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Evaluating the effectiveness of artemisinin combination therapy (ACT) in treating malaria in East Africa

Submission date
02/04/2020

Recruitment status
No longer recruiting

Registration date
10/04/2020

Overall study status
Completed

Last Edited
18/05/2020

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
Accurate diagnosis followed by prompt and effective treatment is the backbone of any malaria control programme. However, malaria treatment has been facing huge challenges in recent years, especially the emergence and spread of resistant parasites to the commonly-used treatment. Today, the World Health Organization (WHO) recommends the use of combination therapies for falciparum malaria, preferably those containing artemisinin derivatives (ACTs – artemisinin-based combination therapies). Artemisinin derivatives, e.g. artesunate, artemether and dihydroartemisinin, being extremely potent antimalarial agents are the ideal partners in combinations with other antimalarial drugs.

In East Africa, there are a few institutions that have the scientific and infrastructural capability to carry out GCP and GLP compliant efficacy studies/ trials. The World Bank East Africa Public Health Laboratory Networking Project initiative links the best African institutions that are well-positioned to assess the efficacy of artemisinine-based combinations for treating uncomplicated malaria and to build capacity across the East African region.

This trial in Rwanda forms on of four groups in East Africa who will be conducting a multi-centre, randomised, two arm
trial to assess the efficacy of a drug (Duo-cotexin®) against a comparison drug (CoArtem®). Duo-cotexin® is cheaper and has a once daily, 3-day treatment regimen which is less complex than the regimen for CoArtem®. The network will determine antimalarial drug efficacy using standardised protocols and collate the information gathered on clinical responses and adverse events. Information on molecular markers to drug resistance and comparison of parasites profiles in drug failure cases will also be investigated.

Who can participate?
Children aged 1 to 14 years with confirmed uncomplicated infection with P. falciparum, whose parents/guardians have given written informed consent.

What does the study involve?
The study will involve receiving a 3-day treatment with either Duo-cotexin® or CoArtem®. Blood samples to measure the response to treatment will be taken on the 2nd and 3rd day of treatment. At 28 and 42 days after treatment began participants will be assessed for outcomes of the treatment.

What are the possible benefits and risks of participating?
The study will provide evidence-based data on the safest and most effective antimalarial drugs that should be recommended in Rwanda.

The risks of the participants are reduced as all treatment have been approved by institutional regulatory agencies. Any serious adverse event occurring after termination of the trial and likely related to the trial drug will be reported to safety monitor, investigated, and subject followed up until complete resolution of the event.

Where is the study run from?
Masaka, Ruhuha, Bugarama, Kibirizi, Nyarurema and Rukara health centres (Rwanda)

When is the study starting and how long is it expected to run for?
From September 2012 to December 2015

Who is funding the study?
World Bank Group (USA)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Rwanda Protocol

Study information

Scientific Title
Evaluation of the Efficacy of Artemisinin Combination Therapy in East Africa: A World Bank Multi-country East Africa Public Health Laboratory Networking Project. Rwanda Protocol

Acronym
TES Rwanda

Study objectives
How effective is the Artemisin combination therapy (ACT), Duo-cotexin®, compared to CoArtem®, in children with uncomplicated malaria? Can markers for resistance or reduced susceptibility of parasites to ACTs and the transmission potential of mutant parasites be detected?

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 16/05/2012, the Rwanda National Ethics Committee (MInistry of Health, P.O. Box. 84, Kilgali, Rwanda; +250 2 55 10 78 84; rnec@moh.gov.rw), ref: RNEC129/RNEC/2012

Study design
This study is part of a multicentre, two-arm, randomised controlled, phase IV trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Uncomplicated P. falciparum malaria

Interventions
The choice of study drugs has been made deliberately in response to the needs of each country in malarial treatment particularly with the need to provide treatment beyond the formal public sector and through home treatment.

Duo-cotexin®-This is a combination of dihydro-artemisinine and piperaquine. The drug is referred here as Duo-cotexin® and has been tested extensively in Asia and recently in clinical trials in Uganda and Rwanda and already proposed as second line in some countries.

CoArtem® –This is a combination of artemether and lumefantrine. It is the the comparator because it is the only fixed dose combination with artesunate currently available and first line treatment. The proposed studies will give an opportunity to accrue a large body of data on efficacy of CoArtem® in different countries.

The study drugs will be administered orally according to standard dosing schedules. Patients who vomit the first dose within 30 minutes of intake will receive a repeat dose. Since this project will compare different treatment regimens, it is important that children or their guardians and clinician or nurse are unaware of the administered treatment in order to prevent biased results.

Treatment with artemether-lumefantrine (CoArtem®) will be based on the Rwanda National Malaria Treatment Guidelines 2012 revised, based on patient body weight. Over 3 days, CoArtem® will be given at 0, 8, 24, 36, 48, and 60 h.

Treatment with Duo-cotexin® will follow the Kenya National Malaria Treatment Guidelines 2010, based on patient age. Over 3 days, Duo-cotexin® will be given at 0, 24 and 48 h.

Any use of concomitant medications (including paracetamol) will be documented in the CRF.

If at any time the progress of the child is unsatisfactory the child’s parent/guardians will be instructed to report immediately to the hospital for evaluation. Objective criteria for discontinuation from study medication and institution of rescue treatment are
1. Any sign of severe malaria, as per WHO definition, or a requirement for parenteral treatment
2. Any severe adverse event requiring treatment withdrawal in the treating physician’s opinion or at the patient’s or parent/guardian’s request
3. Parent/guardian’s decision

Anyone who develops danger signs and/or severe malaria will be referred to the inpatient ward for rescue treatment (quinine infusion/ parenteral or Artesunate as indicated in new updated guidelines of case management).

Assessment will occur through blood smears (taken at baseline, 1, 2, 3, 7, 14, 21, 28, 42 and 68 days), QT-NASBA (taken at baseline, 1, 2, 3, 7, 14, 21, 28, 42 and 68 days), genotyping (taken at baseline, and if necessary, 7, 14, 21, 28, 42 and 68 days, and hemoglobin levels (assessed at baseline, 14, 42 and 68 days).

Participants are randomly assigned to receive either or Duo-cotexin® or CoArtem®.

A randomization list will be computer generated for different age-strata (<2 years; 2-5 years; 5-10; 10-14 years) using MS-Excel. Sequentially numbered sealed envelopes containing the treatment group assignments will be prepared from the randomization list for each age category. The study doctor will assign a study number to the participant and the study nurse administers treatment by opening the envelope corresponding to the treatment number. The randomization codes will be secured in a locked cabinet accessible only by the study nurse. Only the study nurse and patients will be aware of treatment assignments whereas the study doctor will be blinded to the treatment assignments.
A unique identification number (IDNR) will be assigned to all participants participating in the drug study and written on the patient card and CRF. Patient cards and CRFs of study participants will be available only to the investigators directly involved with the child for clinical care and follow-up. Data analysis will be done based on the unique IDNR. Data management includes data collection, data entry and storage, quality assurance and data analysis. Details of each patient's symptoms, physical examination findings, laboratory results and treatment outcomes will be recorded in case record forms (CRF). Data from the CRF will be entered into a MS access database already in use. Data will be updated after each follow up visit. Double data entry and validation in each site will be performed by trained officers supervised by the data manager.

Adverse events:
An adverse event will be considered serious if it results in death; is life threatening; requires hospitalisation or prolongation of existing hospitalisation; or results in persistent or significant disability/incapacity. Any serious or unexpected adverse event, including abnormal laboratory and clinical findings, will be reported to the safety monitor immediately. The serious adverse event form will be completed by the investigator and transmitted immediately to the safety monitor who will review and make a recommendation. These events will be classified as either mild, moderate, severe or life-threatening, and ascribed to the study drugs as definite, probable, possible, unlikely, or no chance of being related to the medication. Any serious adverse event occurring after termination of the trial and likely to be related to the trial drug will be reported to safety monitor, investigated, and subject followed up until complete resolution of the event.

A Data and Safety Monitoring Board (DSMB) will be established for the purpose of providing independent advice on the safety of the treatments tested. The DSMB will be composed of three members with expertise in malaria, biostatistics and other appropriate disciplines. The DSMB will function as an independent body: it will regularly review interim analysis reports and will be informed by the sponsor on any serious adverse event occurring site and trial documents /records during the trials. The DSMB will be able to make decisions on whether the trial or arms of the trial, needs to be stopped. A Trial Monitor will inspect the site and trial documents /records. The members of the DSMB will be identified prior to enrolling the first patient.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Duo-cotexin® (this is a combination of dihydro-artemisinine and piperaquine) and CoArtem® (this is a combination of artemether and lumefantrine)

Primary outcome(s)
PCR-unadjusted and PCR-adjusted adequate clinical and parasitological response (ACPR) at 28 and 42 days follow-up. ACPR, Early treatment failure (ETF), late parasitological failure (LPF), and late clinical failure (LCF) will be classified in accordance with the WHO protocol. A participant will be considered as experiencing ACPR if they are not classified as experiencing ETF, LPR or LCF. Parasite clearance will be determined from Giemsa-stained blood films on day 2 and day 3. Blood smears will be taken at baseline, 1, 2, 3, 7, 14, 21, 28, 42 and 68 days. Trained microscopy technicians will quantify asexual parasites on thick smears (per 8000 white blood cells) and thin smears will be used for species identification. A minimum of 100 fields will be read before slides were deemed parasite negative. Each slide will be assessed independently by two microscopy technicians at each health centre and a geometric mean parasite density will be calculated.

Key secondary outcome(s))
1. Adverse events on CoArtem® and Duo-cotexin® assessed through serious adverse event forms completed by the investigators by 68 days follow-up
2. Proportion of parasites associated with molecular markers related to reduced susceptibility to Duo-cotexin® and CoArtem® assessed through dried filter paper blood spots from patients at baseline and from patients with parasite recurrence on day 7 and onwards if necessary (at 14, 21, 28, 42, and 68 days). These will be placed in a 96-well plate, lysed overnight in a saponin solution and DNA will be extracted with the InstaGene Matrix resin (Bio-Rad, Hercules, CA, USA) as described previously by Canier et al. DNA samples from day 0 and from the day of parasite recurrence will be analysed for genotyping of msp1, msp2 (merozoite surface proteins 1 and 2) and glurp. Mutations in the propeller domain of PfKelch13 (PF3D7_1343700, codons 440–680, 720 bp), associated with resistance to artemisinin, will be identified by capillary sequencing of PCR products, as described by Menard et al, NEJM 2016.
3. Post-treatment gametocytaemia & malaria transmission will be assessed by quantitative nucleic acid sequence-based amplification (QT-NASBA) and real-time molecular beacon detection. The multiplex assay will consist of both 18s rRNA QT-NASBA to quantify P. falciparum and pfs25 mRNA QT-NASBA to specifically quantify mature gametocytes at baseline, 1, 2, 3, 7, 14, 21, 28, 42 and 68 days

Completion date
31/05/2016

Eligibility

Key inclusion criteria
1. Aged 1 to 14 years
2. A slide-confirmed mono-infection of P. falciparum, asexual parasitemia between 1000 and 100000 p/ul
3. Able to attend follow-up visits

4. Written informed consent provided by parent or guardian. If the parent/caretaker is illiterate, a witness' signature and the thumbprint of the participant's parent/caretaker will be required.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
1 years

Upper age limit
14 years

Sex
All

Total final enrolment
536

Key exclusion criteria
1. Severe malnutrition
2. Co-morbidity including but not limited to: infection, severe anaemia, epilepsy, abnormal cardiac rhythm, hypoglycemia, jaundice, respiratory distress, and recent history of allergy,
3. Presence of danger signs including: an inability to drink, vomiting in the past 24 h, an axillary temperature of > 37.5°C or rectal/tympanic temp > 38.0°C, a history of fever within past 24 hours, and/or a recent history of multiple convulsions, unconsciousness, inability to stand or sit

Date of first enrolment
01/09/2012

Date of final enrolment
31/12/2015

Locations

Countries of recruitment
Rwanda

Study participating centre
Masaka health centre (Bugesera District)
Masaka

Masaka
Rwanda
00

Study participating centre
Ruhuha health centre (Kicukiro District)
Ruhuha
Rwanda
00

Study participating centre
Bugarama health center (Rusizi District)
Bugarama
Rwanda
00

Study participating centre
Kibirizi health center (Nyamagabe District)
Kibirizi
Rwanda
00

Study participating centre
Nyarurema health center (Nyagatare District)
Nyarurema
Rwanda
00

Study participating centre
Rukara health center (Kayonza District)
Rukara
Rwanda
00

Sponsor information

Organisation

Rwanda Biomedical Centre

Funder(s)

Funder type
Industry

Funder Name
World Bank Group

Alternative Name(s)
World Bank, The World Bank, Grupo Banco Mundial, Groupe Banque Mondiale, , Группа Всемирного банка, WBG

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/06/2019		Yes	No
Basic results			18/05/2020	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes