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Effect trial: Treatment of cryptococcal antigen-positive patients identified through screening using fluconazole plus flucytosine vs fluconazole alone

Submission date
10/02/2021

Recruitment status
Recruiting

Registration date
04/03/2021

Overall study status
Ongoing

Last Edited
18/09/2024

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English Summary

Background and study aims
Over the last 10 years, many more people living with HIV in Africa have been able to start antiretroviral treatment (ART). However, about one-third of people living with HIV only seek care when they have advanced HIV disease (when their CD4 count falls below 200 cells/µl). The frequency of infections such as cryptococcal meningitis in this group is high. Cryptococcal meningitis, caused by a fungus, is the commonest form of meningitis in sub-Saharan Africa, resulting in about 180,000 deaths per year globally with over 75% of these occurring in sub-Saharan Africa.
Over half of the patients diagnosed with cryptococcal meningitis die within 10 weeks in sub-Saharan Africa, a death rate similar to Ebola virus disease. Fortunately, cryptococcal disease can be diagnosed earlier, before the development of life-threatening meningitis, using a simple blood test to detect a part of the fungal cell called cryptococcal antigen (CrAg). Studies have shown that 70% of people testing positive for CrAg in blood would progress to develop meningitis or die without a diagnosis if they are not given antifungal treatment. Routine screening for CrAg among people presenting to HIV centres, combined with oral antifungal (fluconazole) treatment for those who screen CrAg-positive, can therefore decrease the risk of cryptococcal meningitis and death. CrAg screening has now been recommended in the national HIV guidelines of 28 countries and screening programmes are being rolled out across sub-Saharan Africa.
However, there is now also evidence showing that CrAg-positive patients who are treated with fluconazole alone have a 2.5 to 3 times higher chance of dying compared to people with similar CD4 counts who test CrAg-negative, despite receiving this antifungal treatment. Up to 40% of people testing blood CrAg-positive may have asymptomatic (subclinical) cryptococcal meningitis diagnosed at the time of the screening test; these people need a combination of antifungal medicines to treat meningitis. Yet many patients decline the procedure to diagnose meningitis (lumbar puncture) and are thus not treated appropriately for meningitis.
Recent studies have shown that combined oral treatment of fluconazole plus flucytosine for 2 weeks is safe, has few unwanted side effects and works as well as the standard of 2 weeks of

intravenous amphotericin B plus flucytosine for people treated in hospital with symptomatic cryptococcal meningitis. This study aims to compare how well this oral combination of fluconazole plus flucytosine works compared to fluconazole alone (the current recommended treatment) in reducing 6-month mortality in asymptomatic people with advanced HIV disease and a CrAg-positive blood test in Tanzania, South Africa and Vietnam.

Who can participate?
HIV-infected adults (>18 years old) identified through routine laboratory screening at participating centres as CrAg-positive in blood and who are also cerebrospinal fluid CrAg-negative or who decline a lumbar puncture.

What does the study involve?
Eligible participants are randomly allocated to be treated with either fluconazole (1200 mg) plus flucytosine OR fluconazole (1200 mg) alone for 14 days. Fluconazole (800 mg daily) will be given to all participants for a further 8 weeks and fluconazole 200 mg/d thereafter as per national guidelines. Participants who are treated as outpatients will be seen in clinic on day 1 and 14 and contacted on days 3 and 9 by telephone for adherence counselling and at 1, 2.5 (10 weeks), 4 and 6 months to determine survival status. Mortality (death rates) will be compared between the two groups.

What are the possible risks and benefits of participating?
The ultimate goal of this project is to reduce mortality due to HIV-associated cryptococcal disease by ensuring universal access to affordable, safe, and effective treatment. If a combination therapy of fluconazole and flucytosine is shown to be safe and more effective than fluconazole alone, results from this study would lead to evidence-based changes in regional and international treatment guidelines, and provide an effective and practical treatment, which could be administered to outpatients, with the potential to prevent a significant number of HIV-related deaths.
Risks associated with the oral combination of fluconazole and flucytosine are expected to be low, with little toxicity observed for CM patients in a recent phase III randomised controlled trial (ACTA trial) treated with the same combination. However, the risk-benefit for flucytosine in asymptomatic out-patients is not defined, and flucytosine can be associated with neutropenia. Toxicity in study participants will be closely monitored with adjustments made as necessary and adverse events regularly reported to the Data Monitoring Committee.
An additional potential risk is a lack of adherence to the medications due to an increased daily pill count for the first 14 days. Participants will be counselled on the importance of adherence and will be seen face-to-face twice during induction phase treatment (on day 1and 14) and called by telephone on days 3 and 9 to encourage adherence to medication and discuss any issues. As the intervention is given over the first 2 weeks, a pill count will be performed on day 14. If significant issues are identified for some participants, patient advocates (including CM survivors) will be asked to assist.

Where is the study run from?
1. Mycology Division, WITS Health Consortium (Based at the National Institute for Communicable Diseases) (South Africa)
2. St George's University of London (UK)

When is the study starting and how long is it expected to run for?
November 2020 to August 2026

Who is funding the study?
The study is funded through the Joint Global Health Trials (JGHT) Scheme with funding from the

UK - Department of Health and Social Care (DHSC), the Foreign, Commonwealth & Development Office (FCDO), the Medical Research Council (MRC), Wellcome and National Institute for Health Research (NIHR).

Who is the main contact?
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Study website
https://witsmycology.co.za/projects/EFFECT/index.html

Contact information

Type(s)
Scientific

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Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
JRES 2020.0308

Study information

Scientific Title
Fluconazole plus flucytosine vs fluconazole alone for cryptococcal antigen-positive patients identified through screening: a phase III randomised controlled trial

Acronym
EFFECT - Efficacy of Flucytosine and Fluconazole as Early Cryptococcal Treatment

Study hypothesis
Pre-emptive combination treatment of fluconazole plus flucytosine for 2 weeks will be more efficacious in reducing 6-month all-cause mortality than standard treatment of fluconazole alone among CrAg-positive HIV-infected adults

Ethics approval required
Old ethics approval format

Ethics approval(s)

1. Approved 22/01/2021, St George's, University of London (SGUL) Research Ethics Committee (Joint Research and Enterprise Services, Ground Floor, Jenner Wing, St. George's, University of London, Cranmer Terrace, London, SW17 0RE, UK; +44 (0)208 266 6073; sgulrec@sgul.ac.uk), ref: 2020.0308
2. Approved 21/07/2021, National Institute for Medical Research (NIMR) REC (PO Box 9653, Dar es Salaam, Tanzania; +255 22 2121 400; ethics@nimr.or.tz), no ref provided
3. Approved 12/08/2021, University of Cape Town Faculty of Health Sciences Human REC (Room G50, Old Main Building, Groote Schuur Hospital, Observatory, Cape Town 7925, South Africa; +27 (021) 650 5184; hrec-enquiries@uct.ac.za), ref: 274/2021
4. Approved 21/05/2021, University of the Witwatersrand Human REC (Suite 189, Private Bag x2600, Houghton, Johannesburg 2021, South Africa; +27 (0)11 275 9200; HREC-Medical.ResearchOffice@wits.ac.za), ref: 210305
5. Approved 22/07/2022, University of KwaZulu-Natal Biomedical REC (UKZN Research Office, Govan Mbeki Building, Westville Campus, University Drive, Durban 4001, South Africa; +27 (031) 260 1074; brec@ukzn.ac.za; ref: BREC/00002777/2021
6. Approved 30/06/2021, Walter Sisulu University Health Research Ethics and Biosafety Committee (Academic Health Services Complex of the Eastern Cape, Postgraduate Research and Training, Faculty of Health Sciences, Walter Sisulu University, Private Bag X1, WSU, South Africa 5117; +27 (0)47 502 2100; ggeorge@wsu.ac.za), ref: 067/2021

Study design
Open-label multicentre phase III randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Condition
Asymptomatic cryptococcal antigen (CrAg)-positive individuals with advanced HIV infection

Interventions
Individual randomisation using SAS PROC PLAN via a permuted-block randomisation method stratified by site. Block sizes will vary.

1. Fluconazole 1200 mg/day plus flucytosine 25 mg/kg four times daily PO (intervention arm) for 2 weeks
2. Fluconazole alone 1200 mg/day PO (standard dose 'control arm') for 2 weeks

All participants will then receive fluconazole 800 mg/day to 10 weeks, and fluconazole 200 mg /day thereafter for a minimum of 12 months as per national guidelines. ART will be commenced on day 14 as per current international (WHO) and national guidelines.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Flucytosine, fluconazole

Primary outcome measure
All-cause mortality, measured using patient medical records and interviews, at 6 months after randomisation

Secondary outcome measures
1. Time to all-cause mortality, measured using patient medical records and interviews, within the first 6 months
2. All-cause mortality, measured using patient medical records and interviews, at 10 weeks
3. Cryptococcal meningitis-free survival, measured using patient medical records, to 6 months
4. Incidence rate of symptomatic laboratory-confirmed cryptococcal meningitis, measured using patient medical records, over 6 months
5. Tolerability and safety: proportions of patients developing clinical and laboratory-defined grade III/IV adverse events measured using patient medical records and interviews up to 21 days
6. Efficacy outcomes by baseline CrAg titre and semi-quantitative assay score at 10 weeks and 6 months
7. Health service costs per life-year saved, measured using participant and health service provider interviews, over 6 months

Overall study start date
09/11/2020

Overall study end date
31/08/2026

Eligibility

Participant inclusion criteria
1. Consecutive patients aged >18 years
2. HIV-seropositive
3. CD4 count of <100 cells/µl
4. Serum/plasma Cryptococcal antigen (CrAg) test positive within the last 14 days
5. Cerebrospinal fluid (CSF) CrAg test negative or lumbar puncture not done (declined)
6. Willing to participate in the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
600

Participant exclusion criteria
Current exclusion criteria:
Initial exclusion criteria:
1. Prior episode of cryptococcal meningitis
2. Pregnancy (confirmed by urine or serum pregnancy test) or breastfeeding
3. Previous serious reaction to flucytosine or fluconazole
4. Already taking high-dose fluconazole treatment (800-1200 mg/day) for ≥1 week
5. Contraindicated concomitant medications including cisapride and the class of antihistamines including terfenadine
6. HIV-seronegative
7. Clinical symptoms/ signs of symptomatic meningitis at any time since CrAg screening, i.e. a progressively severe headache OR a headache and marked nuchal rigidity OR a headache and vomiting OR seizures OR a Glasgow Coma Scale (GCS) score of <15
8. Jaundice
9. CSF positive for cryptococcal meningitis (i.e. positive microscopy with India Ink, culture, or CrAg test) at any time between the CrAg test and screening for eligibility, while the patient remained without clinical symptoms/ signs of meningitis as described in 7 (late withdrawal criterion)

Late exclusion criteria: (after randomisation and day 1 visit)
10. DAIDS grade 4 abnormalities of platelets, neutrophil count or creatinine level on baseline bloods:
10.1. Platelets <25,000 x 10^6/l
10.2. Neutrophils <400 x10^6/l
10.3. Creatinine > 3.5x upper limit of normal (with standardised ULN of 114 µmol/l, this includes any creatinine level ≥400 µmol/l)
11. Microbiological evidence of CM on CSF if full CSF results not present at randomisation (e.g. screening CSF CrAg negative but culture on same sample later returns positive for CM)

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Previous exclusion criteria:
1. Prior episode of Cryptococcal meningitis
2. Pregnancy (confirmed by urine or serum pregnancy test) or breastfeeding
3. Previous serious reaction to flucytosine or fluconazole
4. Already taking high-dose fluconazole treatment (800-1200 mg/day) for ≥1 week
5. Contraindicated concomitant medications including cisapride and the class of antihistamines including terfenadine
6. HIV-seronegative
7. Clinical symptoms/ signs of symptomatic meningitis at any time since CrAg screening, i.e. a

progressively severe headache OR a headache and marked nuchal rigidity OR a headache and vomiting OR seizures OR a Glasgow Coma Scale (GCS) score of <15
8. Jaundice
9. CSF positive for Cryptococcal meningitis (i.e. positive microscopy with India Ink, culture, or CrAg test) at any time between the CrAg test and screening for eligibility, while the patient remained without clinical symptoms/ signs of meningitis as described in 7 (late withdrawal criterion)

Recruitment start date
08/05/2022

Recruitment end date
31/10/2025

Locations

Countries of recruitment
South Africa

Tanzania

Viet Nam

Study participating centre
Khayelitsha Site B Clinic and Mitchell's Plain Hospital
Cnr Walter Sisulu & Steve Biko Road
Khayelitsha
Cape Town
South Africa
7784

Study participating centre
Chris Hani Baragwanath Academic Hospital
26 Chris Hani Rd
Diepkloof 319-Iq
Johannesburg
South Africa
1864

Study participating centre
Helen Joseph Hospital
Rossmore
Johannesburg
South Africa
2092

Study participating centre
Klerksdorp/Tshepong Hospital
Jouberton
Klerksdorp
South Africa
2574

Study participating centre
King Edward VIII Hospital
Sydney Rd
Umbilo
Durban
South Africa
4013

Study participating centre
Harry Gwala Regional Hospital (formerly Edendale Hospital)
89 Selby Msimang Rd
Plessislaer
Pietermaritzburg
South Africa
3201

Study participating centre
Livingstone Hospital
Lindsay Rd, Industrial
Gqeberha
South Africa
6020

Study participating centre
Amana Regional Referral Hospital
Uhuru St, Ilala
Dar es Salaam
Tanzania
-

Study participating centre

Mwananymala Regional Referral Hospital
Kinondoni
Dar es Salaam
Tanzania
-

Study participating centre
Temeke Regional Referral Hospital
Temeke
Dar es Salaam
Tanzania
-

Study participating centre
Dora Nginza Hospital
Spondo St
Gqeberha
South Africa
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Sponsor information

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Sponsor type
University/education

Website
http://www.sgul.ac.uk/

ROR
https://ror.org/040f08y74

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

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 of Health and Social Care

Alternative Name(s)
Department of Health & Social Care, DH

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Foreign, Commonwealth and Development Office

Alternative Name(s)
Foreign, Commonwealth & Development Office, Foreign, Commonwealth & Development Office, UK Government, FCDO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Planned publication of the protocol
2. Planned publication of the results in a high-impact peer-reviewed journal

Intention to publish date
31/08/2026

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