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Comparison of four Fixed Dose Combinations versus standard treatment with separate anti-TB drugs for treatment of pulmonary tuberculosis

Submission date
12/07/2011

Recruitment status
No longer recruiting

Registration date
26/01/2012

Overall study status
Completed

Last Edited
21/06/2016

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Tuberculosis (TB) of the lungs is one of the most common diseases in this region. At the moment, people with TB need to take at least four different type of TB drugs. These drugs are available both in combined (fixed dose combination) and loose forms. The length of both treatments is the same i.e. six months in total. The reason we are doing this research is to find out if the combined drugs are as good as the loose drugs which are available.

Who can participate?
We are inviting all adults between 18 and 60 years old with TB of the lungs who attend this clinic to participate in this research.

What does the study involve?
If you agree to participate, we will examine you to be sure you are suitable for the study. We will do blood tests, sputum tests and a urine test for women of child bearing age. You will provide about two tablespoon of blood from your arm to check your liver and kidneys. You will provide sputum samples for laboratory examination at weeks 8, 20, 24 of treatment. These examinations are necessary to confirm successful treatment. In addition, you will be required to come to this clinic for check up at the end of 36 weeks (9 months), 48 weeks (12 months), 72 weeks (18 months) and 96 weeks (24 months) after starting your treatment. Sputum samples collected from you will be used for this research and will be destroyed after the research is completed.
All patients in this study must have an HIV test. If you agreed to have an HIV test and counselling through the existing VCT (Voluntary HIV Counselling and Testing) clinic, we will have access to your test result and will refer you to the nearest HIV treatment centre.
If you choose not to take the test, you will still receive the standard treatment for TB.

What are the possible benefits and risks of participating?
If you participate in this research, you will be treated with the anti-TB drugs for a total duration of 6 months rather than for the current practice of 8 months. You will be followed up closely by

the research team. You will be reimbursed for your transport costs for all your visits to the treatment centre for the duration of your treatment. Your participation may help find the answer to the research question and benefit other future TB patients.
Risks and discomforts: although the dosage of the loose and fixed tablets are the same, we do not yet know for sure if there might be a difference in how your body handles the combined TB drugs. This might mean that the combined TB drugs do not work as well as the loose drugs. If the combined TB drugs are not working well, we will change your treatment to the established standard treatment available. By participating in this research you are likely to have some discomfort. These are repeated requests to provide sputum and the discomfort of blood sample collection. You will be required to come to the clinic to swallow your drugs under observation daily for the duration of the study i.e. six months. While it is standard for the first two months for all patients, the request to come to the clinic daily for the following four months is a particular feature of this study.

Where is the study run from?
Ethiopia and Nigeria

Where is study starting and how long is it expected to run for?
The study started in January 2007 and ended in January 2011

Who is funding the study?
UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR)

Who is the main contact?
Dr Joseph Chukwu
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Contact information

Type(s)
Scientific

Contact name
Dr Joseph Chukwu

Contact details
Medical Co-ordinator
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
A two-arm single-blind randomised comparison of four Fixed Dose Combinations versus standard treatment with separate anti-TB drugs for treatment of pulmonary tuberculosis

Acronym
4FDC

Study objectives
Cure rate when taking four fixed -dose combinations is not inferior to the standard treatment with separate anti-TB drugs for treatment of pulmonary tuberculosis (TB).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Local Institution Review Board (AHRI/ALERT Ethical Clearance Committee), the Ethiopian and Nigerian National Ethical Clearance Committee and the WHOs ERC, Geneva, Switzerland, 22/06 /2006

Study design
Single-blind randomised 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 the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Tuberculosis

Interventions
Test arm: 4 FDC formulation (ethambutol (275 mg)/ rifampicin (150 mg)/ isoniazid (75 mg)/ pyrazinamide (400 mg) followed by 2 FDC formulation (rifampicin (150 mg)/ isoniazid (75 mg))

Control arm: Loose formulations of ethambutol (400 mg), rifampicin (450 mg), isoniazid (225 mg), pyrazinamide (400 mg) followed by loose formulations of rifampicin (150 mg), isoniazid (225 mg) and isoniazid (100 mg)

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ethambutol, rifampicin, isoniazid, pyrazinamide

Primary outcome measure
Cure rates at end of treatment (6 months)

Secondary outcome measures
1. Early response rates: proportion of patients with negative culture results at 8 weeks after initiation of therapy
2. Proportion of patients with relapses during the 72 weeks follow up period after the end of treatment. A relapse is a patient previously treated for tuberculosis who has met the case definition of cure (as defined above) and been declared cured by a physician and who has now been diagnosed with bacteriologically positive (two positive smears and culture positive) tuberculosis. If there is discordance between smear and culture results, a clinical decision will be made regarding further management:
2.1. Smear positive, culture negative, and
2.2. Smear negative and culture positive
3. Cure rates in HIV positive TB patients
4. Proportion of patients with clinical deterioration of pulmonary tuberculosis with the need for hospitalisation
5. Proportion of patients with serious adverse events any time during chemotherapy
6. Proportion of patients with any adverse events during chemotherapy
7. Proportion of patients completing treatment (defined as patients who achieved a total of 54 out of 56 doses in the first eight weeks of treatment and 107 out of 112 doses at a daily rate during the subsequent 16 weeks of treatment) within each group. (96% doses taken considered as completed in intensive and maintenance phases).
8. Proportion of patients who developed multi-drug-resitant (MDR)-TB

Overall study start date
15/01/2007

Completion date
28/12/2011

Eligibility

Key inclusion criteria
Patients with newly diagnosed pulmonary tuberculosis (with or without pleural effusion) will be admitted to the study provided they fulfill the following criteria:
1. Two sputum specimens positive for tubercle bacilli on direct smear microscopy. A patient is

considered smear positive if:
1.1. 2 out of 3 consecutive sputum smears are read as positive, or
1.2. 2 out of 5 are read as positive in the event that only one of the first three smear is positive, in which case the patient will be asked for two more specimens: one morning and one spot.
2. No history of previous anti-tuberculosis chemotherapy, or antiretroviral therapy
3. Aged 18 years and over
4. A firm home address and intent to remain there during the entire treatment and follow up period
5. Informed consent to participate in the study
6. Weight between 40.00 kg and 70.00 kg inclusive
7. Acceptance of human immunodeficiency virus (HIV) counselling and testing
8. CD4 more than or equal to 220 cells/microlitre blood if the patient is HIV positive in Nigeria
9. CD4 > 350cells/microlitre blood if the patient is HIV positive In Ethiopia

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
1,000

Key exclusion criteria
1. Positive urinary pregnancy test or obviously pregnant on physical examination
2. Additional extrapulmonary TB (e.g. bone, meningeal, peritoneal or miliary)
3. Contraindications to any medications in the study regimens (e.g. documented allergy, optic neuritis, blurred vision, red-green colour blindness and poor visual acuity any active hepatic diseases
4. Evidence (laboratory and/or clinical history) of pre-existing non-tuberculous disease likely to affect the response to, or assessment of, treatment:
4.1. Diabetes mellitus
4.2. Liver impairment
4.3. Renal impairment
4.4. Peripheral neuropathy
4.5. Terminal illness such as malignancy
5. Requirement for hospitalisation for any reason other than directly observed treatment (DOT)
6. Concomitant immunosuppressive treatment during the whole study period
7. Psychiatric illness, alcohol or drug abuse likely to lead to uncooperative behaviour
8. Patients on antiretroviral treatment during TB treatment period

Date of first enrolment
15/01/2007

Date of final enrolment

28/12/2011

Locations

Countries of recruitment
Ethiopia

Nigeria

Study participating centre
German Leprosy & Tuberculosis Relief Association
Enugu
Nigeria
100004

Sponsor information

Organisation
UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR)

Sponsor details
World Health Organization
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CH-1211 Geneva 27
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Sponsor type
Government

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Government

Funder Name
UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	20/06/2016		Yes	No