ISRCTN83323477 https://doi.org/10.1186/ISRCTN83323477

Bioavailability of the fixed dose formulation Rifafour containing isoniazid, rifampicin pyrazinamide, ethambutol and the World Health Organization (WHO) recommended first line antiretroviral drugs zidovudine, lamivudine, efavirenz administered to new Tuberculosis (TB) patients at different levels of immunosuppression

Submission date
29/03/2006

Registration date
29/03/2006

Last Edited
17/09/2007

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

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

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Dr Philip Onyebujoh

Contact details
World Health Organization
20 Avenue Appia
Geneva-27
Switzerland
CH-1211
+41 (0)22 791 4478
onyebujohp@who.int

Additional identifiers

Protocol serial number
A40607

Study information

Scientific Title

Acronym
PK-TB-HAART

Study objectives
The optimal time to initiate concomitant therapies is currently not known but is based on balancing the risk of HIV disease progression against the discontinuation of therapies due to toxicities, side effects and/or unforeseen drug-drug interactions.

The study will investigate the bioavailability of anti-tuberculosis drugs and anti-retroviral drugs administered in fixed dose combinations to HIV/TB co-infected immuno-compromised individuals commencing concomitant HIV and TB therapy compared with anti-retroviral drugs administered to HIV-infected patients without clinical TB and anti-tuberculosis drugs to TB patients with HIV commencing TB therapy only, thereby determining the effects of the level of immunosuppression on the bioavailability of the drugs and any drug interactions.

Please note that ethics approval and secondary outcome measures were added to this record on 17th September 2007. Any changes are noted under this date.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Amended as of 17/09/2007:
Ethics approval received from the MRC South Africa on the 17th May 2006.

Study design
Randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Tuberculosis (TB) and Human immunodeficiency virus (HIV)

Interventions
Patients are assigned to the following groups:
1. TB/HIV co-infected (220 - 349 CD4 T cells/µl) treated with anti-TB chemotherapy and Highly

Active Anti-Retroviral Therapy (HAART)
2. TB/HIV co-infected (220 - 349 CD4 T cells/µl) treated with anti-TB chemotherapy
3. TB/HIV co-infected (350 - 500 CD4 T cells/µl) treated with anti-TB chemotherapy and HAART
4. TB/HIV co-infected (350 - 500 CD4 T cells/µl) treated with anti-TB chemotherapy
5. TB/HIV co-infected (less than 200 CD4 T cells/µl) receiving anti-TB chemotherapy and HAART
6. HIV infected without active TB (less than 200 CD4 T cells/µl) receiving HAART

There are 20 patients in each arm. Patients are randomised to groups 1 - 4. In groups 5 and 6 the first 20 patients in each arm meeting the inclusion/exclusion criteria and consenting to be in the study will be included.

The trial aims:
1. To investigate whether the bioavailability of both anti-retroviral drugs and anti-TB drugs (rifampicin and isoniazid) are affected by CD4 count levels in co-infected TB-HIV patients (comparison of drug levels of highly active anti-retroviral therapy [HAART] by CD4 count stratum, stratified by presence/absence of Anti-Retrovirals [ARVs])
2. To investigate whether the bioavailability of anti-TB drugs are affected by drug-drug interactions with anti-retroviral drugs in co-infected TB-HIV patients (comparison of TB drug levels between subjects given both ARVs and anti-TB drugs and those given anti-TB drugs alone, stratified by CD4 count stratum)
3. To investigate whether the bioavailability of anti-retroviral drugs is affected by drug-drug interactions with anti-TB medications (comparison of ARV drug levels between HIV infected non-TB infected individuals with CD4 count less than 200 cells/µl given only ARVs and TB/HIV co-infected subjects at the same CD4 count given both anti-TB and HAART)

For further information please contact Dr Onyebujoh at the address listed below or Dr Melba Gomes at gomesm@who.int

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Rifafour containing isoniazid, rifampicin pyrazinamide, ethambutol and zidovudine, lamivudine, efavirenz

Primary outcome(s)
To investigate the bioavailability of anti-tuberculosis drugs and anti-retroviral drugs administered in fixed dose combinations to HIV/TB co-infected immuno-compromised individuals commencing concomitant HIV and TB therapy compared with anti-retroviral drugs administered to HIV-infected patients without clinical TB and anti-tuberculosis drugs to TB patients with HIV commencing TB therapy only thereby determining the effects of the level of immunosuppression on the bioavailability of the drugs and any drug interactions.

Key secondary outcome(s))
1. Bioavailability of both Antiretroviral drugs and anti-TB drugs (rifampicin and isoniazid) as affected by CD4 count levels in co-infected TB-HIV patients (Comparison of drug levels of HAART by CD4 count stratum, stratified by presence/absence of ARVs)
2. Bioavailability of anti TB- drugs as affected by drug-drug interactions with anti-retroviral

drugs in co-infected TB-HIV patients (comparison of TB drug levels between subjects given both ARVs and anti-TB drugs and those given anti-TB drugs alone, stratified by CD4 count stratum)
3. Homogeneity between drug-drug interactions over the two CD4 strata, or extent of modification by CD4 count of the effect of drug-drug interaction
4. Bioavailability of anti-retroviral drugs as affected by drug-drug interactions with anti-TB medications (comparison of ARV drug levels between HIV infected non TB infected individuals with CD4 count less than 200 cells/ µl given only ARVs and TB/HIV co-infected subjects at the same CD4 count given both anti-TB and HAART)
5. Safety parameters - including biochemical and haematological Adverse Events (AE) and Serious Adverse Events (SAE)

Completion date
30/05/2008

Eligibility

Key inclusion criteria
1. Aged 18 to 65 years
2. Human Immunodeficiency Virus (HIV) treatment-naive patients (established by history)
3. No history of previous anti-TB chemotherapy within the previous 24 months
4. A traceable home address and contact details to facilitate home visits with a firm commitment to remain traceable and to be able to access a defined treatment/service point for 24 months
5. Not currently enrolled in any other drug or treatment trials
6. Informed consent for HIV testing and PK testing
7. Informed consent to participate in the trial
8. For female subjects, the following conditions are to be met:
8.1. Has been post-menopausal for at least one year, or
8.2. Is surgically incapable of bearing children, or
8.3. Is of childbearing potential and all of the following conditions are met:
8.3.1. Has a negative pregnancy test (urine) immediately before study entry (and later confirmed by a another pregnancy test)
8.3.2. Must agree to use an accepted method of contraception (i.e. barrier methods or intrauterine device [IUD]). The subject must agree to continue with the same method throughout the study
Note: If a patient is using a long-acting hormonal contraceptive (such as Depot-Provera), the patient can be enrolled in the study, however she should be advised to use it in conjunction with a barrier method or IUD due to the known pharmacokinetic interaction between the various study medications and hormonal contraceptives. If an oral hormonal agent is in use, the patient will be advised to change the method of contraception in favour of barrier methods. No patient will be enrolled who does not accept to use barrier methods or IUD for contraception.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit

18 years

Sex
All

Key exclusion criteria
1. Evidence (laboratory and clinical history) of pre-existing non-tuberculosis disease likely to affect the response to, or assessment of treatment effects or represent contraindications to the study medication:
1.1. Diabetes mellitus
1.2. Liver impairment (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] greater than 2.5 x the upper limit of normal value)
1.3. Renal failure (serum creatinine greater than 1.5 x the upper limit of normal value)
1.4. Epilepsy
1.5. Optical neuritis
1.6. Pancreatitis (lipase greater than 1.5 x the upper limit of normal value)
1.7. Neutropenia (total neutrophil count less than 1200 cells/l)
1.8. Anaemia (haemoglobin less than 8 g/dl)
1.9. Any other condition that in the view of the country Principal Investigator represents a contraindication to the study medication
2. Mental illness (clinical suspicion of schizophrenia, manic-depressive illness, dementia)
3. Stage IV disease requiring concomitant medications that may potentially interact with study drugs (according to WHO staging system)
4. Weight below 30 kg
5. Moribund or clinical evidence of severe illness
6. Patients exposed to other medication that may (on the basis a known interaction, or a strong theoretical basis) affect study drug levels. Exclusion of a volunteer on the basis of a potential interaction will be at the discretion of the principal investigator
7. Of childbearing age and refusing to use either barrier or IUD method of contraceptive for the duration of the study

Date of first enrolment
30/05/2006

Date of final enrolment
30/05/2008

Locations

Countries of recruitment
South Africa

Switzerland

Study participating centre
World Health Organization
Geneva-27
Switzerland
CH-1211

Sponsor information

Organisation
World Health Organization (WHO) (Switzerland)

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Research organisation

Funder Name
World Health Organization (WHO) (Switzerland)

Alternative Name(s)
, , Всемирная организация здравоохранения, Organisation mondiale de la Santé, Organización Mundial de la Salud, WHO, , ВОЗ, OMS

Funding Body Type
Government organisation

Funding Body Subtype
International organizations

Location
Switzerland

Funder Name
GlaxoSmithKline (GSK) - drug supply

Funder Name
Merck & Co Inc. - drug supply

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary