)
2. Amphotericin-B 1mg/kg/d for 7 days (standard dose “control arm”)
The intake will take place over a 3-year period, and follow-up will occur for 16 weeks after the start of treatment.

Previous interventions:
850 patients will be enrolled and randomised 1:1 into two arms:
1. L-AmB 10 mg/kg day 1 (single dose)
2. Amphotericin-B 1mg/kg/d for 14 days (standard dose “control arm”)
The intake will take place over a 3-year period, and follow-up will occur for 16 weeks after the start of treatment.

Randomisation
Patients will be randomised individually and randomisation codes will be generated using SAS PROC PLAN via permuted-block randomisation method stratified by site. Block sizes will vary at 4 and 6. Randomisation lists will be created for each site by an independent statistician and each list will be housed on the electronic database system (EDC) for that particular site, and will be inaccessible to trial staff except to randomise the next eligible participant. Randomised allocation for each trial participant will be provided to trial staff by extracting the next available randomisation allocation, obtained from the randomisation list for that site housed on the database. Internally the EDC selects against an electronic randomization list prepared in advance by the Statistician. The EDC guarantees to make the selection in the natural order of the list

filtering by study site only. Once a selection is made, the randomization record is tagged with the patient study allocated identifier, date and time of randomization and other EDC system audit values (username, machine name, etc). A tagged record cannot be selected more than once. It is impractical to blind the study because of the very high doses of short course L-AmB (currently up to 20 drug vials per dose depending on patient weight) used in the intervention arm, compared to the standard amphotericin B deoxycholate (often only a single vial per patient), given daily, in the control arm. Bias will be minimised by the use of an objective clinical endpoint “all-cause 10-week mortality” as the primary outcome. Laboratory technicians performing EFA will be blinded to study arm. The trial statistician will be blinded regarding the treatment code when developing the statistical analysis plan and writing the statistical analysis programmes, which will be validated and completed using dummy randomisation codes.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
L-AmB, amphotericin-B

Primary outcome measure
All-cause mortality within the first 10 weeks after randomisation (non-inferiority)

Secondary outcome measures
1. Early fungicidal activity, derived from serial lumbar punctures on days 1, 7 and 14
2. Clinical and laboratory-defined grade III/IV adverse events; median % change from baseline in laboratory defined parameters as and when AEs occur
3. Pharmacokinetic parameters and pharmacokinetic/pharmcodynamic associations of single high-dose L-AmB at 3, 6, 8 and 24 hours post L-AmB dose
4. Health service costs within the first 10 weeks
5. All-cause mortality within the first 2 and 4 weeks
6. All-cause mortality within the first 10 weeks (superiority)
7. Rates of cryptococcal relapse/immune reconstitution inflammatory syndrome within the first 10 weeks
8. Disability, measured using a simple two-question assessment and modified Rankin Score at 10 weeks

Overall study start date
01/01/2017

Completion date
30/06/2021

Eligibility

Key inclusion criteria
1. Consecutive patients aged >18 years with a first episode of cryptococcal meningitis (CSF India ink or CrAg test)
2. Known to be HIV positive or willing to undertake an HIV test

3. Willing to participate in the study or, if unable to consent, has a next of kin who agrees to the patient participating in the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
850

Total final enrolment
844

Key exclusion criteria
1. Pregnancy (confirmed by urinary or serum pregnancy test) or lactation
2. Previous serious reaction to study drugs
3. Already taking antifungal treatment at cryptococcal meningitis treatment doses (amphotericin B ≥0.7 mg/kg or fluconazole ≥800 mg/day) for >48 hours
4. Concomitant medication that is contraindicated with study drugs
5. HIV negative

Date of first enrolment
01/09/2017

Date of final enrolment
28/02/2021

Locations

Countries of recruitment
Botswana

Malawi

South Africa

Uganda

Zimbabwe

Study participating centre

Princess Marina Hospital
Gaborone
Botswana
PO Box 258

Study participating centre
Mitchells Plain District Hospital
Cape Town
South Africa
7786

Study participating centre
Khayelitsha Hospital
Cape Town
South Africa
7784

Study participating centre
Parirenyatwa Central Hospital
Harare
Zimbabwe
-

Study participating centre
Harare Central Hospital
Harare
Zimbabwe
-

Study participating centre
Queen Elizabeth Central Hospital
Blantyre
Malawi
PO Box 95

Study participating centre

Kamuzu Central Hospital
Lilongwe
Malawi
-

Study participating centre
Mulago Hospital, Infectious Disease Institute
Kampala
Uganda
PO Box 22418

Study participating centre
Mbarara Hospital
Mbarara
Uganda
PO Box 7272

Sponsor information

Organisation
London School of Hygiene and Tropical Medicine

Sponsor details
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United Kingdom
WC1E 7HT

Sponsor type
University/education

Website
https://www.lshtm.ac.uk/

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type

Other

Funder Name
European and Developing Countries Clinical Trials Partnership

Alternative Name(s)
Le partenariat Europe-Pays en développement pour les essais cliniques, A Parceria entre a Europa e os Países em Desenvolvimento para a Realização de Ensaios Clínicos, The European & Developing Countries Clinical Trials Partnership, European and Developing Countries Clinical Trials, EDCTP

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Netherlands

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Department for International Development Joint Global Health Trials (JGHT)

Alternative Name(s)
Department for International Development, UK, DFID

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal within 6-12 months of overall trial end date.

Intention to publish date
30/12/2021

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		23/11/2018		Yes	No
Protocol article	Economic evaluation protocol	01/04/2019	04/04/2019	Yes	No
Results article		24/03/2022	24/03/2022	Yes	No
Other publications	Analysis of HIV drug resistance mutations	02/11/2022	03/11/2022	Yes	No
Results article	Cost-effectiveness	01/12/2022	21/11/2022	Yes	No
Other publications	Sub-study	27/08/2024	02/09/2024	Yes	No
	Sub-study				

Other publications	01/06/2025	06/06/2025	Yes	No