




# Artemether/ Lumefantrine & Nevirapine-based antiretroviral therapy


-

## A pharmacokinetic and safety study


Tamara Kredo  
Lead Investigator  
University of Cape Town  
SEACAT Evaluation Team




## Background



- **SEACAT 2.4.1** is a single centre, parallel-design, open-label, pharmacokinetic drug interaction and safety study



- Two groups of HIV-infected patients included:
  - HIV-infected adults not yet on ART (n=18)
  - HIV-infected adults on nevirapine-based ART (n=18)

## Outcomes



- **Safety** of ART, ACTs and the combination assessed in detail



- **Define the drug interactions**

The pharmacokinetics of lumefantrine, artemether, dihydroartemesinin, nevirapine, lopinavir/ritonavir, zidovudine, stavudine and lamivudine will be compared between groups

## Baseline characteristics



Baseline characteristics	Nevirapine ART (n=18)	ART naïve (n=18)
Sex (female) %	15 (83)	17 (94)
Median age (yrs) (IQR)	32 (29-40)	27 (25-32)
Median CD4 count (x10 <sup>6</sup> /L) (IQR)	343.5 (263-470)	355.5 (260-507)
Median Viral load (log copies/mL) (IQR)	<3.9	8.5 (7.8-9.3)
Median Weight (kg) (IQR)	58.5 (53.5-67)	58 (55-67)
Race: Black	16	18
Mixed race	2	0
Median lumefantrine total dose (mg/Kg) (IQR)	49.2 (42.6 - 53.4)	49.8 (42.6 - 52.2)

## WHO definition of adverse events



- Adverse events (AEs) - any untoward medical occurrence in a clinical investigation subject who is administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment.
- Adverse drug reactions (ADRs) are AEs for which a founded suspicion exists that the event is caused by the study medication.

## WHO Classification



### Intensity

- **Mild:**  
Transient and easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:**  
Sufficiently discomforting to interfere with normal everyday activities.
- **Severe:**  
Prevents normal everyday activities

### Causality

- **Certain**
- **Probable/likely**
- **Possible**
- **Unlikely**
- **Conditional/Unclassified**
- **Unassessable/unclassified**

## Adverse event results



- 95 adverse events overall
- No Serious adverse events
- Causality was assessed in all cases

	Nevirapine arm	Antiretroviral naïve arm
overall	46	49
Possibly related	15	17

- **Most c** related gastrointestinal e.g. nausea, diarrhoea, bloating, dyspepsia  
OR other such as - headache
- No clinically or statistically relevant changes in biochemistry, haematology and viral loads

## Cardiac safety of Lumefantrine

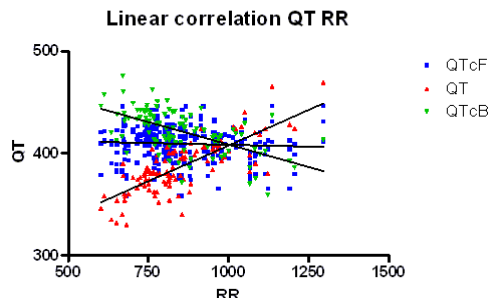


- Lumefantrine is chemically similar to halofantrine, which has well described cardiotoxicity
- Close monitoring of ECG criteria were included in the safety plan of this PK study
- ECGs performed at
  - screening
  - pre-dose
  - expected Tmax - 68 hours
- QT intervals, QRS, RR, PR were assessed

## QT interval



- 108 ECGs performed
- Fridericia (QTcF) and Bazett's (QTcB) calculation
- Compared variability over the RR range



- There was no difference in the median QTcB (p-value=0.182) or QTcF (p-value=0.505) intervals between treatment groups.
- There was no difference in the median QTcF intervals between screening and  $\sim T_{max}$  (68 hours) (p-value=0.8)

## Risks in pregnancy



- **WHO:** ACTs should be used in the 2<sup>nd</sup> & 3<sup>rd</sup> trimester in uncomplicated malaria
  - 1<sup>st</sup> trimester if it is the only effective treatment option
- *Published:* No adverse effects were observed in 125 women treated for uncomplicated *P. falciparum* malaria from 13.4 weeks of pregnancy with standard doses of Artemether-Lumefantrine.
- *Unpublished:* 1<sup>st</sup> trimester exposures to antimalarials in 1,530 pregnancies on the western border of Thailand. Analysis found that antimalarial drug treatment per se was not associated with abortion

McGready 2008 PLoS Med 5(12): e253.  
doi:10.1371/journal.pmed.0050253

## Pregnancy exposure



- Coartem® exposure at 4 weeks gestation
- Ethics and NRA informed
- Ultrasound at 11 weeks - no anomalies noted
- Delivery by caesarean section at 35 weeks for foetal decelerations
- Baby well at delivery, APGAR 9 at 5 minutes
- Review by paediatrician at 1 month– “ No indication of teratogenicity, problems of labour likely maternal related”
- Baby well, mother bottle-feeding

## B-M and daughter



Recently diagnosed  
HIV-negative by  
DNA-PCR

## Nested study of elicitation methods



- No consensus on elicitation of patient-reported data in clinical trials
- Checklists ↑ detection vs. unstructured enquiries
- The influence of individual idiosyncratic and socio-cultural factors on reporting are largely unknown
- Checklists may miss data, be burdensome and ↑ sensitivity rather than specificity
- Responses to unstructured enquiries followed by checklists will be described in a SEACAT/INTERACT substudy
- Patients reporting differently will be invited to focused interview to explore barriers to reporting

## Conclusion



- Artemether/Lumefantrine given to 36 HIV-infected volunteers
- Good evidence to support safe use with Nevirapine
- Minor AEs detected with stimulated enquiry
- Supports cardiac safety of Artemether/Lumefantrine
- First-trimester exposure with no evidence of teratogenicity



