



# Combating malaria in pregnancy

The **PREGACT** initiative, established as a European and Developing Countries Clinical Trials Partnership, and benefiting from a widespread consortium of key funders, is undertaking pioneering research to address the dearth of antimalarial drugs during pregnancy

**WE ARE CURRENTLY** witnessing a positive development in the fight against malaria, with substantial decreases in mortality being seen in a number of countries, including some of the malaria-endemic countries of sub-Saharan Africa. Although in 2010, malaria was the cause of an estimated 655,000 deaths worldwide, this figure actually represents a 5 per cent decrease from the 781,000 in 2009. Increased commitment and funding for malaria control activities have undoubtedly played a large part in this success, with scientists and healthcare professionals now talking about malaria elimination. This represents a major shift; the idea would have been thought impossible even a few years ago.

Despite continuing progress in reducing overall mortality, however, testing the safety and efficacy of new combination drugs on specific groups can still prove challenging due to the lack of comprehensive clinical trials in some of the worst-affected countries, where the need for this data is most pressing.

The biggest challenge will be to maintain or increase the levels of commitment we see today

PREGACT is a four-year project funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) and designed to study the effects of newly-available antimalarial treatments, such as artemisinin-based combination treatments (ACTs), in African pregnant women with malaria. Pregnant women are a high-risk group for malaria infection, but because they are systematically excluded from clinical trials, there is insufficient information on the safety and efficacy of both currently-used and potential new antimalarials in pregnancy.

The project coordinator is Professor Umberto D'Alessandro, formerly head of the epidemiology unit in the Department of Parasitology at the Institute of Tropical Medicine in Antwerp. He has recently been seconded to the Medical Research

Council unit in The Gambia as theme leader for disease control and elimination, though is still part of the academic staff in Antwerp. "We hope that by providing this information, the use of these new treatments among pregnant women will increase," outlines D'Alessandro, "particularly in sub-Saharan Africa where the study is carried out. These treatments have already been shown to be extremely efficacious and well-tolerated in children and non-pregnant adults."

## SAFE TREATMENTS

The relationship between malaria in pregnant women and low birth-weight has been known about for decades. In endemic areas, low birth-weight is even more likely to occur in primigravidae – women who are pregnant for the first time – who are often adolescents. They comprise a very high-risk group which is more difficult to reach with control interventions. Though most of the evidence comes from Asia, the World Health Organization recommends antimalarial treatments for women in the second and third trimesters of pregnancy, on the basis that the adverse effects of malaria on mother and foetus outweigh any risk related to the treatment, and there is already evidence that the treatments are safe in the second and third trimesters.

"This information is given to the women before any study procedure is carried out, and they have the freedom to refuse without compromising the health care provided to them," points out D'Alessandro. "For those who accept, the study teams are always ready to answer any questions a patient might have. She has the freedom to stop her participation to the study at any time. Most women are happy to participate – we have very few who withdraw their consent."

The study will see a total of 870 patients recruited to each of the four treatment centres, giving a total study sample size of 3,480 patients. A three-arm trial using a 'balanced incomplete block design' allows the treatments to be distributed in a way which allows head-to-head comparisons and the establishment of the treatment's relative value according to a series of outcomes. All women fulfilling the criteria



## INTELLIGENCE

### PREGACT - ANTIMALARIAL TREATMENT FOR AFRICAN PREGNANT WOMEN

#### OBJECTIVES

To determine the safety and efficacy of 4 ACTs (amodiaquine-artesunate or AQAS, dihydroartemisinin-piperazine or DHAPQ, artemether-lumefantrine or AL, Mefloquine-artesunate or MQAS) when administered to pregnant women with *P. falciparum* infection during the second and the third trimester, and collect explanatory variables for treatment failure (PCR-corrected) and for recurrent parasitaemia.

#### KEY COLLABORATORS

Belgium: **Raffaella Ravinetto** (Head of the Clinical Trial Unit), **Joris Menten** (Statistician), **Yves Claeys** (Data Manager), **Celine Schurmans** and **Maaïke De Crop** (Research Associates), **Chantal Van Overmeir** and **Evi Pockele** (Lab Assistants)

Burkina Faso: **Halidou Tinto** (PI), **Marc Tahita**, **Maminata Traoré**

Ghana: **Harry Tagbor** (PI)

Malawi: **Linda Kalilani-Phiri** (PI) and **Gertrude Kalanda**

Zambia: **Michael Nambozi** (PI), **Sebastian Hachizovu** and **Modest Mulenga**

#### FUNDING

The study is funded by the European and Developing Countries Clinical Trial Partnership (EDCTP) and by the Gates Foundation through the Malaria in Pregnancy Consortium coordinated by Prof Feiko ter Kuile at the Liverpool School of Tropical Medicine.

#### CONTACT

**Professor Umberto D'Alessandro**  
Theme leader, Disease Control and Elimination

Medical Research Council Unit  
The Gambia

T +220 449 5917  
E [udalessandro@mrc.gm](mailto:udalessandro@mrc.gm)

[www.cure.med.ucla.edu](http://www.cure.med.ucla.edu)  
[www.uclacns.org](http://www.uclacns.org)  
[www.uclamindbody.org](http://www.uclamindbody.org)

**PROFESSOR UMBERTO D'ALESSANDRO** (MD, MSc, PhD) has been the Head of the epidemiology unit at the Department of Parasitology at the Institute of Tropical Medicine in Antwerp. He has been recently seconded to the Medical Research Council unit in The Gambia as theme leader disease control and elimination.

are recruited from the weekly antenatal clinic sessions held at the study sites, over a period of about 18 months. Recruitment is conducted by teams that include medical doctors, research midwives and their assistants, trained by local investigators. Pregnant women will be assessed clinically and obstetrically, with those of at least 16 weeks' gestation systematically screened for malaria infection. If positive, a blood sample determines the presence of peripheral parasitaemia, as well as the parasite species and density.

On the basis of the current projections, PREGACT will have recruited all 3,480 patients by the end of 2012. The research teams on-site are continually screening potential study subjects to identify those eligible.

"We try to keep the rate of recruitment constant, although sometimes events outside our control may slow it down," reveals D'Alessandro. "For example, there might be a delay in obtaining the necessary permits for the import of study treatments."

#### A SPECIAL PROJECT

The principal investigators on the project are based at sites in Belgium, Burkina Faso, Ghana, Malawi, and Zambia. The Institute of Tropical Medicine in Antwerp is both a sponsor and the coordinator of the study and as such guarantees the quality of the data collected. The other four countries are malaria-endemic, where malaria in pregnancy is a major public health problem. There is a history of collaboration between the institutions involved in the trial, which was designed to include countries from the West, Burkina Faso and Ghana, and Eastern-Southern Africa, Malawi and Zambia.

PREGACT is in some senses a special project. It sits within the framework of the Malaria in Pregnancy Consortium, a large network of scientists working on malaria in pregnancy, which is part-funded by the Bill & Melinda Gates Foundation. This creates opportunities around multidisciplinary research and the possibility of coordinating submission of research proposals to different funding agencies, including the EDCTP. There are nevertheless difficulties in undertaking such a project: it is a clinical trial carried out to the highest possible standards, but with funds from a public donor which are by definition limited.

While commercial trials have a relatively higher flexibility in terms of funding, D'Alessandro and his team must ensure the project remains within the original budget – an exacting task, as it is not possible to predict all potential bottlenecks, such as slower patient recruitment.

It can also prove challenging to run a clinical trial concurrently at several sites to the highest possible standards, while at the same time providing opportunities for capacity building. PREGACT takes advantage of the opportunity to train young researchers to PhD level, as they gain experience and expertise within the framework of an ongoing clinical trial; the project is currently enabling three PhD students to complete their theses.

#### MAINTAINING COMMITMENT

Malaria has received increased attention on the global stage in recent years, which goes some way toward explaining recent successes in tackling the spread of the disease. Insecticide-treated bed nets or artemisinin-based combination treatments, which are among today's essential interventions, are products of the research conducted over the past 20 years or so. But the recent shift from malaria control toward possible elimination calls for an investment in additional research, as without that, little if any progress will be possible. The biggest challenge will be to maintain or increase the levels of commitment we see today, and this may be particularly difficult in places where malaria has already seen a decline.

"Experience teaches us that malaria can come back extremely rapidly if the pressure is not maintained," cautions D'Alessandro. "There is also a very real threat of resistance to the treatments and insecticides we use, and so we need to continue our efforts to develop new products. It is possible that climate change may play a part, but the impact on the overall prevalence will be determined by factors related to the vector, the parasite and our own commitment to addressing the problem."

