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A phase III, randomised, controlled trial for the treatment of HIV-associated cryptococcal meningitis: oral fluconazole plus flucytosine or one week amphotericin B-based therapy vs two weeks amphotericin B-based therapy

Submission date
19/06/2012

Recruitment status
No longer recruiting

Registration date
31/07/2012

Overall study status
Completed

Last Edited
18/05/2026

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
In developed countries, the current standard for initial treatment of HIV-associated cryptococcal meningitis is 2 weeks of amphotericin B-based therapy. However, in many settings in Africa, amphotericin B is not available or not used due to its requirements for in-hospital care and close monitoring. The combination of fluconazole with a second oral drug, flucytosine, has been shown to lead to much more rapid control of infection, and to be associated with fewer deaths than fluconazole alone in a small study. In addition, shorter 5-7 day courses of amphotericin B have been shown to be much better tolerated than 2 weeks amphotericin B, reducing the length of hospital stay and the need for intensive monitoring of treatment. Such short-course amphotericin B would be much more easily implemented in the many centres in Africa and Asia currently using fluconazole, and may not be associated with any loss in effectiveness compared with 2-week courses. Therefore, this study will compare the best oral treatment, a combination of fluconazole and flucytosine, with a one-week amphotericin B-based strategy, and with the standard of 2 weeks amphotericin B, in resource-limited settings where implementation of 2 weeks of amphotericin B would be difficult to sustain, and therefore would not be used unless shown to be superior to more readily implementable alternatives. Additionally, fluconazole and flucytosine will be compared as additional drugs to be given with amphotericin B, in the two amphotericin B treatment strategies.

Who can participate?
The study population will be HIV-seropositive patients, > 18 years of age, with cryptococcal meningitis, at participating centres in Malawi, Zambia, Cameroon and Tanzania.

What does the study involve?
Patients will be randomly allocated into one of three alternative treatment strategies for the initial treatment of HIV-associated cryptococcal meningitis:

1. Fluconazole plus flucytosine for 2 weeks
2. Amphotericin B plus EITHER fluconazole OR flucytosine for 7 days
3. Amphotericin B plus EITHER fluconazole OR flucytosine for 14 days

What are the possible benefits and risks of participating?
Patients enrolled in the study will benefit from access to essential antifungal drugs that may otherwise not be available to them, and expert medical care from clinicians experienced in the management of cryptococcal meningitis. Patients will undergo two study lumbar punctures at study days 7 and 14. These lumbar punctures will determine patients' response to treatment and help in the management of raised intracranial pressure, which is a common complication of cryptococcal meningitis in over two thirds of cryptococcal meningitis patients. Any potential discomfort will be alleviated by experienced clinicians performing the procedure and, of course, adequate analgesia.

Where is the study run from?
The study is run from St George's University of London. Patients will be recruited at sites in Lusaka (Zambia), Blantyre, Lilongwe and Zomba (Malawi), Yaoundé and Douala (Cameroon), and Dar es Salaam (Tanzania).

When is the study starting and how long is it expected to run for?
The study started recruitment in January 2013 and is expected to run for 4 years.

Who is funding the study?
The project is funded by the Medicines Research Council (MRC) London (Malawi, Zambia and Tanzania sites), and Agence National de Recherches sur le SIDA et les hepatites virales (ANRS) (Cameroon sites).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number

12.0053 (Sponsor number)

Study information

Scientific Title
A phase III, randomised, controlled trial for the treatment of HIV-associated cryptococcal meningitis: oral fluconazole plus flucytosine or one week amphotericin B-based therapy vs two weeks amphotericin B-based therapy

Acronym
ACTA (Advancing Cryptococcal meningitis Treatment for Africa)

Study objectives
Treatment with a combination of fluconazole and flucytosine or with a one week amphotericin B-based strategy is non-inferior to the current standard of two weeks amphotericin B treatment for initial treatment of human immunodeficiency virus (HIV)-associated cryptococcal meningitis in resource-limited settings

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Zambia - ERES Converge, 26/09/2012, ref: 2012-May-003
2. Lilongwe, Malawi - National Health and Science Research Council (NHSRC), 21/12/2012, ref: Protocol #1003
3. Blantyre, Malawi - College of Medicine Research Ethics Committee (COMREC), 13/11/2012, ref: P.04/05/352
4. Zomba, Malawi – National Health and Science Research Council (NHSRC), 17/09/2015, ref: Protocol #1003
5. United Kingdom - London School of Hygiene and Tropical Medicine Research Ethics Committee, 19/07/2012, ref: 6212
6. Yaounde, Cameroon - Comite National d'Ethique, 27/02/2014
7. Douala, Cameroon - Douala General Hospital Research and Scientific Committee, 14/03/2014
8. Dar es Salaam, Tanzania – National Institute for Medical Research REC, 17/12/2014

Study design
Open label phase III randomised non-inferiority multi-centre trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
HIV-associated cryptococcal meningitis

Interventions

Study Regimen 1:
Fluconazole 1200 mg /d plus
Flucytosine 25 mg/kg four times a day (qds) for 2 weeks

Study Regimen 2:
Amphotericin B (AmB) 1 mg/kg/d plus EITHER
2A: fluconazole 1200 mg /d, OR 2B: flucytosine 25 mg/kg qds, for 7 days

Study Regimen 3:
Amphotericin B (AmB) 1 mg/kg/d plus EITHER
3A: fluconazole 1200 mg /d, OR 3B: flucytosine 25 mg/kg qds, for 14 days

In regimen 2, patients will receive fluconazole 1200 mg /d during the second week. In all arms, after 2 weeks, patients will receive fluconazole 800 mg/d until ART started (at 28 days +/- 4 days after start antifungal therapy), then fluconazole 400 mg/d to complete 10 weeks treatment, and fluconazole 200mg/d thereafter.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Fluconazole, flucytosine, amphotericin B

Primary outcome(s)
Mortality at 2 weeks by treatment group (regimen 1 and regimen 2 vs regimen 3)

Key secondary outcome(s))
1. Mortality at 10 weeks by treatment group, as above
2. Mortality at 2, 10 weeks by treatment group (regimens [2A + 3A] vs regimens [2B + 3B]; and 2A vs 2B, 3A vs 3B)
3. Mortality at 2, 4, and 10 weeks by treatment group, as above, adjusted for site and other possible confounders.
4. The proportion of patients in each arm suffering clinical and laboratory-defined adverse events
5. Rate of clearance of infection by treatment group based on cerebrospinal fluid (CSF) quantitative cultures at baseline and days 7 and 14
6. The proportion of patients in each arm suffering pre-defined Immune reconstitution inflammatory syndrome (IRIS) reactions to 10 weeks

Completion date
01/06/2017

Eligibility

Key inclusion criteria
Current inclusion criteria as of 21/10/2013:
1. Consecutive patients age 18 years or over with a first episode of cryptococcal meningitis on

basis cerebrospinal fluid (CSF) India ink and/or CSF cryptococcal antigen.
2. Willing to agree to HIV testing
3. Willing to consent to participate in the study.

Previous inclusion criteria:
1. Consecutive patients age > 18 years with a first episode of cryptococcal meningitis on basis cerebrospinal fluid (CSF) India ink and/or CSF cryptococcal antigen
2. Willing to agree to HIV testing
3. Willing to consent to participate in the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
110 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current exclusion criteria as of 15/12/2014:
1. Pregnancy or lactation
2. Previous serious reaction to study drugs
3. Concomitant medication that is contraindicated with any study drugs
4. Received >1 dose of Amphotericin B therapy within 2 weeks of screening
5. Received > 1 cryptococcal treatment dose (up to 1200 mg) of fluconazole or > 7 days low dose (200 mg) fluconazole within 2 weeks of screening

Previous exclusion criteria from 21/10/2013 to 15/12/2014:
1. Pregnancy or lactation.
2. Previous serious reaction to study drugs
3. Concomitant medication that is contraindicated with any study drugs.
4. Received >1 dose of amphotericin B or fluconazole therapy within 2 weeks of screening

Original exclusion criteria:
1. Pregnancy or lactation
2. Previous serious reaction to study drugs
3. Concomitant medication that is contraindicated with any study drugs
4. Already on anti-retroviral therapy (ART)

Date of first enrolment
28/01/2013

Date of final enrolment
31/12/2016

Locations

Countries of recruitment
United Kingdom

England

Cameroon

Malawi

Tanzania

Zambia

Study participating centre
St George's University of London
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London
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Sponsor information

Organisation
St George's University of London (UK)

ROR
https://ror.org/040f08y74

Funder(s)

Funder type
Research council

Funder Name

Medical Research Council (MRC) (UK)

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Agence Nationale de Recherches sur le Sida et les Hepatites Virales

Alternative Name(s)
National Agency for AIDS Research, National Agency for Research on AIDS and Viral Hepatitis, National Agency of Research on AIDS and Viral Hepatitis, ANRS | Maladies infectieuses émergentes, ANRS MIE, ANRS

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
France

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	15/03/2018		Yes	No
Results article	results	01/08/2019	17/06/2020	Yes	No
Other publications	Nested observational study	07/05/2026	18/05/2026	Yes	No