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Longitudinal comparison of combination antimalarial therapies in Ugandan children: evaluation of safety, tolerability and efficacy

Submission date	Recruitment status	[_] Prospectively registered
16/05/2005	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/06/2005	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
09/08/2010	Infections and Infestations	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title

Study objectives
We will test the hypothesis that the malaria treatment incidence density (number of treatments for malaria per time at risk) will differ among patients randomised to our three treatment groups (amodiaquine and sulfadoxine-pyrimethamine versus amodiaquine and artesunate versus artemether-lumefantrine).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Amodiaquine plus sulfadoxine-pyrimethamine versus amodiaquine plus artesunate versus artemether-lumefantrine

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Amodiaquine, sulfadoxine-pyrimethamine, artesunate, artemether-lumefantrine

Primary outcome(s)
The effect of antimalarial drug therapy can be measured both in terms of drug efficacy (risk of true treatment failure) and post-treatment prophylactic effect (risk of new infection). To best reflect the overall impact of therapy, our primary outcome measurement will be the treatment incidence density (treatments per time at risk) for each treatment arm. To eliminate the period not influenced by study drugs, treatment count will exclude the first episode.

Follow-up time will be from the first episode to the end of the study. Treatment count will include both first-line treatments with study drugs and second-line treatments with quinine following study drug failure. It will be assumed that participants will not be at risk for repeat therapy for 14 days after treatment with quinine, for which resistance has not been reported, so this time will be excluded when calculating total time at risk.

Key secondary outcome(s))
1. Drug efficacy:
We will examine the efficacy of the different treatment groups using each episode of malaria treated with a study drug as the unit of analysis. We will examine the risk for repeat treatment as a function of time. Short-term (14-day) assessments of treatment efficacy will provide a standard analysis that will be useful for comparisons with other studies.
1.1. Specific short-term outcomes to be assessed will include:
1.1.1. Clinical and parasitological outcome
1.1.2. Rates of fever and parasite clearance
1.1.3. Change in hemoglobin level from day zero to 14
1.1.4. Presence of gametocytes following treatment
1.1.5. Safety and tolerability of study medications
1.2. Long-term (beyond 14-day) outcomes will be:
1.2.1. Risk of recrudescence
1.2.2. Risk of new infection using Kaplan-Meier product limit estimates of risk at various time intervals (i.e. four, six, and eight weeks after initiation of therapy)
In the analysis of long-term outcomes, molecular genotyping will be used to distinguish recrudescence (true treatment failure) from new infections.

2. Safety and tolerability:
All adverse events will be catalogued based on their frequency, severity, and relationship to study medication using standardised protocols. These indices of safety and tolerability among treatment groups will be compared using each episode of malaria treated with a study drug as the unit of analysis.

3. Other long-term outcomes that will be assessed will include:
3.1. Incidence of asymptomatic parasitemia
3.2. Change in haemoglobin level over time
3.3. Perceived tolerability of study medications among subjects and care givers
3.4. Drug costs (comparison of total cost per patient)

Completion date
20/04/2007

Eligibility

Key inclusion criteria
1. Aged one to ten years
2. Agreement to come to the study clinic for any febrile episode or other illness
3. Agreement to avoid medications administered outside the study
4. Willingness of parents or guardians to provide informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
1 years

Upper age limit
10 years

Sex
All

Key exclusion criteria
1. History (obtained from the parent/guardian) of any known serious chronic disease requiring frequent medical care (e.g. Acquired Immune Deficiency Syndrome [AIDS], sickle cell disease, malignancy)
2. Intention to move from Kampala during the follow-up period
3. History (obtained from the parent/guardian) of serious side effects to study medications or sulfa drugs
4. Weight less than 10 kg
5. Severe malnutrition defined as weight-for-height or height-for-age Z-score less than -3
6. Homozygous haemoglobin SS (sickle cell) result by haemoglobin electrophoresis
7. Life-threatening screening laboratory value in the absence of malaria:
7.1. Absolute neutrophil count: less than 250/mm^3
7.2. Hemoglobin: less than 5.0 g/dl
7.3. Platelet count: less than 25,000/mm^3
7.4. Creatinine: less than two years: more than 1.5 mg/dl, more than two years: more than 2.0 mg/dl
7.5. Alanine transaminase (ALT): more than 15.0 x Upper Limit of Normal (ULN)
7.6. Bilirubin: more than 7.5 x ULN

Date of first enrolment
01/11/2004

Date of final enrolment
20/04/2007

Locations

Countries of recruitment
Uganda

United States of America

Study participating centre
San Francisco General Hopital
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Sponsor information

Organisation
National Institutes of Health (NIH) - National Institute of Allergy and Infectious Diseases (NIAID) (USA)

ROR
https://ror.org/043z4tv69

Funder(s)

Funder type
Government

Funder Name
The National Institute of Allergy and Infectious Diseases (NIAID) (USA)

Results and Publications

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	23/05/2007		Yes	No
Results article	results	30/07/2010		Yes	No