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EDCTP Fourth Annual Forum



# Building Bridges for Better Health

22 – 24 October 2007  
Ouagadougou, Burkina Faso

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# Foreword

**Prof. Charles Mgone**  
**EDCTP Executive Director**

**Dear Colleagues,**

The EDCTP forum is rapidly becoming one of the most prominent forums on HIV/AIDS, tuberculosis and malaria in Africa. At this forum we come together to share experiences and benefit from other people's experiences. We gather to share best practices in clinical trials, capacity building and networks, and to establish new collaborations and strengthen the already existing ones.

We have come a long way. Since 2004 the EDCTP forum has been an annual event with alternating venues between Africa and Europe. The first forum took place in Rome in September 2004 and the second in Durban in October 2005 under the theme *HIV/AIDS, TB and malaria in Africa: from knowledge to implementation*. In October 2006 the third forum was held in Stockholm, Sweden, with the theme *Partnership and African leadership: Challenges and Opportunities*.

The theme of this year's forum is *Building bridges for better health*. This theme underpins the key objectives of EDCTP: to encourage the development of clinical trial networks in Africa and to facilitate the coordination of research activities

on HIV/AIDS, tuberculosis and malaria of the participating European Member States in collaboration with their African counterparts. Also, EDCTP recently committed to strengthen key institutions in Africa as 'Networks of Excellence' which will have the remit to strengthen regional capacity for the conduct of clinical trials, with the support, as required, of European Member States.

The forum comes at an exciting time when EDCTP has revised its strategy and intensified its activities with the intention to deliver more and faster. As we look ahead we believe there is now a genuine partnership coming out of EDCTP. Achievements of this partnership will lead to delivery of new or improved interventions for fighting HIV/AIDS, malaria and tuberculosis in Africa and will therefore contribute to the exploration of the theme Building bridges for better health. I invite you to profit from this report, which assembles a wealth of information on research on HIV/AIDS, tuberculosis and malaria. I hope the report will play a useful role in our joint effort to fight poverty, the global public health enemy number one.





The Fourth EDCTP forum was held from 22 to 24 October 2007 in Ouagadougou, Burkina Faso with the theme *Building Bridges for Better Health*. The main objectives of the forum were to present an overview of ongoing clinical trials on the three poverty-related diseases (HIV/AIDS, tuberculosis and malaria) in Africa and to identify future priorities, particularly with respect to the promotion of South-South, North-South and North-North networking activities.

## Forum programme, sub-themes and recommendations

EDCTP was honoured that Madame Pascaline Tamini, Minister of Social Action and National Solidarity of Burkina Faso officially opened the forum. In his keynote speech Prof. Charles Mgone, EDCTP's Executive Director, explained that EDCTP uses comprehensive mechanisms to ensure that, while conducting clinical trials into HIV/AIDS, tuberculosis and malaria in sub-Saharan Africa, capacity is also developed through training, skills development and creating the correct environment to establish proper ethical conditions and rigorous testing methods. By working on the required clinical trials techniques, personnel and equipment Africa can conduct clinical trials in a very competitive professional matter, just as the rest of the world. He outlined the forum's main themes:

- Ongoing clinical trials in Africa
- Clinical trial networks in Africa
- Challenges in building clinical trial capacities in Africa
  - Regulatory and ethics environment
  - Networks of excellence

## Ongoing clinical trials in Africa

After a review of the current status of prevention and treatment of the three poverty-related diseases in sub-Saharan Africa, researchers presented progress and results of EDCTP-funded clinical trials. In the plenary and parallel sessions surrounding the trials, participants identified research gaps, shared best practices and drew recommendations and agreed on priorities for research into HIV/AIDS, tuberculosis and vaccines.

### HIV/AIDS clinical trials: recommendations

- There is a need to understand basic epidemiology more for the design of vaccines
- Biomarkers for efficacy for microbicides and protective immunity for vaccines are required
- Genetics studies in MTCT are required
- Response of children to ART should be studied.

### Tuberculosis clinical trials: recommendations

- Networking among groups working on similar research should be encouraged
- Understanding of therapeutic vaccines is required.

### Malaria clinical trials: recommendations

- EDCTP must continue to support malaria research
- There is a need for attractive conditions for African scientists in terms of salary increases
- The follow up period for monitoring ACTs' efficacy must be extended
- The assessment of chloroquine resistance should continue
- Continue researching methotrexate as an antimalarial drug.

## Clinical trials networks in Africa

A variety of centres funded by EDCTP or active in the field of HIV/AIDS, malaria and tuberculosis presented an overview of their networking activities: African AIDS Vaccine Programme AAVP, Malaria Clinical Trials Programme MCTA, Microbicides Development Programme (MDP), The Wellcome Trust, Africa Malaria Network Trust AMANET, Pan-African Bioethics Network (PABIN), Vienna School of Clinical Research (VSCR).

## Challenges in building clinical trials capacity in Africa

Discussions on the challenges in building clinical trials capacity in Africa were based on innovative ways of enhancing capacity, drawing lessons from TDR's research and capacity development strategy, distance learning and research ethics in Malawi.

Challenges in building clinical trials capacity in Africa - recommendations:

There is need to:

- Build on country networks where these exist
- Minimise complexity in capacity development through increased collaboration
- Involve host African countries in resource mobilisation and prioritisation
- Pay attention to regional variations in capacity and encourage mentorship schemes
- Encourage focused well designed lines of research with monitoring and evaluation
- Promote best practices and encourage quality control
- Put in place innovate collaborative work between Franco, Anglo and Lutherphone institutions
- Improve institutional infrastructure including IT support to assist distance learning
- Retain more staff longer by creating a critical mass of researchers
- Continue mentorship between North and South scientists
- Disseminate research findings to local communities and sensitise them to findings.

### Regulatory and ethics environment

There were discussions on the need for new drugs and high-quality research taking place in an adequate environment. Various initiatives are ongoing in terms of aims, and across many different bodies. Although there have been some achievements in terms of capacity building and networking, all speakers believed challenges remained. Recommendations resulting from these discussions are:

There is need to:

- Improve coordination between stakeholders and joint activities
- Collect and disseminate information on ongoing activities
- Harmonise standards of practice and regulations, but avoid too much uniformity

- Continue to support networking
- Clarify the different functions of ethics review committees and national authorities
- Provide tools and guidelines in different languages
- Advocate that ethics committees are funded sustainably
- Strengthen the capacity of ethical and regulatory bodies.

### Networks and Nodes of Excellence

Regional Networks of Excellence (NoE) can be used to streamline and coordinate the multitude of research projects into HIV/AIDS, tuberculosis and malaria. Forum participants pointed out that these networks should aim to reduce overlapping activities in their mandates. To do this, there is a need for more information so that the individuals managing them have a better idea of what others are doing. That requires complementarity and a recognition of the different strengths each can bring. Recommendations were:

- We need to continue supporting the networks and initiatives already in place
- We need to invest more in the development and harmonisation of standard operating procedures guidelines for ethics committees and NRAs in Africa
- It is critical to have an accelerated regulatory pathway
- It is in our best interests to look at ways of developing better synergies or reducing duplication in terms of Article 58 and pre-qualification procedures. There are ethical questions around holding back some of these life-saving products for a long time due to the bureaucratic procedures in place.

### EDCTP future and perspectives

Prof. Charles Mgone shared his dream of a genuine partnership between Europe and Africa. He said that the outcomes of the forum together with the recommendations from the external mid-term review of EDCTP and other ideas from stakeholders provided a firm base for an EDCTP strategy for the future. He concluded that the partnership between Europe and Africa has strengthened and that African countries are now joint owners of the EDCTP programme. He stressed the importance of making the programme sustainable developing research capacity and utilising it immediately, thus making sure the capacity is retained.



In 2008, the European Commission will decide whether or not EDCTP will be extended after 2010. The forum therefore provided an opportunity for drawing out recommendations and priorities for the next year and for going forward. Many suggestions were made for a possible extension of EDCTP's scope, including extending the scope of the programme to include development of diagnostic tools, phase I and phase IV research, traditional medicine, other neglected diseases and broadening coverage beyond sub-Saharan Africa.

Dr Manuel Romaris, EDCTP focal point in the EC, mentioned EDCTP should increasingly become a public-private partnership, and called for full Member State involvement.

Charles Mgone concluded the look into EDCTP's future with: "Let us decide and plan for the future with our HEADS, but commit ourselves to our decisions and the Partnership with our HEARTS."



# Plenary session: Overview

## Welcome Address



**Prof. Charles Mgone**  
**EDCTP Executive Director**

### I. Bridges to the Future

#### 1. Clinical trials

Honourable guests, EDCTP is a partnership between European member states and African counterparts that aims to integrate programmes on three poverty-related African diseases – HIV/AIDS, malaria and tuberculosis. Working together with African counterparts, we try to rid ourselves of these diseases through clinical trials, looking for new tools, drugs and vaccines that we can use. We conduct clinical trials that are safe, efficacious and effective, ultimately aiming for the protection of human beings.

#### 2. Networking and capacity building

Our programme also deals with capacity development and networking. These trials require special techniques, personnel and equipment we have to provide for Africa in a very competitive professional matter, just as for the rest of the world. Networking is both North-South, in the transfer of technology, and South-South, in proliferating our capacity as well as understanding one another within our own continent. EDCTP uses comprehensive mechanisms to ensure that, while conducting clinical trials, capacity is also developed through training, skills development and creating the correct environment to establish proper ethical conditions and rigorous testing methods. Additionally, EDCTP supports ethics and regulatory capacity in Sub-Saharan Africa.

### II. Forum Activities

We normally meet annually to exchange views and discuss general activities, as well as how we are advancing research. Also this week, we will hold roundtable discussions on capacity development and ways to improve sharing best practice. We will have a chance to discuss the future of EDCTP's programme, because we try as much as possible to form a mutual partnership in which all stakeholders jointly formulate plans, agree on what is to be done and carry out trials as equal partners. We will discuss how to make this programme become sustainable and increase African stewardship.

## Building Bridges between Clinical Trials and Healthcare Delivery in Africa



### Dr Pascoal Mocumbi EDCTP High Representative

#### I. EDCTP's Goal

I join the Executive Director in saluting all present and appreciating the hosting country for the warm Burkinabe hospitality. I was asked to speak about “Building bridges between clinical trials and healthcare delivery in Africa”. The overall goal of EDCTP is to reduce poverty in developing countries by improving the health of the populations most affected by HIV/AIDS, malaria and tuberculosis. For these three diseases, there are no effective clinical tools available. They persist in Africa and continue to cause ill health and mortality, and to impact the economic development of individuals, the family and the community at large. This cannot only be attributed to the lack of effective tools, but also to weaknesses of the healthcare system and other factors associated with poverty.

#### II. Poverty Reduction

Poverty reduction requires concerted collaboration between organisations like EDCTP, which works to accelerate the development of research tools, and other stakeholders interested in reducing the diseases' burden for health improvement, in particular organisations that work for strengthening healthcare systems, to ensure that populations have equal opportunities to access healthcare of good quality that will enable them to lift themselves up. The development of new products and subsequent access to them for prevention and cure has a unique contribution to the reduction of diseases' burden, permitting individuals and communities to enjoy better health and make use of their

potential to engage in productive opportunities to reduce poverty and promote sustainable development.

#### III. Building Bridges

##### 1. Capacity building

Building bridges for better health is at the core of linkages between EDCTP and stakeholders in evidence-based research and best practices. It enhances national capabilities to strengthen community-based health systems, procurement and deployment of public goods, and the training of vibrant and creative health-research networks in sub-Saharan Africa.

##### 2. Why now?

EDCTP now has more than 70 projects, some still under negotiation and others already upcoming. These achievements open a unique window of opportunity to engage stakeholders in enhancing capacity and participation to close the gap in health systems. As most of you know, the most important gap is illustrated by the fact that most of our health systems stop at the district level, in terms of infrastructure. Communities are at the bottom and, most of the time, there is no clear linkage between the health system and the community itself, without appropriate, adapted systems that enable this link to flow on a regular basis.

##### 3. EDCTP achievements

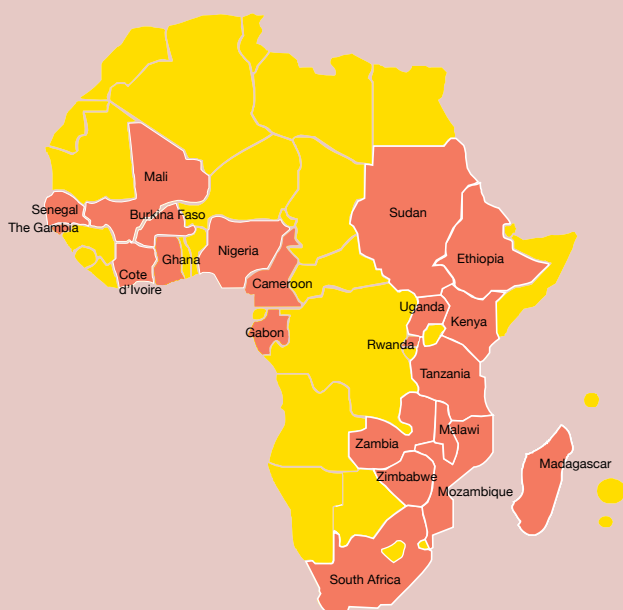
###### a. Triomune

After an EDCTP-conducted HIV clinical trial in Zambia, the Food and Drug Administration (FDA) granted tentative approval to prescribe Triomune Baby and Junior, the first fixed-dose HIV product designed for children infected with HIV/AIDS.



## b. Malaria interventions

New malaria artemisin-based combination therapies (ACTs) could be approved for use in about a year's time from now. Current malaria interventions such as bed nets and mosquito control are reaching more and more people across Africa, and are making a difference.



74 EDCTP-funded projects in 21 countries

## 4. Connector

EDCTP is ready to expand its integrated approach to clinical trials and supporting capacity development in Africa, as illustrated by the current calls for capacity building. Progress made in recent achievements urge that we bridge clinical research to healthcare delivery. We are here to discuss how EDCTP can become that bridge. The way forward requires us to translate commitments into facts. This partnership must continue the mobilisation of its constituencies, which must work together to achieve their agreed mission. I remind you: our ultimate goals are to reduce poverty and promote sustainable development. Now that EDCTP has overcome the difficulties that characterised the initial stages of its existence, it is set to scale up its activities as a trusted connector. The experience of stakeholder meetings has demonstrated its usefulness in exploring synergies and complementarities between interested parties to accelerate the development of new clinical tools to effectively control poverty-related diseases and improve the health of affected populations.

## 5. Parallel investments

Site visits to EDCTP-funded projects have already clearly shown that clinical trials conducted in endemic areas are addressing the same communities that also require healthcare providers. Visiting sites in Kenya and Gabon with the EDCTP team, I was impressed by the level of receptiveness of the communities, which appreciate the upgrades we have made in clinics, medical training in the latest treatment techniques and access to modern equipment for improved diagnosis. It therefore makes sense to plan parallel investments in healthcare delivery systems whenever clinical trials are being conducted.

I have noticed in my own country that, during clinical trials, populations in the regions where they are taking place believe they are witnessing the improvement of their own healthcare institutions but, when the clinical trial is over, and the healthcare system has not been upgraded, the populace asks themselves why it is that things appear to have moved backwards. That is why it is important to make parallel investments. We need more financial resources to do both.

## IV. Partnership

### 1. Global

The Global Forum for Health Research meets in a few days' time in Beijing. Next year will be Africa's turn to receive this Forum. We need to think now about how we link activities in this Forum with what we are doing in order to develop new clinical tools. Another important organisation is the Global Fund to fight AIDS, tuberculosis and malaria, where most of the money to achieve the Millennium Development Goals for these three diseases goes. However, we are now aware of the opportunities for us to raise money from this fund to develop new clinical trial sites.

### 2. African

At the regional level, EDCTP has already collaborated with the New Partnership for African Development (NEPAD), whose ministers of health recently made a declaration in Johannesburg to strengthen the capacity of health systems. This is a good opportunity for joint advocacy of connected actions in support of research and strengthening capacity for healthcare delivery. Health organisations all over Africa may help us to harmonise ethics committees and drugs authorities, and to translate research outcomes into

policies and practice to reduce the burden of poverty-related diseases. Another opportunity is to promote collaboration between African thematic networks, like the African AIDS Vaccine Programme (AAVP), African Malaria Network Trust (AMANET), Malaria Clinical Trials Alliance (MCTA) and many more.

### **3. National**

In Africa, we have to invest in research and development. We need to engage governments to contribute to funding of health research institutions and populations participating in clinical trials; connect investigators to policymakers, and scientists to decision-makers; engage communities to be an integral link in any system set up to serve them; establish integral relations with community-based organisations.

## **V. Conclusions**

EDCTP is set to move forward and translate its intentions into facts. The current platform must be transformed into a connector of national systems to produce and deliver health-research outcomes to meet the Millennium Development Goals, and national and global priorities. The Fourth EDCTP Forum offers the opportunity to get ready, to scale up implementation of EDCTP joint programmes of action based on our achievements so far and to continue working together towards sustainable partnerships. I wish you success.

## Linking European and African Programmes: The Role of European Member States and Agencies



**Dr Diana Dunstan**  
**EDCTP General Assembly Chair**

### I. Since Last Year's Forum

We were able to report progress to you in last year's Forum in Stockholm but, since then, EDCTP has matured into a fully effective organisation. Charles Mgone has been appointed executive director; there has been effective activity on all fronts in delivering the road map; we have established new ways of working; and all component parts of EDCTP are now better linked than before, as we come to understand our particular roles.

### II. Successes

#### 1. Clinical achievements

We can report real success in our output already. Dr Alexis Nzila has been awarded a Royal Society prize for advancing discoveries in antifolate drugs for the treatment of malaria, and Dr Abraham Alabi is developing colorimetric assays for monitoring viral load in HIV-infected individuals on antiretroviral therapy in developing countries. A number of clinical trials are also underway. Those are wonderful achievements.

#### 2. Partnership

We have also had real success in collaboration with other funders, such as the €20 million call from EDCTP and the Bill & Melinda Gates Foundation (BMGF), a real example of how we can all work together – African and European researchers, as well as three different funding organisations. I want to say thank you to you all for the hard work and contributions you have made to our overall progress, especially to Charles Mgone, who took on a difficult role in a

fragile organisation. His leadership has enabled us to develop into a robust, new EDCTP.

### III. Member States

#### 1. Categories

Overall, the European member states are beginning to work well together. How can we build on this progress and develop better integration? There are three categories of people included – researchers; their representatives in the EDCTP European Economic Interest Group General Assembly (GA) and the European Network of National Programmes (ENNP); and the politicians.

#### 2. Researchers

The researchers are doing well to increase their partnerships across the member states and with African scientists, but individual researchers can spread the word about the effectiveness of EDCTP, encourage colleagues to increase their partnerships across Europe and Africa, apply for grants and contribute their ideas to the development of our future plans.

#### 3. ENNP and GA

The ENNP has good collaborations with the Developing Countries Coordinating Committee (DCCC), and is currently working on an analysis of member state activities, looking at the possibility of validating existing co-operations between member states for joint EDCTP programmes, where there may be an opportunity to apply for additional EDCTP funds. In addition, they can think ahead and look for opportunities for future synergy.

The GA is working more collaboratively, but could do better. Have we all engaged development agencies in our member states? I encourage you to make these links now, building on them to work well for EDCTP in the future. We also

need to spread the word, show that we are effective and are implementing our road map as planned. If this message is communicated to politicians, they will understand why funds are needed and how enabling measures could be taken to ensure better integration of the member states' programmes. I encourage all member states' representatives to ensure the message about EDCTP's effectiveness is delivered to their political masters.

#### **4. Other opportunities**

Other possible links are being developed, like that initiated through the Canadian International Development Research Centre (IDRC). There are more opportunities through the BMGF and through some complementary plans of the

Wellcome Trust. To remind you all, there are seven calls out now and will be three more before the end of the year. We must show we can continue to deliver and that high-quality awards can be made through these cofunded programmes.

#### **5. Key recommendations**

The European Commission receives regular reports on EDCTP and is pleased with our recent progress. Our success is important to demonstrate that an Article 169 mechanism can be delivered in the EU and that EDCTP remains an important part of the EU's relationship with Africa. I am sure this week will be productive and enable us to make even greater progress in 2008.



## Official Opening Address



### **Pascaline Tamini Minister of Social Action and National Solidarity, Burkina Faso**

#### **I. Welcome**

Excellencies, ambassadors, representatives of international organisations, honourable executive director of EDCTP, high representative of EDCTP, Madame chairperson of the GA, directors and heads of health services, ladies and gentlemen; I would first of all like to say, on behalf of the State Minister and Minister of Health, how honoured we are to host the Fourth Forum of this EDCTP Partnership. This is the second time this Forum has been in Africa, and translates to the will of international stakeholders to unite to overcome poverty-related diseases and resolve their social and economic issues. This Forum is a step forward in looking for effective health solutions in the face of those diseases.

#### **II. Poverty-related Diseases**

##### **1. Malaria**

Malaria is a major public health issue in most developing countries in sub-Saharan Africa. In Burkina Faso, it accounts for 66% of hospital referrals and 48% of deaths in children under five. The economic repercussions of this plague are huge; Africa loses about \$12 billion GDP a year because of this disease.

##### **2. HIV/AIDS**

HIV/AIDS is a significant public health issue in Africa, in spite of the political commitment of various governments. Burkina Faso is a reference in terms of the successful fight against this plague, with high-level political commitment able to shift the prevalence rate from 7.2% to 1.7% between

1997 and 2006. However, today, about 150,000 people are HIV-infected in Burkina.

##### **3. Tuberculosis**

After a drop-off some years ago, tuberculosis is today in upsurge everywhere in the world, particularly in developing countries, due to the HIV epidemic and expanding resilience of the germ. It is urgent we discover therapeutic and preventive means that are accessible to our communities.

#### **III. EDCTP**

##### **1. Mission**

The mission set out by EDCTP to accelerate the development of new vaccines and strategies should contribute to improving the health of our nations. We need this kind of collaboration to establish health strategies in our poor populations. The success of your mission remains a challenge to be taken up by all of humanity, African countries in particular. That is why the philosophy of your partnership consists in establishing close links between scientists from the South and North operating in similar areas.

##### **2. Partnership**

This approach, consisting of joining scientific, political and financial effort from European and African countries, I am convinced will help to develop vaccines and drugs to combat these poverty-related diseases. I would like to reassure you of the availability of the Government of Burkina Faso through the Ministry of Health to support any initiative for partnership and research that will help to speed up the achievement of health objectives. On behalf of the Government of Burkina Faso, I would like to take this opportunity to thank EDCTP for support of our research institutions and contributing to developing the sustainability of our national expertise. I believe that health is first of

all the responsibility of populations themselves and, by strengthening national institutions, local populations will be at a closer proximity to accessible health services. The Ministry of Health will spare no effort in facilitating the participation of Burkinabé members in various EDCTP bodies.

### 3. Tributes

I would also like to pay a specific tribute to Prof. Charles Mgone, whose appointment as the first African to occupy this position has established a new vision for North-South partnership.

I would also like to pay tribute to Dr Pascoal Mocumbi. I give you my commitment of support in your tough work of advocacy. Your speech was a call to all African countries to join in this effort of health for all.

To Dr Diana Dunstan, I commend you for your work in promoting EDCTP in Europe.

I would like to thank Centre National de Recherche et Formation sur le Paludisme (CNRFP) for facilitating the organisation of this Forum in Ouagadougou.

### IV. Conclusions

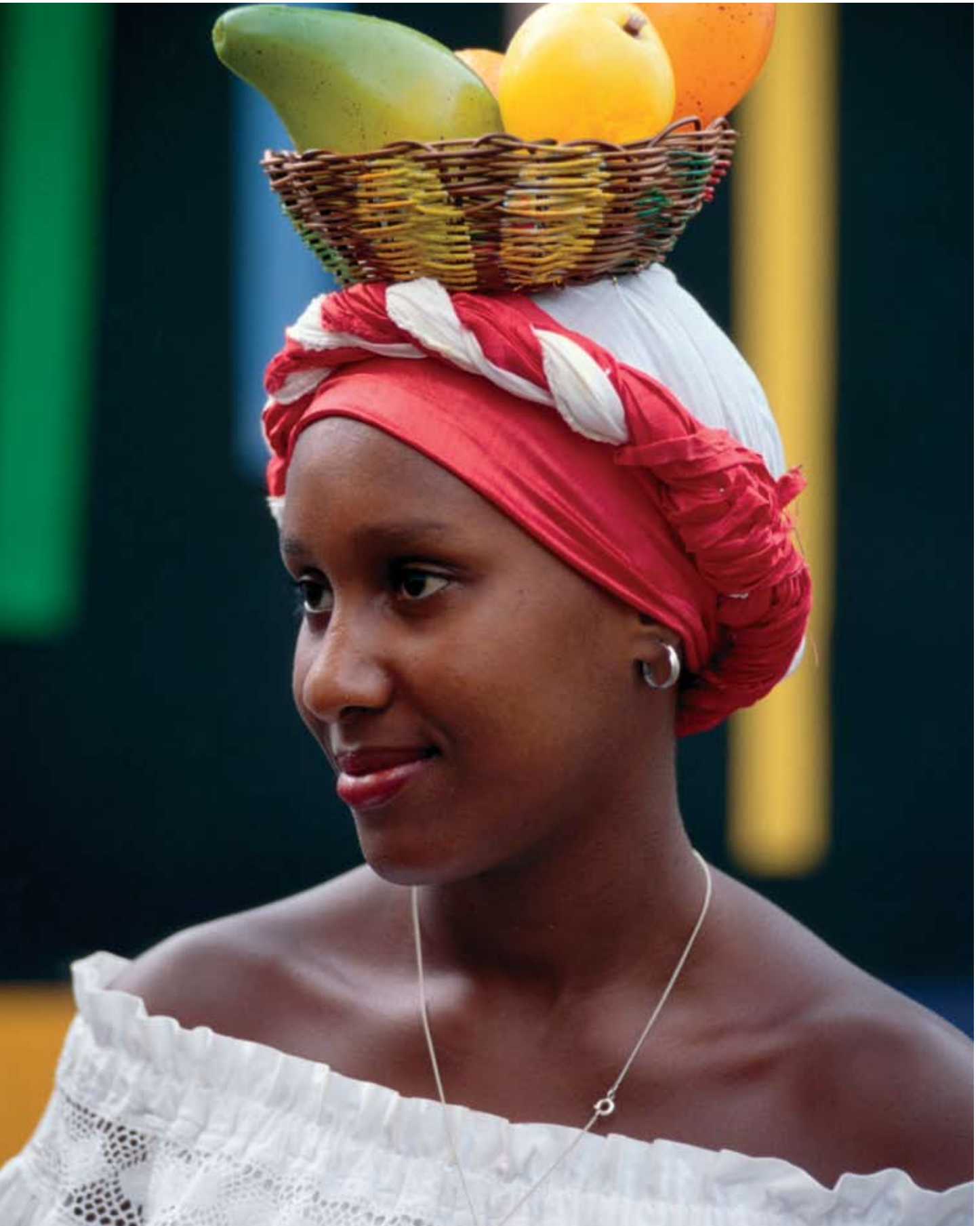
I wish you successful proceedings culminating in proposals our countries can use to fight these three diseases. By joining our efforts, I believe that internationally we will be able to

overcome diseases like malaria. We know that, if children are healthy and well-nourished, we will make huge step forwards in resisting malaria. We believe prevention is an effective course as there is no use waiting until children are dying before we start treatment; we need to start early. International organisations like yours will be able to provide us with initiatives, supplemented by scientific research, that make affordable drugs accessible to our poor communities.

Health is an integrated fight; fighting for health is fighting first against poverty, where each citizen is able to afford the drugs they need. I wish you all the best and am sure you will come up with pertinent proposals to fight HIV/AIDS, malaria and TB. I declare the Fourth Forum open.



Centre National de Recherche et Formation sur le Paludisme (CNRFP)







**Chairs: Prof. Patrice Debré (EDCTP PB),  
Dr Simon Agwale (EDCTP DCCC)**

## Tuberculosis in Africa

**Prof. Richard Adegbola  
Bacterial Diseases Programme, Medical  
Research Council (MRC), the Gambia**

### I. Outline

Many of us are familiar with this quote:

*'TB is out of control in the world and disproportionately affects people in developing countries, in terms of morbidity and especially in terms of mortality.'*

Of those who die of TB, 98% are from developing countries, most of which are in Africa. I will give you some of the background to this story, explain the diagnostics research, introduce a new TB treatment regimen and give an outlook going forward.

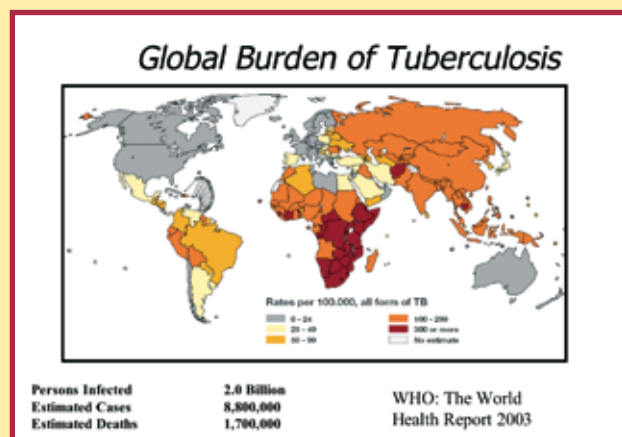
### II. Overview

#### 1. Epidemiology

TB is caused by the *mycobacterium tuberculosis* bug, which is transmitted by aerosol through the mouth. It is a chronic infection of the lungs, bones and brain. One third of the world is latently infected with TB, but only 10% progress to disease. The issues are complicated and overlap with many associated with the HIV epidemic. Despite all our best efforts, TB is increasing. In 2003, 8.8 million new cases were identified, bringing the total to 15.4 million worldwide. Last year, reports were emerging of an extensively drug-resistant TB (XDR-TB).

#### 2. Global burden

The heavy burden of this disease is localised around southern and eastern Africa, which coincides with the high prevalence of HIV/AIDS.



#### 3. Epidemiology

The global plan is to diagnose at least 70% of people with infectious TB and cure over 85%. Success there will bring TB under control. By 2050, we want to reduce global TB incidence to under 1 person per million. How?

#### 4. Tools

The current tools are working but have problems. Directly observed therapy – short course (DOTS) uses TB drugs under supervision but, if we are to successfully put TB in check, new tools are required – new drugs, new diagnostics and new vaccines.

#### 5. Knowledge gaps

BCG (*Bacillus Calmette-Guérin*) is probably the most widely used vaccine in developing countries, but we know there is huge variability in its efficacy. We do not know the biomarkers that might reveal why only 10% of infectious TB cases progress to disease. If we can distinguish these, we might take advantage of them. We need to improve diagnosis, learn about drug resistance and use novel vaccines that capitalise on BCG.

### III. Diagnosis

#### 1. Current methods

The diagnosis of TB is based on clinical history – coughing, sweating, etc – but these are not diagnostic markers. The chest X-ray is simple and rapid, but has been complicated by the HIV problem. Sputum for acid-fast bacilli (AFB) has been the cornerstone of detection in many African countries for many years, but its sensitivity is poor and the outcome depends on the operator. The tuberculin skin test (TST) is also useful, but again has problems with specificity and sensitivity.

#### 2. New diagnostic methods

##### a. Assays

Interferon-gamma (IFN- $\gamma$ ) release assays in the form of T-SPOT and QuantiFERON assays are simple immunological tests of immune responses, but do they work in our setting compared to the West? Methods like BACTEC or the Mycobacterium Growth Indicator Tube (MGIT) are also improvements, but the facilities to support them are not available in developing countries, in terms of expertise, management and cost. We can also take advantage of molecular techniques to study the different strains and clones of the organism.

##### b. The ELISPOT plate

The idea of the enzyme-linked immunospot (ELISPOT) is to use antigens more specific to TB to detect immune responses.

##### c. T-SPOT TB

This is still useful in the West to diagnose infection accurately, but in our setting this is not so. A series of studies conducted in the Gambia, looking at the contact of TB cases over time and classifying them according to proximity to the case, showed that, as you move farther away towards real exposure, there is huge difference in sensitivity between ELISPOT and the skin test. We have to be cautious: T-SPOT can be used in addition to the skin test, but not as a replacement in our setting.

#### 3. Biomarkers of protective immunity

In collaboration with colleagues from the West, and support from the BMGF, a number of countries in Africa

are participating in a large study to follow contact of cases over time, then working back using periodic samples to compare the biomarkers you can use as predictors of disease to patients who do not develop the disease. At each stage, different studies are going on in an attempt to better understand the natural history of TB, improve diagnosis and develop vaccines to take advantage of biomarkers.

### IV. Treatment Regimen

#### 1. The problem

We know that TB is treatable; the problem is with resistance. Resistance develops either through misuse of drugs or mismanagement of patients. Patients do not comply with their regimens because courses are too long, so people stop when they start to feel better. One of the attempts of the EU-funded multi-site gatifloxacin-containing regimen in Africa is to see whether you can reduce the number of months of treatment from six to four. We also need to improve access to and delivery of treatment.

#### 2. Proof of concept

A pivotal phase III trial is being proposed to shorten the treatment of pulmonary TB to four months with the inclusion of a fluoroquinolone. This is an open-label, randomised, controlled trial (RCT), hoping to substitute ethambutol with gatifloxacin. The primary endpoint is the percentage of unfavourable outcomes at 24 months after treatment.

### V. Vaccination

#### 1. New vaccines

About 80% of the world's population is vaccinated with BCG, which has been the only licensed TB vaccine available for many years. Despite this wide coverage, the endemic is on the increase, but BCG has some non-target beneficial effects too, so needs improving, not replacing. It could perhaps be boosted with a subunit vaccine.

#### 2. MVA85A

One approach far ahead of the others is the modified vaccinia virus Ankara expressing antigen 85A (MVA85A). It promises to be a heterologous prime-boost strategy to BCG during infancy, and has already been shown as protective in animal

models, and safe and immunogenic in adults in the UK, South Africa and the Gambia. However, it is not clear at the moment whether the immune responses you see in these tests will translate to protection in real use. There is an attempt to show that this vaccine will not interfere with the Expanded Programme on Immunization (EPI) vaccines, and a study is ongoing at the moment to establish which dosage levels are best. A phase II trial is now being contemplated in South Africa.

## VI. The Future

Efforts are now being made to improve diagnostics, look for a regimen of drugs to improve what we have at the moment and also to develop vaccines, but we need continuing epidemiological studies as background to these new strategies. That is where organisations like EDCTP can help. There are unprecedented efforts at the moment between private, public and academic bodies to combat the disease in Africa and obtain the Millennium Development Goals (MDGs). EDCTP is providing funding and support for capacity development through networking and the preparation of clinical trial sites in Africa.

## ► Questions and Answers

### I. Treatment

The first question was about difficulties in treatment compliance with TB patients. The problem here was that, two or three months into a six-month course, patients would begin to feel better and so gain a false sense of confidence and stop taking their drugs. There were other issues with compliance in an African context like accessibility. Why would someone walk 10km to get their drugs when they were feeling better? Methods are required for early detection so patients can take effective drugs before they start infecting others.

### II. Production

The second question turned to the subject of dosing levels of MVA85A, and also asked how responses to the vaccine compared to individuals with natural immunity.

The presenter explained that the best dosage level has not yet been established, although immune responses have been demonstrated after just one dose. The EDCTP Executive Director praised the presenter's demonstration of the importance of both diagnostics and assays, both issues that EDCTP was not currently addressing. He asked if the organisation should be. Yes, the presenter replied immediately; there will be no success against TB in Africa without simple, cheap laboratory tests to detect cases early. The drugs are working, but they are not making sufficient an impact because of the speed of infection

## HIV/AIDS in Africa

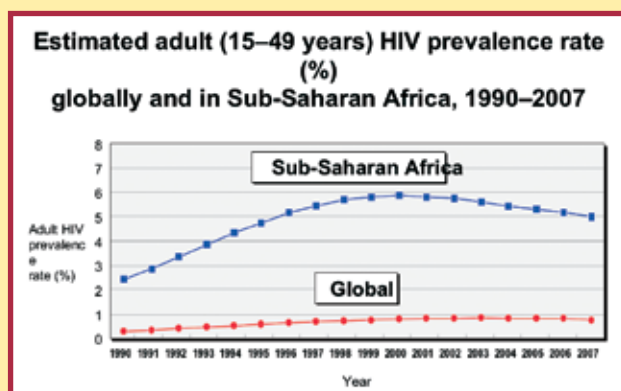
**Prof. Peter Ndumbe**  
**Dean of Faculty of Health Sciences,**  
**University of Yaounde, Cameroon**

### I. Outline

I will identify the major clinical research activities related to HIV/AIDS that have been conducted in Africa over the last few years, and comment on the utilisation of research results.

### II. Background

The number of people living with HIV/AIDS has not changed very much since 2002. Last year, there were reported declines in prevalence in Kenya, Zimbabwe and certain areas of Burkina Faso, while there has been an increase in people on antiretroviral drugs (ARVs) since 2003.



### III. Prevention

#### 1. Adolescents

Adolescents are still at high risk. Although the number of new cases has not changed much, Nigerian studies found that only 16% of youths there knew what caused HIV/AIDS and that girls tended to be at least as ignorant as boys. Even educated mothers do not offer their daughters sex education due to traditional barriers and religious inhibitions.

#### 2. Male circumcision

Random Controlled Trials (RCTs) carried out in South Africa, Kenya and Uganda provided evidence of an over 50% protective benefit from infection if male circumcision has taken place. If 100% of men were circumcised, an estimated 2 million infections in sub-Saharan Africa would be averted over 10 years. The real challenges are related to integration and scaling up of the existing system, but there are social and cultural barriers, problems with training, availability of sterile instruments and costs. Each procedure is expected to cost USD\$25. The effect on HIV control programmes and women is uncertain, but we hope to have data from Rakai *et al.* by 2008.

#### 3. Vaccines

The recent EDCTP-sponsored meeting in Antwerp concluded clearly that we do not yet have vaccines to offer, but that does not mean we do not have work to do. One problem is that cytotoxic T-lymphocyte (CTL) responses for multiepitope DNA vaccines are not sustained in vaccinees. Antibodies to B-cell epitopes result in rapid evolution of HIV escape mutants, error-prone replication and high frequency of recombination during reverse transcriptors causing rapid change in the HIV genome. We also know that peptide vaccines are poorly immunogenic, partly due to their small size. Recombinant subunit gp120 is poorly protective for natural HIV infections.

#### 4. Innovative project

The goal of Innovative Biotechnology is to develop an HIV vaccine capable of inducing broadly neutralising antibodies and CTLs to prevent and treat HIV infection. The findings from these studies are quite encouraging. The gag construct induced a very strong antigen-specific CD8-positive T-cell-mediated response as detected by Fluorescence Activated Cell Analysis (FACS) and ELISPOT.

#### 5. Oral manifestations

Of paramount clinical interest are oral manifestations of HIV/AIDS. Unfortunately, these are not foremost in the work carried out by clinicians but, as we know, oral disease may worsen the evolution of HIV, affect drug compliance and the nutritional status of the subject. Most caregivers do not know how to manage oral manifestations of HIV, and therefore Rudolph and colleagues formulated a programme for caregivers, which they think should be extended to traditional healers.

### IV. Drug Research

#### 1. CYP2B6

The CYP2B6 polymorphism, either alone or linked with 983T>C, again either alone as CYP2B6\*18 or linked with 785A>G as the CYP2B6\*16 allele, has been found in Africans and African Americans, but not in Caucasians or Asians. We know this polymorphism is associated with significantly higher means of plasma efavirenz (EFV) levels in African HIV patients. We also know that EFV and nevirapine (NVP) are commonly used in our national programmes, and are principally metabolised by CYP2B6. This gene that controls this cytochrome, chromosome 19, is highly polymorphic. The variant allele CYP2B6\*6 has shown a 50% decrease in the main enzyme activity. Studies have shown that these alleles are associated with two or three times higher plasma EFV which, therefore, leads to 50-60% lower EFV clearance, with increased neuropsychiatric side effects, resulting in decreased compliance in the drugs.

#### 2. Some problems

There are problems with adherence, with the expansion of antiretroviral therapy (ART) and the efficacy of cotrimoxazole. There have also been studies into the role of microbicides in prophylaxis.

#### 3. Cryptococcus resistance to fluconazole

Christine Bii worked with 80 clinical isolates of *Cryptococcus neoformans*, using broth microdilution susceptibility testing to amphotericin, flucytosine, fluconazole, itraconazole and miconazole. Only 23.8% of the strains were susceptible to fluconazole with 65% susceptible dose-dependent and 11.2% resistant. Therefore, antifungal drug resistance surveillance within the context of HIV case management is important.

#### 4. Mother-to-child transmission (MTCT)

There is an urgent need for us to review the UNICEF-WHO guidelines on HIV and breastfeeding.

### V. Conclusions

Important studies on HIV/AIDS in Africa, prevention drugs, MTCT and AIDS in children have been done with the real, not perceived, participation of African scientists, but there is still a wide gap between the knowledge we have accumulated so far and its implementation. We are working within the context of a healthcare system, but the integration of activities, training of personnel and rolling out of strategies remain key challenges. It is necessary for research to be relevant to solving problems on the ground, with interventions accompanied by meaningful studies. EDCTP can help by building bridges for better health.

### ► Questions and Answers

#### I. Innovative Biotechnology

One participant asked if it was thought that recent failures to find an HIV vaccine would instil the fear that future clinical trials would be unsuccessful. The DCCC Chair answered by explaining that he was taking a slightly different approach by aiming to induce neutralising antibodies accompanied by CTLs. Another person asked if EDCTP would fund a phase I clinical trial of the Innovative vaccine. The EDCTP Executive Director offered to pursue the matter. The next participant pointed out that both these concepts had failed so far, and suggested that more restricted trials were needed into particular vaccines at the mucosal level. This led to the general point that a combination of both cellular and humoral responses was required. Someone asked if the mechanism by which Innovative's vaccine worked could be explained. The initial stage of the study was to establish whether the construct introduced CTLs; they were not yet addressing the mechanism by which this works.

#### II. Drug Resistance

Although the increase of ARV use was heartening, a participant asked how resistant the virus was becoming and

how prepared Africa was to deal with this. The presenter had seen resistance among treatment-naïve subjects estimated at between 6% and 20%. Therefore, it was crucial drug-therapy expansion programmes were associated with drug-resistance monitoring, not just because of resistance but because of high rates of non-compliance brought about by the drugs' side effects. There was a prior question on whether EDCTP should be involved in evaluating monitoring methods for TB. The presenter was asked whether it should also support monitoring methods in Africa. He thought that sensible, as few other bodies were doing this.

### III. Types of Vaccine

The Chair of EDCTP's Partnership Board (PB) believed that the general tendency of vaccines was that some prevented infection and others prevented the disease. Would the presenter accept a vaccine that did not prevent infection but did prevent the disease? The problem here was that there might never be a silver bullet. Raising awareness has been tried, as had free condoms and numerous drugs. We have to look at the whole and consider everything that can help. Within the context of a holistic HIV programme, if there is a vaccine that prevents disease, it should be used, not forgetting all the other elements that can help.

## Malaria in Africa

**Dr Roma Chilengi**  
**Clinical Trials Coordinator, AMANET**

#### I. Overview

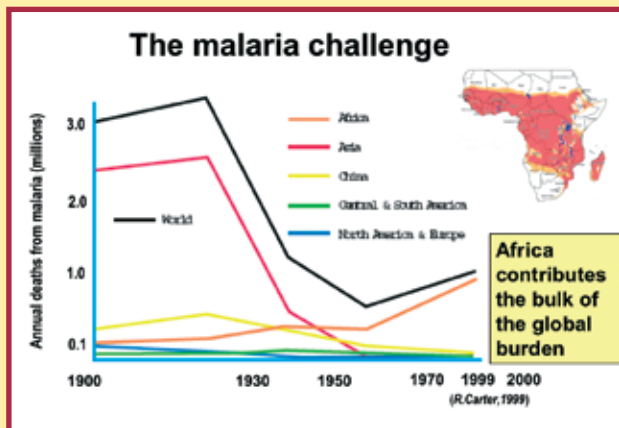
I will go through the clinical research in Africa, outline recent developments, explain the historical burden of malaria and African gaps, detail the financial trends, look at the anti-malarial-drug pipeline and vaccines, give you some thoughts on traditional medicines, immunoassay efforts, diagnostics and product development partnership (PDP) issues.



## II. The Malaria Challenge

### 1. Global burden

Historically, the malaria burden was much higher in Asia until the 1950s. Today, Africa makes up the bulk of cases.



### 2. Research gap

Only 1.2% of biomedical publications focusing on malaria come from Africa and northern collaborations. 79% of malaria papers have authors from Europe and the US and 88% of African laboratories are managed outside Africa. Gaps like these contribute to the worsening trend of the malaria burden.

### 3. R&D expenditure

We see that the majority of malaria R&D is spent by public and government bodies, while only 12% comes from for-profit organisations. Overall investment is growing, but is still only a drop in the ocean. Vaccine development accounts for 24% of total expenditure, 37% goes into drugs, 16% is allocated to basic research and 17% to implementation and operational research. While we are aware we have had difficulties since the failure of chloroquine, there is currently no preventive vaccine. Although vector research and control was previously successful, it seems to have been abandoned and needs to be taken on more seriously. The Helsinki Declaration reminded us that:

*'Even the best proven prophylactic, diagnostic and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality'*

### 4. Some recent successes

We know that sustained environmental management with indoor residual spraying (IRS) can achieve some control of malaria, as substantiated reports from South Africa have shown. We also know that use of insecticide-treated bed nets (ITNs) if properly deployed can contribute to control of malaria. An important issue concerns the spin-offs from research into malaria, where we know that in areas where research is ongoing, malaria cases decrease.

## III. Drugs in Development

### 1. Overview

The current pipeline is mixed with drugs at various stages of development. There are some breakthrough innovations targeting malaria in completely new ways and known classes of drugs with novel candidate molecules.

### 2. Pipeline summary

There are up to six ACTs currently undergoing clinical trials in Africa. There is one ACT paediatric formulation, coartem (artemether-lumefantrine) dispersible. Two non-ACTs are currently being trialled, and some monotherapies are being developed. Non-ACTs are being developed for malaria in pregnancy, intermittent preventive treatment intervention (IPTi) and intermittent preventive therapy (IPTp). Preclinical candidates include those targeting *plasmodium vivax* and *falciparum* in various stages.

### 3. Drug development

One important point to make concerning drug development is that the recent recommendation concerning ACTs would have obvious regulatory implications, in the sense that, if you are to develop combined drugs, you first have to develop the individual components and show the proof of concept. This has obvious implications for the cost of development and pressure on the clinical trials side.

## IV. Malaria Vaccines

### 1. Challenges

It cannot be overemphasised that we have a difficult and elusive target in *plasmodium falciparum*. We also lack a clear regulatory pathway to follow, which is critical for developing

countries. Trials will be larger and more expensive, and the lack of a reliable animal model requires us to do trials in humans to evaluate vaccines.

## 2. Current targets

We have pre-erythrocytic, erythrocytic and sexual-stage targets, for each of which there is a lot of work ongoing. Some are targeting the circumsporozoite protein, the liver stage of the parasite, the many merozoite proteins, the PfEMP1 cell and the gametocytes.

## 3. Vaccine portfolio

We presently have 47 different malaria vaccine candidates at various stages, 31 of which are in preclinical development with 16 in clinical trials. We have observed a recent increase in antigen diversity. Work is going on with expression systems for these targets, ranging from an approach with the whole sporozoite target to recombinant proteins to viral-vectored approaches. Chimeric candidates are also in the pipeline.

## 4. Some problems

It is a general complaint that the many players need to be better coordinated in their efforts. Although we have an excess of 5,000 potential targets on the malaria parasite, the focus is on very few antigens. If we improve our coordination, perhaps we can progress faster and deal with our resources better. The development of a malaria vaccine has to be an iterative process, between clinical pathways and the preclinical arena in order to deal with mechanisms of action and correlates of protection. That has obvious cost implications. Possibly 90% of all work is now done by PDPs, where scientists play innovative, leading roles. However, we need more input from the pharmaceutical industry to drive this developing innovation.

## 5. Effects in immunological assays

Some urgent work is needed on the immunological assays we use to evaluate these vaccines. There is some effort going on here: Afro-Immunoassay (AIA) is a network we are responsible for funding and coordinating that has worked to standardise ELISA assays.

## 6. Traditional and herbal remedies

Increasingly we shrink when talking about traditional medicines, but this needs to be addressed. In Ghana, Mali,

Nigeria and Zambia, the first-line treatment for 60% of children with fever resulting from malaria includes one form or another of traditional medicine. Trials are being supported by WHO to evaluate some of these methods.

## 7. Basic science research

There is a call for organisations like EDCTP to consider thinking about basic science research in Africa to prevent the research gap from widening.

## V. Diagnostics

Much work is going on, but mainly focusing on operational research and rapid diagnostic tests. There are some novel approaches on the use of other secretions and improving microscopy. One of the challenging issues here is defining the endpoints or sets of symptoms that indicate malaria, which is particularly challenging across multi-centre trials.

## VI. Public Development Partnerships

AMANET is a not-for-profit organisation with good collaboration with the European Malaria Vaccine Initiative (EMVI). We have at least four clinical trials of candidate malaria vaccine currently ongoing.

## VII. Conclusions

We need to persuade our African governments to think about funding research, consider enhancing the regulatory and ethical review framework and also have African-driven R&D with intellectual property (IP). We also need to improve training of postgraduates and create more opportunities for young, fresh medical graduates.

## ► Questions and Answers

### I. Vaccine Targets

#### 1. Acceptable efficacy

The first to speak stated that African scientists and regulatory authorities need to state the acceptable level of efficacy of

any vaccine to be deployed in their countries. The current reference level is 30%. The presenter was asked if that was good enough. He replied, similarly to other speakers, that when there is nothing in the basket, half a loaf of bread is better than none. RTSS has shown it is possible to develop a vaccine for malaria, which has motivated many groups to continue working on improving efficacy. 30% is not good enough, but there are technical challenges to raising that figure.

## 2. Infection prevention

One participant asked what work is currently taking place on clinical malaria vaccines. The presenter explained that pre-erythrocytic vaccines target prevention of infection, whereas blood-stage vaccines are designed to prevent the disease or reduce its severity, which is where the bulk of products is focused.

## 3. Alternative methods

The presenter had described some of the problems faced by clinical trials when their activities lower the local malaria burden. One participant suggested that this money would be better spent on known preventative methods such as IRS and ITN, especially when it was acknowledged that a 30% efficacious vaccine was insufficient and might only be seen as an addition to existing control tools. The presenter backed such a holistic approach, where stakeholders would work to ensure investments were channelled appropriately. A mechanism is needed to even the playing field, as often funding goes to those groups best able to sell their projects.

## II. Investment Gap

Addressing the gap in studies of a European and African provenance, a participant felt that it was difficult for Africans to carry out even basic research without Western funding. He asked what could be done. Challenging Africa, the presenter defined research as a 'game' overseen by productivity and the availability of competent scientists. African researchers need to rise to that challenge, increase their productivity and not depend on continuous European grants, as donors will not entrust researchers with funds through word of mouth alone; they need to see that earlier studies have been productive. Another part of this problem was that the focus of funding relates to current areas of interest. When it appeared that there was a vaccine for malaria, funding withdrew, and the prevalence of malaria rose as a consequence. Perhaps funding is needed that will attract African researchers into an area before projects are proposed. The PB Chair hoped the DCCC of the EDCTP could help pinpoint the needs of Africans.

**[The morning session was followed by Electronic Poster Sessions]**









# HIV/AIDS Clinical Trials in sub-Saharan Africa

**Facilitator: Lynn Zijenah, (EDCTP DCCC)**

**Rapporteur: Souleymane Mboup (EDCTP PB)**

## I. Trial Findings: Children with HIV in Africa – Pharmacokinetics and Adherence of Simple Antiretroviral Regimens (CHAPAS)

**Dr Veronica Mulenga,  
Tropical Diseases Research centre (TDR)**

### I. Background

This was a phase I/II trial, the main objective of which was to assess the appropriate dosing and adherence of a fixed-dose combination (FDC) ARV consisting of stavudine, lamivudine and NVP, in a new formulation developed for children by CIPLA Pharmaceuticals of India.

There had been problems accelerating ART in children, especially in resource-poor countries, because of a lack of appropriate formulations. Many people would use syrup formulations, which are difficult to store and transport, and so incur high costs. It was also very difficult for caregivers to administer syrup when they are not used to measuring anything before. Most have resorted to adult FDC tablets; however, there were problems dividing these for children, as the concentrations were inappropriate and there were issues with cutting. There was an urgent need for an easy, practical formulation to give to children. CIPLA devised two forms: Triomune Baby, and Junior, which is double the Baby dose.

### 2. Trial design

We were to recruit 200 previously untreated children, who were eligible to start ARV drugs. These were randomised either to a full dose of Triomune treatment, or the recommended half-dose of NVP and an additional tablet of lamivudine and stavudine, before going on to the full dose of Pedimune, Triomune Baby or Junior. From that, they could

go into either the pharmacokinetics or adherence sub-studies or both. The adherence study used a visual analogue scale to ask primary carers how much of the drug had been taken over the past 28 days. We were to assess this method and compare it to other standards.

### 3. Follow-up

Children were screened four weeks before entering the study, again at baseline, then at frequent intervals, visiting the clinic every four weeks to collect their drugs.

### 4. Primary outcomes

For the whole trial, adverse events of grades three or four, possibly related to NVP, was the main endpoint. For the pharmacokinetics study, the outcomes were parameters of the ARVs. We have nearly completed recruitment for the main trial, and have finished recruitment for the pharmacokinetics sub-study.

### 5. Pharmacokinetics summary

64 children were recruited, and divided into four weight groups for dosing. After being on the drug for four weeks, they came in for pharmacokinetic sampling. 2ml of blood would be collected before intake of their morning ARV, then at pre-determined intervals afterwards. The specimens were later transported to the Netherlands for analysis. Children in the weight band 3-6kg were excluded from analysis as the sample size was too small, but more recruitment will take place in the future.

### 6. Pharmacokinetics results

All weight groups showed plasma levels above the therapeutic levels of NVP, and similarly for stavudine and lamivudine. There was not a suitable comparison group, so compared to the adult reference ranges available. The minimum concentration of NVP was 6 mg/L in our children compared to the adult 3.7 mg/L and the maximum concentration was 10 mg/L compared to 5.7 mg/L in adults. When it came to stavudine and lamivudine, mean levels were similar to adult levels. Even though we found good plasma levels overall for NVP for all children, four children of varying weight ranges showed sub-therapeutic NVP levels, but there was no evidence of difference in the area under the curve across the different weight groups.

## 7. Adverse events

Three children had a grade 2 NVP rash. They were managed according to the protocol, in the knowledge that NVP has a long half-life. Three children had grade 3 raised liver enzymes, which returned to normal on NVP. Treatment was not stopped in these instances.

## 8. Conclusions

NVP levels were generally much higher than those previously reported in adults. The pharmacokinetic parameters of stavudine and lamivudine were comparable to those previously reported in adults, so it appears that Triumune Baby and Junior are appropriate for children with HIV infection over the entire range of weights.

## 9. Discussion

The presenter was asked whether the children showing sub-therapeutic levels of NVP were at the upper end of their weight groups, which might show there was a reason to adjust cut-offs. Another query was about the infants' z-scores, and the possible conclusion that not only weight but age affects pharmacokinetic data, and that many of those studied were underweight. The presenter explained that her analysis was not yet complete but she would take both these suggestions into account.

## II. Toward the Complete Eradication of Mother-to-child transmission of HIV at Saint Camille Medical Centre (SCMC), Burkina Faso

**Prof. Jacques Simpore,  
Saint Camille Medical Centre, Burkina Faso**

### I. Objectives

This centre possesses a maternity unit, an immunopathology service, an infant care service and a laboratory for routine analysis. The aim of our work is to prevent HIV MTCT, detect HIV in children by using the reverse transcription polymerase chain reaction (RT-PCR) technique and to test ARV resistance of children and mothers in order to offer them a suitable therapy.

## 2. Subjects and methods

At this centre, 6,227 pregnant women with less than 32 weeks of amenorrhea and between 15 and 44 years old received a counselling course and voluntarily accepted a MTCT prevention protocol. This can be divided into:

- Voluntary counselling and HIV testing for all pregnant women.
- ART for all HIV-positive pregnant women who fulfil WHO criteria for treatment, or monoprophylaxis with NVP for HIV-positive women not fulfilling these criteria.
- Monoprophylaxis with NVP, or azidothymidine (AZT) in HIV-1 and -2 co-infections, either artificial milk feeding or short breastfeeding and RT-PCR tests for all children.
- HIV-1 pol gene sequencing and identification of ARV resistance among HIV-positive mothers and children.

## 3. Results

The HIV tests allowed us to identify 421 HIV-positive women, representing 6% of the population. The RT-PCR test detected 23 positive children from 406. Among these, we did not find any HIV-positive children in women under ART. There were 23 HIV-positive children of mothers under monoprophylaxis with NVP or AZT. Phylogenetic studies showed a high predominance of recombinant HIV-1 strains. Several RT mutations in the samples were also found, as well as major and minor protease (PR) mutations.

## 4. Conclusions

Prevention by NVP single dosage significantly reduces MTCT. Nevertheless, it caused many mutations and resistance to ARV drugs. This ARV protocol, together with artificial feeding, could be the ideal strategy, with 0% MTCT.

## 5. Future perspectives

Considering the efficacy of our protocol for prevention of HIV MTCT at this centre, this protocol could be adopted by the Ministry of Health in all the medical centres in Burkina Faso. We are also making progress with a preventative therapeutic vaccine to block MTCT of HIV during labour and postpartum breastfeeding.



use is more flexible, with products that could offer sustained protection during the sexual act. They may combine active ingredients that work in different ways, as we are looking at a combination of different products. There is a phase IIb trial of the tenofovir gel that has been initiated this year and there are additional candidates and delivery mechanisms in safety trials.

## 6. Assessment of safety

We were disappointed by the outcome of nonoxinol 9 trials where the vaginal mucosa was damaged. In response, WHO developed manuals on colposcopy to be used in microbicide safety studies but, even here, there remains an inter-observer variability. Sometimes we are unable to detect markers of increased susceptibility invisible to the naked eye. We need biomarkers of microbicide safety, such as cytotoxicity markers. Groups are working on this, but we need to advance faster with reliable markers to avoid another catastrophe like nonoxinol 9, which could cause people to lose faith. Constraints also include the lack of validation of existing models and biomarkers. We need an assessment of the impact of reproductive hormones, hormonal fluctuations and their impact on the vaginal mucosa. We need also to look at the determination of microbicide effects on mucosal inflammation and innate immunity.

## 7. Uptake and adherence

Even in the best-guided trials, compliance rates can be very low. In this instance, we have to monitor the impact diaphragm use can have on condom replacement. Furthermore, during trials, incidence of HIV goes down against the population average. How will pregnancy interfere with adherence and efficacy of microbicides? In some countries, there are mandatory fees for women in microbicide trials, which encourages people to take part. We have to realise such effects and ensure we monitor them.

## 8. Microbicide use

We have to consider how these products are integrated into different cultural vaginal practices, including condom replacement. Microbicides will never be a silver bullet, but can only be one of the weapons against HIV. A multi-centric study with WHO, across Thailand, Indonesia, South Africa, Mozambique and Kenya is examining vaginal practices around the world. This considers how common household products may interfere with microbicides or are associated with bacterial vaginosis and disruption of the genital mucosa.

## 9. Statistical considerations

We have prepared our Mombassa site to be eligible for microbicide studies and are looking at sex workers. However, the HIV incidence rate is too low at 4% because, if you prepare your site well, the incidence rate goes down, in this case from 14%. This needs to be considered when calculating sample sizes.

## 10. The diaphragm

The answer to female protection will probably not be a diaphragm or a microbicide but a combination of both. It takes years for us to gain evidence of their positive effect, but we know it results in fewer STIs and reduces pregnancy, so it must do something against HIV.

[Video presentation]

## II. Discussion

### a. Funding mechanisms

One representative explained that the UK Department for International Development (DfID) is financing microbicide trials and HIV vaccines using development funds. He asked if this idea could be exported to other countries. The presenter hoped so, believing that many European countries currently did not use all mechanisms for funding they had available.

### b. The diaphragm

Another participant applauded this proponent of the diaphragm, which was often neglected in public messages as an effective means to fight HIV transmission. Awareness-raising activities in Africa have focused on the man and not the woman, so there is little concrete knowledge of what the diaphragm can do. This is an old method and has been proven as safe; it must not be forgotten because women are desperately looking for ways to protect themselves. Even if home-made methods only provide 30% efficacy, using them would have saved many lives already.

### c. Other microbicides

Turning to the female condom and the use of ARV-based microbicides, many concerns have been expressed about drug resistance developing during sexual intercourse. The presenter was asked for her opinion on best approaches. She was worried that our expectations for the female

condom were too high, because this was not an invisible device, so required partners' consent. One high-risk and often-neglected population is postpartum women, where men take other partners during their wife's pregnancy then return at a time when their wife is quite vulnerable anatomically. On resistance, the presenter stressed this should be monitored, but did consider it a primary point of concern.

## **IV. A Phase II HIV Preventive Vaccine Trial in Lusaka, Zambia**

**Dr Cheswa Vwalika,  
Zambia Emory HIV research project**

### **I. Methods and objectives**

This is the first HIV vaccine in the country. We are proud to be part of the race to find a HIV vaccine for the world as a whole. This is a phase II, randomised, placebo-controlled, double-blind trial to evaluate the safety and immunogenicity of tgAACO9, an HIV vaccine containing clade C gag-pr-ΔRT DNA in an adeno-associated virus (AAV) capsid administered twice, at three dosage levels and two dosing intervals.

This is a multi-site trial, across South Africa, Zambia and Uganda. It involves 91 low-risk volunteers, all of whom were healthy and HIV-negative between the ages of 18 to 15. They came in for four visits over a period of 10 months, so were familiar with our research. They also received two information sessions on general research and detailed vaccine trials before the informed-consent process. There were 16 protocol visits, 14 of which were for blood draws. We finished our last follow-up visit on 16 October. All volunteers were divided into six groups according to dosing levels.

### **2. Results**

We reached our enrolment target for screening. The study is still blinded, so I cannot present any immunological analysis yet. There were no serious adverse events, and 144 adverse events, mild to moderate in severity and not related to the study product. There was one inter-current HIV infection and no pregnancy was reported.

### **3. Challenges**

We faced a number of challenges, this being the first HIV trial in our country. People in our part of the world found out about it, and visited the centre when they needed treatment. Another major challenge was translating scientific terms into the local language, which meant we spent a lot of time ensuring our volunteers knew what we were talking about. Another problem was the common misconception that HIV could be contracted from taking the vaccine. There were also fears about volume and frequency of blood draws, for which we sought the help of our Zambia National Blood Transfusion Service. They started by reassuring our staff to understand the amount drawn would be okay. We started with the couple dealing with concordant HIV-negative couples, so did not expect HIV infection to occur. When it did, we realised we had to emphasise other prevention messages for these couples but, even though we did this and gave out free condoms, behavioural change is ultimately in the hands of each volunteer.

### **4. Lessons learned**

With high retention rates, we learned that recruiting participants from existing cohorts is a good strategy to ensure high follow-up rates. Based on the clinical data so far, the vaccine is well tolerated. However, despite clinical visits, there will always be a risk of HIV infection from unsafe sexual behaviour. We therefore still need an HIV vaccine.

### **5. Discussion**

#### **a. Vaccine**

The presenter confirmed that the vector used in the trial was AAV1. She is hoping to have the results for this study soon, and explained how it differed from the recently closed Merck trial.

#### **b. Sample group**

The discussion moved on to why women were disproportionately represented among the sample population and when the HIV-positive individual was infected. The presenter could not fully explain the low proportion of women in Lusaka, but explained that other sites had more proportional ratios. HIV testing was carried out during volunteers' first visits. The one incidence of infection was due to this male not using a condom during an extra-marital relation. Clients' understanding was tested when signing the



informed consent to ensure they did not have a false sense of protection after being given the vaccine, and that they were aware other preventative methods were needed.

## V. Phase III Microbicide Trial Preparations in Kigali, Rwanda: A Prospective Cohort HIV-incidence Study

**Dr Joseph Vyankandondera,  
Kigali Belgian Technical Cooperation**

### 1. Project Ubuzima

Rwanda is a small country in which 90% of the population work as subsistence farmers. There is no data of HIV incidence but adult prevalence is 5%. Project Ubuzima was started from scratch in 2004 as an international NGO, in partnership between Rwandan institutions, a Dutch academic institution and the International Partnership for Microbicides. It is governed by a management team, a governing council and a local community advisory group. Ubuzima has participated in many trials, such as two international capacity-building programmes for medical research. It is currently conducting HIV incidence studies in two populations.

### 2. HIV incidence study

Current HIV incidence data are not available for Rwanda because we are missing critical updates. We need to characterise the HIV epidemic in Rwanda correctly so that we can intervene properly, focus on resources and evaluate new preventive interventions. We aimed to estimate HIV-1 incidence in higher-risk women in Kigali, and assess Ubuzima's ability to recruit and retain a cohort of 400 women in Rwanda in preparation for a phase III trial. Secondly, we wanted to estimate incidence in sub-groups, compare three assays in a Rwandan context and estimate the prevalence of reproductive-tract infections among high-risk women.

### 3. Study design

The study was a cross-sectional survey of 800 high-risk women above the age of 18, who were able to give informed consent, were HIV-negative but sexually active with multiple

partners. In the follow-up, we retained 400 women if they were HIV-negative, and not pregnant or planning to become pregnant. All women were recruited via community mobilisers, who in turn were identified by community advisory groups in collaboration with local authorities. We started recruitment in October 2006.

### 4. Study procedures

Before recruitment, there is an eligibility screening list, an informed-consent process, counselling, free condoms, HIV testing, interviews about sexual behaviour and tests for other STIs.

### 5. Results

We have completed the cross-sectional survey of 800 women, but the cohort of 400 is still ongoing. In high-risk women, preliminary data show the majority were identified as sex workers with 1-35 clients a week. The majority also said that they used condoms with their clients often, but not all the time. Condom use with steady partners was very low. HIV prevalence in the cross-sectional study was 24% and HIV incidence in the cohort of 400 was around 4 per 100 woman-years of follow-up. Herpes simplex virus type 2 (HSV2) prevalence was almost 60%; *trichomonas vaginalis* was 17%; and syphilis was 7.3%. Testing of other STIs is still ongoing. Pregnancy prevalence in the cross-sectional survey was 7.4%.

### 6. Challenges

We have found that we need to gain trust to access study populations but, for that, we use the community advisory groups and mobilisers. We also had problems gaining proof of identification for each participant. There were also problems with the effect of the HIV prevention package on risk behaviour, as conducting studies results in decreased incidence. Ensuring and maintaining a high quality of laboratory testing is not easy either.

### 7. The way forward

In the next 12 months, we would like to continue capacity-building activities within EDCTP and Interact Worldwide programmes, especially strengthening reproductive health services at referral sites through cervical cancer screening and treatment, management of reproductive-tract infections and family planning. We hope to offer clinical training to the staff of Kigali teaching

hospital, and will strengthen quality assurance systems for laboratory testing at Ubuzima.

## 8. Discussion

### a. Recruitment and adherence

The presenter was first asked how he addressed problems of stigmatisation in the way people were recruited and what benefits the participants were offered to adhere to the trial. He answered that this was not a problem in Rwanda because awareness of methods for HIV prevention was high, and any stigma was avoided because of the inside knowledge of the community mobilisers. They could not incentivise participants other than reimbursing their time.

### b. Exclusion criteria

This study had excluded people who planned to fall pregnant. Did they exclude people from follow-up who had fallen pregnant but not planned to? Joseph explained that clinical trials do not generally include pregnant women and also aim to maintain the original conditions of participants. If women fell pregnant unplanned, they would be referred to the national HIV clinic to follow guidelines to prevent MTCT. The presenter was then asked whether the study had encouraged its participants to stop prostitution and, if they stopped, if they were then asked to exit the study. It had; they were encouraged to join other associations that might persuade them to stop. Follow-up would continue should they stop, but these women would no longer be considered high-risk.

## VI. V001: Phase I HIV-1 Preventive Vaccine Trial in Kigali, Rwanda

**Dr Kayitesi Kayitenkore,  
Project San Francisco**

### I. Objectives

The two vaccine candidates were provided by the Vaccine Research Centre (VRC) at the National Institutes of Health (NIH) and trialled in Kenya and Rwanda. The study started in November 2005 and was completed in April 2007. Vaccine safety and immunogenicity were the primary and secondary objectives respectively. The vaccines tested were: the VRC,

multi-gene, multi-clade, HIV-1 candidate vaccine delivered by a replication-defective recombinant adenoviral vector (Ad5), either alone or in a prime-boost combination with the VRC, multi-clade, HIV-1, DNA plasmid candidate.

### 2. Methods

This was a phase I, randomised, double-blind, placebo-controlled trial with 114 healthy volunteers at low risk of HIV infection. Safety and tolerability were assessed by monitoring study participants for local and systemic adverse reactions after each injection and 12 months after the first injection. Immunogenicity was measured by the proportion of volunteers with HIV-1-specific T-cell responses quantified by IFN- $\gamma$  ELISPOT assay, the magnitude of responses, the proportion of volunteers with HIV-1-specific antibodies and the proportion of volunteers with an increase of recombinant Ad5 antibodies.

### 3. Reactogenicity, systemic symptoms and adverse events

Local reactogenicity was mostly mild. One volunteer had severe pain and tenderness after the Ad5 boost, and two reported severe tenderness after the DNA injection. Systemic symptoms included chills, malaise, fever, headache, nausea and vomiting. It tended to be more severe post-Ad5 boost, with 70% of volunteers presenting severe signs or symptoms. Post-DNA, we had one volunteer with severe myalgia and another one with a severe headache. We had many adverse events, most mild and not related to the vaccine. Of six grade three events, five were not related to the study product. There were five severe adverse events, none related to the study vaccine.

### 4. Safety summary

108 volunteers completed the trial. Local reactogenicity was more common with DNA; systemic reactogenicity was more severe after the Ad5 boost. There were no vaccine-related serious adverse events and no inter-current HIV infections.

### 5. Immunogenicity

Immunogenicity was assessed at several time points. The breadth and magnitude of HIV-1-specific to vaccine peptide were characterised. In general, most volunteers responded to more than one peptide pool.

## 6. Frequency of responses

The responses elicited against envelope were higher than those against gag, pol and nef, but the vaccine construct boost does not contain the nef gene.

## 7. Immunogenicity summary

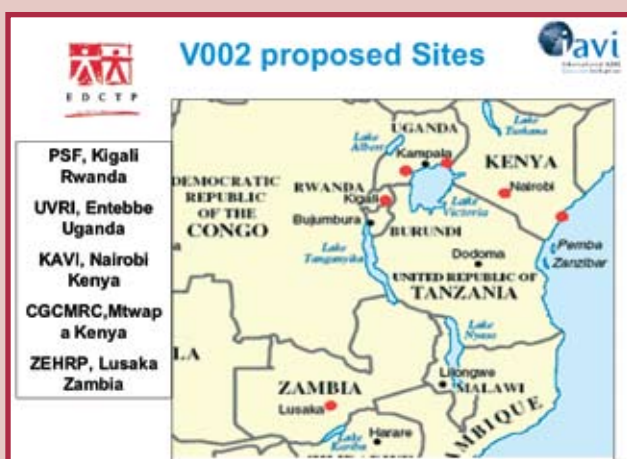
After either Ad5 alone or three injections of DNA, IFN- $\gamma$  ELISPOT responses were detected in about 50% of the vaccinees. In subjects that were primed with DNA and boosted with Ad5, more than 70% had responses.

## 8. Conclusions

At baseline, 74% of volunteers had neutralising antibodies against Ad5; however, the impact of immunogenicity was modest. At the end of the study, 54 of 86 vaccinees had vaccine-induced HIV-positive tests. These data are comparable to other VRC studies. We felt that both vaccines were shown to be safe, relatively well-tolerated and that they induced immune responses.

## 9. Next steps

With discontinuation of the Merck trial, there will be some delay before we initiate following studies. V002 will probably start in 2008 with three 4mg DNA injections at monthly intervals boosted by Ad5. The start of the Partnership for AIDS Vaccine Evaluation (PAVE) 100 phase IIb trial has been postponed as well. For V002, we propose recruiting 300 volunteers across five sites.



## 10. Discussion

One participant asked what criteria studies could use following the Merck data. The presenter had not seen this data yet, but believed Merck's IFN- $\gamma$  responses were lower than those from this study, because this regimen is primed with DNA and boosted with Ad5, which differentiated it from Merck.

## VII. General Discussion

### 1. Outline

Participants were asked to address three main questions:

- What were the main issues raised during these presentations and discussions?
- What can you conclude from these discussions?
- What can you recommend to EDCTP and its partners?

### 2. Study designs

#### a. Implementation

The second vice Chair of DCCC wondered how many of the projects presented today differed from other studies that had failed. Researchers may still perpetuate with plans for future studies, even if they had not been successful in phase I. He encouraged the group to implement things that were known to work, before sitting down to look at the basic immunology. At the moment, he was worried people were only doing what others have done and wanted this group to think differently.

#### b. Understanding

His second point was practical and related to working with groups at high risk. How is it known that vaccines work when study participants are encouraged to use condoms? Is the true intention for high-risk groups not to use condoms or are condoms a cover-up for vaccines known not to work? The second Vice Chair of DCCC stated that many people do not understand what a vaccine trial is, and that community mobilisers may deceive people into participating by using false information and incentives. His recommendations were for more time to be spent on understanding the aims of trials, and for researchers to remember that a failed clinical trial is a good clinical trial.

### 3. Microbicides

#### a. Biomarkers

Another participant asked Prof. Marleen Temmerman what barriers she was facing in gaining sponsorship for future microbicide trials. The recently started tenofovir gel study requires many biomarkers besides colposcopy, but these are not available. Much work has been done recently with new DNA technology to study the vaginal microflora and identify different types of lacto-bacilli. These techniques will have to be used in the monitoring and safety of new microbicide trials. It was thought that a good microbicide was one that prevents HIV and other STIs, but gave women choice over whether it prevented pregnancy. As it was not known how oestrogen interacts with microbicides, post-menopausal women also must be studied.

#### b. Genital infections

Generally there was a recommendation for EDCTP to foster studies focusing on genital infections in the face of failures in HIV vaccines. More research is needed not only on bacterial vaginosis but also markers of innate immunity. Local factors, vaginal practices, oestrogen and hormonal factors all play a role, but little work has been done in this regard. There was a call for more concerted action here.

### 4. African priorities

#### a. Studies

Another participant asked his African colleagues to prioritise what studies they wanted to see in the near future in terms of HIV treatment. The first respondent said they first needed to understand and interpret the primary mutations in response to therapy. Secondly, most programmes focused on first-line drugs; the choice of second-line drugs had to be evidence-based, with treatment programmes accompanied by close monitoring. Another suggested closer comparisons of different regimens.

#### b. Contextual specification

It was suggested that the main problem might not be the accessibility and choice of second-line treatments, but more one of money. One participant asked if there was any evidence that the drugs used in the developed world would not work in Africa. Although it could be admitted the problem is money, and that what works for HIV-1 usually

works for HIV-2, the latter is more difficult to detect, and these drugs were primarily designed for the former variant. However, it was agreed that the first problem is getting the drugs in place, with the proviso that resistance is likely to evolve faster in an African setting.

#### c. Centralised analysis methods

The Chairman of the HIV session summarised that previous discussions had shown there was a need for better monitoring of the efficacy of HIV vaccines and to study emerging resistance. What other recommendations are there? One participant agreed monitoring was fundamental, but also proposed building a standardised, centralised laboratory to carry out assays to interpret all African clinical data, supported by a quick, safe transport service. There was broad support behind this idea, particularly as it allowed Africa more ownership of studies conducted there and required capacity to be built locally. It was suggested that South African genomic studies could be used as a model, where their technology could be spread to other centres.

#### d. Innate immunity

Innate immunity also requires close attention, although it should not be assumed that this is the key to protection. Alongside this, there needs to be an understanding of what controls viral loads in individuals. The Chair of the PB believed nef interfered with natural immunity, which indicated it could be of interest for vaccine studies. It was stressed that clinicians needed more tools to judge when there is a viral failure and when not, and what mechanisms are likely to protect patients from these three diseases. The group was asked if research should revert to trying to dissect the correlates of protection.

#### e. MTCT

Another consideration was whether EDCTP could invest in in-vitro fertilisation to prevent MTCT in discordant couples wishing to conceive.

### 5. Prevention or treatment

Given EDCTP's focus on phase II and III studies, the numerous bodies researching vaccines and the call to go back to more basic studies, there was a suggestion EDCTP should not be in the area of HIV vaccines at all, and that money should be diverted to areas where there was more hope of incremental progress. There is a gap in the treatment

of children with HIV, where EDCTP is able to make real advances. By focusing on niche areas that might make a real difference in HIV, treatment in general may be a better investment than either vaccines or microbicides. However, money, resources and healthcare systems were big barriers

to treatment. Some disagreed that Europe was unable to contribute by helping Africa in the vaccine field. Microbicides was perhaps a better route to prevention. Just because this is a challenge, the organisation cannot give up.





# Malaria Clinical Trials in sub-Saharan Africa

**Facilitator: Christine Manyando,**  
(EDCTP DCCC)  
**Rapporteur: Peter Kremsner (EDCTP PB)**

## I. Evaluation of Four Artemisinin-Based Combinations for Treating Uncomplicated Malaria in African Children

**Prof. Umberto D'Alessandro,**  
**Institute of Tropical Medicine, Antwerp**

### 1. Objective

To establish the impact of using chlorproguanil-dapsone-artesunate (CDA) on the selection of *Plasmodium falciparum* (*P. falciparum*) genotypes linked with sulfadoxine-pyrimethamine (SP) resistance.

### 2. Study design

It is a three-arm, multicentre, randomised, open-label trial. Follow-up is done at 28 days, with passive follow-up for the detection of a second clinical episode within six months, in which case the patient is re-treated. After re-treatment, follow-up is again done at 28 days. Each site will recruit 510 patients, with 170 in each arm.

### 3. Study treatments by country

There are 10 sites in seven countries. Each site tests a different combination of the four treatments.

15/10/2007

Sites	Date I in	Screened	Recruited	
Manhiça	09/07	106	84	
Lambaréné	19/07	219	9	2 SAEs
Fougamu	29/08	133	5	
Nanoro	07/09	285	117	
Ndola	02/10	?	?	Started recruitment
Mbarara	28/08	124	43	2 SAEs
Jinja	?	5	5	Started recruitment
Tororo	?	?	?	Started recruitment
Rukara	NA	0	0	Initiation visit done
Mashesha	NA	0	0	-
Calabar	NA	0	0	Initiation end Oct
Total		872	263	

### Institutions involved

- Institute of Tropical Medicine, Antwerp, Belgium
- Liverpool School of Tropical Medicine and Centre for Medical Statistics and Health Evaluation, University of Liverpool, UK
- East African Network for Monitoring Antimalarial Treatment (EANMAT).
- Centre Muraz, Bobo Dioulasso, Burkina Faso.
- Department of Paediatrics, University of Calabar, Cross River State, Nigeria.
- Tropical Diseases Research Centre, Ndola, Zambia
- Institute of Tropical Medicine, Department of Parasitology, University of Tuebingen, Germany and Medical Research Unit,
- Albert Schweitzer Hospital, Lambaréné, Gabon.
- Uganda Malaria Surveillance Project (UMSP), Kampala, Uganda.
- Epicentre, Paris, France and Mbarara University of Science and Technology, Faculty of Medicine, Mbarara, Uganda
- Programme National de Lutte contre le Paludisme, Kigali, Rwanda.
- Fundacio Clinic per a la Recerca Biomèdica/Centre for International Health, University of Barcelona, Spain and Manhiça Health Research Center, Mozambique.

### 4. Endpoints

#### a. Primary

The two primary endpoints are polymerase chain reaction (PCR)-unadjusted and adjusted treatment failure up to day 28.

#### b. Secondary

The two secondary endpoints are PCR-unadjusted treatment failure up to day 63 and PCR-adjusted treatment failure for the entire period of passive surveillance. Others include:

- Fever clearance time
- Parasite clearance time
- Gametocytaemia
- Haemoglobin (Hb) changes at day 3, 7, 14 and 28
- Clinical malaria after first and second active follow-up
- Change in the frequency of mutation in dihydrofolate reductase (DHFR) in CDA-treated patients
- Safety profiles including significant changes in relevant laboratory values.

## 5. Inclusion criteria

- Age six to 59 months
- Body weight of at least 5kg
- Monoinfection with *P. falciparum* with parasitaemia of 1,000-200,000/ $\mu$ l
- Fever or history of fever, defined as axillary temperature of at least 37.5°
- Hb value of at least 7g/dl
- Signed, informed consent.

## 6. Exclusion criteria

- Participation in any investigational drug study during the previous 30 days
- Known hypersensitivity to the study drugs
- Severe malaria or danger signs
- Presence of concurrent illness that interferes with the interpretation of the follow-up and response to treatment
- Severe malnutrition
- Ongoing prophylaxis with anti-malarial drugs.

## 7. Passive follow-up

- Parents/guardians are asked to attend the health centre for any illness that the child may have
- Monthly home visits but without collecting blood samples, unless the child is sick
- When the child attends the health centre, blood slides for malaria parasitaemia, body temperature and Hb/packed cell volume (PCV) are systematically taken.

If the child has another episode of uncomplicated malaria, they are included in the second follow-up and treated with the same drug that they were treated for during their first episode. If they have a malarial infection that does not fulfil the criteria, they are treated with first-line treatment.

## 8. Current situation

### a. Treatments secured from pharmaceutical companies

The trial has begun, but it has not been easy. All treatments have been secured from pharmaceutical companies:

- Dihydroartemisinin-piperazine (DHA-PPQ) from Sigma-Tau
- Amodiaquine-artesunate (AQ-AS) from Sanofi Aventis
- A co-formulation of chlorproguanil-dapsone (CD) from GlaxoSmithKline (GSK) and artesunate from Sanofi Aventis
- Artemether-lumefantrine (AL) from Novartis.

### b. Biochemistry tests at all sites

All sites are able to carry out biochemistry tests, but there have been some administrative problems.

### c. Electronic case report form (eCRF)

- A standard source document was produced
- eCRF data entry guidelines and a training package were developed
- All sites are equipped with laptops containing MACRO software and the eCRF
- Sites regularly enter data from the source document and send them to Antwerp over the internet
- The data manager in Antwerp can continually check the consistency and quality of the data.

## 9. Data Safety and Monitoring Board (DSMB)

DSMB members are Prof. Bernard Brabin of the Liverpool School of Tropical Medicine (LSTM), Prof. Abdel Babiker of the Medical Research Council (MRC) clinical trial unit in London, and Dr Anja Terlouw, also of LSTM.

The aim of the DSMB is to provide independent advice on the quality of the data produced and on the efficacy and safety of the treatments tested, thereby contributing to safeguarding the interests of the trial participants.

The DSMB is also asked to consider patient safety, particularly any sudden unexpected serious adverse reactions (SUSARs) leading to death, alongside treatment efficacy when making their recommendation as to continuation, amendment or discontinuation of the trial.

## 10. Relationship between DSMB, Trial Management Group (TMG), consortium secretariat and sponsor

Day-to-day activities are taken care of by the TMG, which interacts with the DSMB and the consortium secretariat. This information then eventually reaches the sponsor.

## 11. Interim analyses

The DSMB will undertake three equally-spaced interim analyses using the Haybittle-Peto approach, after 1,300, 2,600 and 3,900 children have been randomised. The final analysis will be undertaken after all 5,100 children have undergone follow-up at day 28.

## 12. Patient recruitment

As of 15 October 2007, we have registered four serious adverse events, which were immediately communicated to the local ethical committee, the Antwerp ethical committee and the DSMB. If they involve children treated with DHA-PPQ or AQ-AS, they are communicated to Sigma-Tau and Sanofi Aventis respectively. So far, 263 patients have been recruited from the 872 screened.

## 13. TMG

The TMG members are spread between Antwerp, Kampala and Liverpool.

## 14. Issues to be discussed

- The decreasing trend of malaria in Africa is good news, but this increases the time and cost involved in reaching the sample size target
- Reviewers of proposals and budgets should be aware of the additional costs involved in carrying out Good Clinical Practice (GCP)/Good Laboratory Practice (GLP)-compliant trials.

## 15. Discussion

It was recognised that any trial is a new experience and hoped that the EDCTP would listen to the organisers' pleas for additional financing. Asked whether the four SUSARs were drug-related, the presenter confirmed that three were not. The remaining incident was possibly related: it was a case of anaemia in a site testing for CDA, but the child had not received that drug. He also confirmed that, while he had not been confronted with demands from various ethics committees on those conducting drug trials to provide participants with insecticide-treated bed nets (ITNs), the nets are distributed as a matter of course in some countries.

One delegate commented on the tendency for African parents to resort to traditional medicine or to a concomitant drug that may affect the final result of the trial. Perhaps what is needed is active surveillance before follow-up at six months. He also asked whether, if the prevalence of the disease is decreasing, he has considered recalculating the sample size. The presenter agreed that it would not be easy to follow the children for six months. He was confident that the on-site investigators would explain the importance of compliance, as well as undertaking monthly at-home visits. In terms of sample size calculations, the presenter was more concerned with recruiting enough children, not reassessing the sample size.

When dealing with a large consortium of African sites, remarked a delegate, there is a lot of heterogeneity between laboratories, and the study is heavily dependent on laboratory outcomes. He asked how the laboratories are sited to ensure that there is comparable data, particularly when dealing with a number of field sites. In terms of the eCRF, the delegate wanted to know how the limited internet connectivity at some field sites was reconciled, given that there is no paper-based data capture. Finally, he wondered how the presenter guided against bias in the treatment of patients, given that this is an open-label study at multiple sites.

Answering the comment on the laboratories, the presenter emphasised that Standard Operating Procedures and similar equipment have been issued to all laboratories. In terms of the eCRF, all sites have a laptop on which data is entered off-line. They then connect to the internet at least once a week in order to send the data to Antwerp. In addition, clinical observations and results are captured in the source document, which acts as a back-up from which to re-enter the data. Finally, the presenter felt sure that there is no treatment bias, since treatment and assessment are done by different people.

## II. AL versus DHA-PPQ for Treatment of Uncomplicated Falciparum Malaria in Uganda

**Dr Joaniter Nankabirwa,  
Uganda Malaria Surveillance Project  
Kampala, Uganda**

### I. Introduction

There is a high re-infection rate, especially in areas of high malaria endemicity.

### 2. Objective

The objective of the trial was to compare the efficacy and safety of AL and DHA-PPQ for the treatment of uncomplicated malaria at a high transmission site in Uganda.

### 3. Study methodology

#### a. Overview

This was a randomised, single-blinded clinical trial, with 42 days of follow-up.

It took place at Aduku Health Centre in Apac District, a site with perennial holoendemic malaria transmission and an entomological inoculation rate (EIR) of 1,564.

Genotyping was done to distinguish between recrudescence and new infection.

The primary outcome was the risk of recurrent parasitaemia at days 28 and 42, unadjusted and adjusted by genotyping.

#### b. Inclusion criteria

- Children aged between six months and 10 years
- Fever or history of fever within the previous 24 hours
- Monoinfection with *P. falciparum*
- Parasite density of 2,000-200,000/ $\mu$ l
- No severe disease or other febrile illnesses.

#### c. Treatment

- AL was given as a six-dose regimen and DHA-PPQ was given as a three-dose regimen, with a placebo given in addition to equalise dosage
- All treatments were given with a fatty meal and directly observed
- All patients enrolled in the study were given two ITNs.

### 4. Assessment of treatment efficacy

#### a. Assessment criteria

We used 2003 World Health Organization (WHO) guidelines to assess early treatment failure, late clinical failure, late parasitological failure and adequate clinical and parasitological response.

#### b. Risk of recurrent parasitaemia

The risk of recurrent parasitaemia, unadjusted by genotyping, was assessed, looking at the proportion of patients with early treatment failure, late clinical failure and late parasitological failure.

#### c. Risk of recrudescence

The risk of recrudescence, adjusted by genotyping, was looked at in terms of the proportion of patients with early treatment failure, late clinical failure or late parasitological failure due to recrudescence, using the Kaplan-Meier product limit formula, thereby censoring new infections.

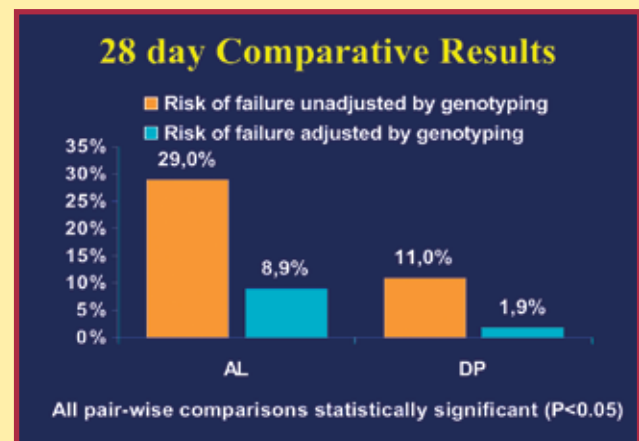
### 5. Baseline characteristics

There were a total of 210 and 211 patients in the AL and DHA-PPQ arm respectively. 99% of patients were followed up in both arms. The median age was 1.8 and 1.5 years of age. 90% of children were younger than five.

### 6. Comparative results

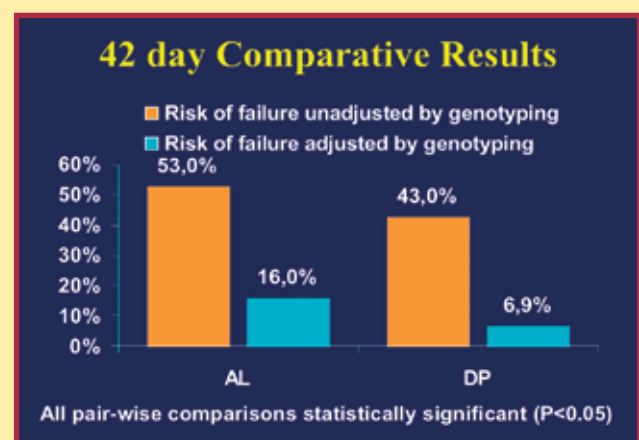
#### a. 28 days

Unadjusted by genotyping, 29% of children in the AL arm were at risk of failure, versus 11% in the DHA-PPQ arm. Adjusted by genotyping, the values were 8.9% versus 1.9%. All these values were statistically significant.



#### b. 42 days

Unadjusted by genotyping, 53% of children in the AL arm were at risk of failure, versus 43% in the DHA-PPQ arm. Adjusted by genotyping, the values were 16% versus 6.9%. All these values were statistically significant.





## 7. Secondary outcomes

- The time to recrudescence in children in the AL arm was 14 days versus 21 days in children in the DHA-PPQ arm, which was statistically significant
- There was no difference between the two arms up to day two, and a slight difference between days two and three
- Parasite clearance by day three was the same in both arms
- At days 15-28, gametocyte carriage was 3.3% and 0% in the AL and DHA-PPQ arms respectively, versus 8.9% and 2.5% respectively at days 29-42. All these values were statistically significant
- The mean increase in Hb was higher in the DHA-PPQ arm than in the AL arm
- Among patients with recurrent parasitaemia, there was no difference in the prevalence of anaemia
- We found no significant difference in adverse events between the two groups.

## 8. Summary

- Both regimens were well tolerated and highly efficacious for the treatment of uncomplicated malaria in an area with very high malaria transmission
- The risk of recurrent parasitaemia was significantly lower in participants treated with DHA-PPQ than in those treated with AL
- DHA-PPQ reduced the risk of gametocytaemia and improved Hb recovery compared to AL.

## 9. Conclusions

- For both artemisinin-based combination therapies (ACTs), the high rate of re-infection and the implications of frequent treatment are a major concern
- The high re-infection rates in areas of very high malaria transmission highlight the need to re-evaluate the approach to treatment of recurrent episodes of malaria following initial ACT.

## 10. Policy implications

Results have important policy implications in that DHA-PPQ is a highly effective alternative to AL as first-line treatment for uncomplicated malaria in Africa.

DHA-PPQ is relatively inexpensive and is easy to use.

DHA-PPQ has a potential role for presumptive treatment of fever in Home-Based Management of Fever.

The slowly eliminated 'tail' of piperaquine, however, may raise concerns due to the risk of resistance to parasites.

## II. Discussion

In answer to a question from the floor, the presenter responded that ACTs have fewer side effects and lead to good clearance of parasitaemia up to day three. However, due to the other issues that they raise, there is a need to look for even better alternatives.

Responding to another question, the presenter explained that the age range in the inclusion criteria was chosen in order to look at children aged younger and older than five. The mothers of younger children are more compliant with follow-up.

Asked about the cost of DHA-PPQ versus AL, the presenter confirmed that, on the Ugandan open market, DHA-PPQ costs about \$5 per full dose versus \$10 for AL. Prof. D'Alessandro added that the development of DHA-PPQ is sponsored by the Medicines for Malaria Venture (MMV), which has stated that each adult treatment should cost less than \$1. The manufacturer of AL has also reduced its price to \$1 per adult treatment. He went on to comment that, while the study was well conducted, it did not comply with EDCTP norms around monitoring and audit.

One delegate stressed that the Tropical Institute in Antwerp should have realised the huge costs involved in the trial previously presented. The presenter of the trial responded that pharmaceutical companies do not want to sponsor trials that evaluate their drugs versus their competitors' if the outcome is unpredictable. Academics have a duty to test the efficacy and safety of these drugs as objectively as possible, he concluded.

## III. Randomised Controlled Trial of the Safety and Immunogenicity of Recombinant PfAMA1-FVO [25-545] in Healthy Adults in Bandiagara

**Dr Drissa Coulibaly,  
Malaria Research and Training Centre,  
University of Bamako**

### I. Background

- PfAMA1-FVO [25-545] is a *Pichia pastoris* expressed protein, with a *P. falciparum* FVO ectodomain

- It was manufactured under Good Manufacturing Practice (GMP) by Eurogentec in Belgium
- The dose used was 50µg
- Aluminium hydroxide, manufactured in Denmark, was an adjuvant to it
- Phase Ia dose and adjuvant selection was done in the Netherlands, which met the go criteria for a safety and immunogenicity trial in endemic areas.

## 2. Primary objective

To evaluate the safety of 50µg with an aluminium hydroxide adjuvant in healthy Malian adults.

## 3. Secondary objectives

- To assess the humoral response to the vaccine by measuring the variation in the level of immunoglobulin G (IgG) in the serum and its ability to recognise the native protein on merozoites
- To assess the cellular immune response by measuring T cell proliferation and cytokine production in *in vitro* tests.

## 4. Study site

The study site was Bandiagara, located 700km from Bamako, or a five-hour drive from Ouagadougou. Since 1998, the site has been supported by the National Institutes of Health (NIH).

## 5. Study design

- The study followed 40 Malian adults between the ages of 18 and 55
- All patients were healthy, and female patients were not pregnant at the time of inclusion
- It was a randomised, controlled, double-blind trial.
- 20 patients received 50µg of PfAMA1 and 20 received a tetanus toxoid
- The immunisation schedule was days 0, 28 and 56
- The safety of our candidate vaccine was overseen by a safety monitoring committee
- Immunisation was done by intramuscular left deltoid injection
- We planned to conduct 19 standardised visits per patient, almost all of which have been done.

## 6. Safety and reactogenicity

- Solicited symptoms were actively monitored for eight days after each immunisation, with patients asked about local symptoms like injection site pain, erythema, swelling, and arm motion limitation, and about general symptoms like headache or chills
- Unsolicited symptoms were monitored for 28 days after each immunisation
- Serious adverse events will be monitored throughout the study duration.

## 7. Immunogenicity

Total IgG titers were measured by enzyme-linked immunosorbent assay (ELISA) on days 0, 28, 56 and 84, and will be measured on days 140 and 364, at the Malaria Research & Training Center (MRTC) central laboratory in Bamako, with an external quality check performed in the Netherlands.

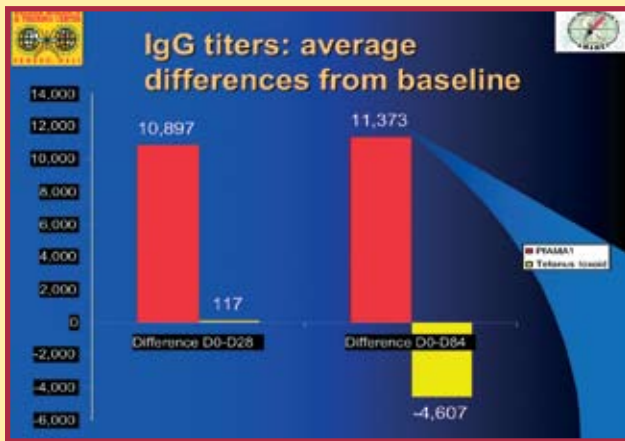
## 8. Results

Of the 90 subjects screened, 40 were enrolled. 20 patients in each group were given the first dose. 20 patients in the treatment group were given the second dose and 19 in the placebo group. The numbers for the third dose were 18 and 19 respectively.

## 9. Baseline characteristics

About 65% of patients were women, and the mean ages of patients were 30.5 and 26 in the treatment and placebo arms respectively.





## 10. Symptoms

### a. Incidence of solicited symptoms during eight-day follow-up period

Two grade 3 adverse events were observed in the treatment arm following the first dose. Four such reactions were seen after the second dose. Only one was seen after the third dose.

### b. Grade 3 solicited symptoms during eight-day follow-up period

There was one case of grade 3 swelling in the control group and six cases in the treatment arm. We detected an increase in IgG titers in the treatment arm.

## 11. Serious adverse events

We observed only one serious adverse event on day 95, in a female patient, who presented with vomiting, diarrhoea, dehydration and weakness. She was hospitalised for 48 hours, during which time she received intravenous rehydration and underwent biologic investigation. Toxi-infection was probably the cause of this serious adverse event, and the patient recovered after four days.

## 12. Discussion

In response to a question from the floor, the presenter confirmed that the study was double-blinded until day 84. A representative from CNRFP asked what the EIR level and transmission season was in the area of the study site; the presenter reckoned there were 10 mosquito bites per month and a transmission season of six months. The participant from CNRFP went on to question whether, given that most female patients in the study will already have received at least five tetanus immunisations during their pregnancy, the addition of three immunisations might expose them to some kind of reaction. The presenter suggested that that might be

a problem. One delegate asked how, with a 364-day follow-up, the study guards against confounding factors and the involvement of the same patients in other interventions. The presenter outlined how patients were invited once a month to the health centre for surveillance if they had any health problems. Another participant returned to the comment about tetanus and explained how all emergency cases in most European countries are given a tetanus shot, with no reaction. A comment from the floor added that the choice of contra-vaccine was deliberated at length with the investigators and that tetanus toxoid was considered to be the best one.

## IV. Clinical Experience with the *P. Falciparum* Merozoite Surface Protein-3/ Long Synthetic Peptide (MSP3/LSP) in Burkina Faso

**Dr Sodiomon Sirima,**  
**Centre National de Recherche et de Formation sur le Paludisme, Ouagadougou, Burkina Faso**

### 1. First clinical experience in naïve volunteers

- The first clinical experience in naïve volunteers was a phase I study in 2002 in Switzerland
- The primary endpoint was safety and reactogenicity.
- The vaccination schedule was 0, 1 and 4 months.
- 35 naïve volunteers were recruited
- Follow-up was done at 14 and 28 days for solicited and unsolicited symptoms respectively
- Serious adverse events were recorded throughout the study duration
- At the end of the trial, the vaccine was considered to be safe and well tolerated
- It induced antibodies capable of neutralising the *P. falciparum* in *in vitro* assays.

### 2. Clinical experience in semi-immune volunteers

#### a. Overview

A Phase Ib trial was conducted in 2003 in a village 50km from Ouagadougou, where 30 male adult volunteers were recruited.

They received three injections of MSP3 subcutaneously. Follow-up was done at 14 and 28 days for solicited and unsolicited symptoms respectively. There were no serious adverse events after one year.

### b. Objectives

- The primary objective of the study was the reactogenicity and safety of three doses of 30µg of MSP3
- The secondary objectives were humoral cell-mediated immune responses to the malaria candidate vaccine.

### c. Findings

- Both vaccines were well tolerated; no unexpected or serious adverse events were reported
- The safety profile of the MSP3 vaccine does not appear to differ substantially from that of the control vaccine
- There was no significant induction of antibody responses, due probably to the high level of pre-existing immunity in adults
- The data are consistent with some enhancement of cell-mediated immune responses occurring following vaccination with MSP3 vaccine.

## 3. Clinical experience in non-immune volunteers

### a. Overview

Based on these results, a protocol was designed to perform the study in non-immune volunteers in endemic countries, meaning children aged between one and two. We designed a double-blind, randomised, controlled dose-escalation trial, with 45 children recruited.

- The first group received 15µg of MSP3 and the second 30µg
- The primary endpoints were reactogenicity and immune response
- Follow-up was performed at seven and 28 days for solicited and unsolicited symptoms respectively
- We recorded potentially serious adverse events for the duration of the study.

### b. Immunisation schedule

Injections were given at days zero, 28 and 56. Follow-up was performed at 12 months after the first dose.

### c. Trial profile

Of the 134 eligible children screened, 110 were randomly selected. Of those 110, four did not enrol and 47 were excluded due mainly to moderate malnutrition and biological abnormalities. One child aged less than a year had been mistakenly screened and the parents of another refused worm treatment. 59 children fulfilled the inclusion criteria, and we randomly selected 45.

### d. Current status

- The study conclusion visit on day 84 was completed for both groups. 30 received the malaria vaccine and 15 the control drug, which was a hepatitis B vaccine.
- Data entry and immunological sample processing are ongoing, with a final study report planned for the first quarter of 2008
- A decision to proceed to phase IIb in children is pending the outcome of this study.



## 4. Conclusion

- Clinical experience with MSP3 malaria candidate vaccine has shown that the vaccine is safe and well tolerated
- Proof of concept studies are awaited to confirm whether the vaccine is effective against *P. falciparum* malaria in children living in endemic areas.

## 5. Discussion

A comment from the floor was that, in an ideal world, one would like the opportunity to evaluate one's candidate vaccines with this kind of adjuvant. It is something worth thinking about.

Another delegate asked what the go/no go criteria are for proceeding with a phase IIb study and whether children in the phase Ib study were categorised according to whether or

not they had a history of malaria. The presenter said that, at 12 months, it is impossible for children living in a natural setting in Burkina Faso not to have been exposed to malaria. The go/no go criteria are based on safety parameters.

## V. Effects of Genetic Variation in *CYP2C* Locus on Pharmacokinetics of Chlorcycloguanil

**Dr Janha Ramatoulie,**  
**Medical Research Council Laboratories (MRC),**  
**Gambia**

### I. Introduction

The *CYP2C* locus gene is mapped to chromosome 10 and encodes cytochrome proteins, *CYP2C9*, *CYP2C8*, *CYP2C19* and *CYP2C18*, which metabolise most clinically important drugs, including antimalarials like proguanil and chlorcycloguanil. Chlorproguanil is converted to chlorcycloguanil, the active antimalarial metabolite, by *CYP2C19* and is a component of Lapdap, which is currently being evaluated as an affordable antimalarial in low-income settings. *CYP2C19* metabolises the dapsone component of Lapdap into its antimalarial metabolite too.

### 2. Methods

We found that this cluster had two main haplotype blocks, consisting of *CYP2C18* and *CYP2C19* in one, and *CYP2C8* and *CYP2C9* in the other. The markers that we typed in the cluster were put into this programme to generate degrees of linkage disequilibrium.

We selected 14 loci to genotype in *CYP2C19* and *CYP2C9* using allele-specific and real-time PCR techniques. We used the National Center for Biotechnology Information (NCBI) reference sequence of the *CYP2C19* gene to select the loci of interest and design primers around these loci using Primer3 software.

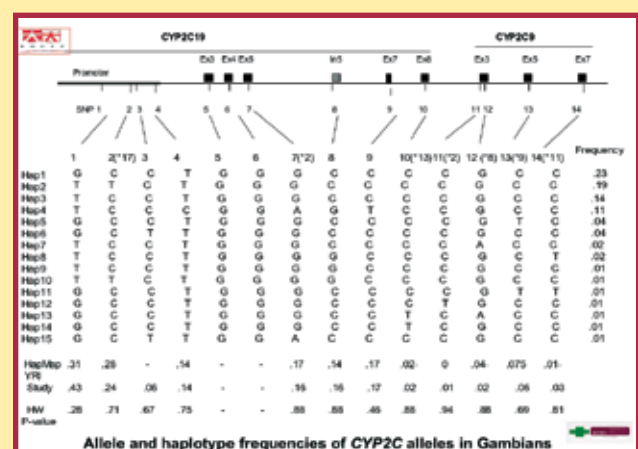
Our study subjects had undergone pharmacokinetic studies on Lapdap. Some of the single nucleotide polymorphisms (SNPs) were available on the Taqman platform and were preferable for real-time typing.

We also generated haplotypes from genotypic data using an algorithm from phase 2.2 and analysed them for association

using MARKER. Among the alleles investigated, *CYP2C19\*17*, a gain of function mutation, causes rapid gene transcription, and *CYP2C19\*2*, a loss of function, causes a splicing defect, producing a non-functional protein.

### 3. Allele and haplotype frequencies of *CYP2C* alleles in Gambians

The *CYP2C19\*17* allele had a frequency of 0.24 in our population and 0.28 in the Yoruba population. We generated 15 haplotypes and the *CYP2C19\*17* increased in function allele was defined by Hap2 and Hap10, while *CYP2C19\*2* was defined by Hap4 and Hap15.



### 4. Effects of genetic variants of *CYP2C19* on antimalarial pharmacokinetics

We also constructed a simple model to categorise individuals into fast, intermediate and slow metabolisers, based on the type of allele they carried:

- Fast metabolisers carried one or two copies of the *CYP2C19\*17* genotype
- Slow metabolisers carried one or two copies of the *CYP2C19\*2* genotype
- Intermediate metabolisers carried neither genotype.

We realised that fast metabolisers had higher drug concentrations, in that they had area under the plasma concentration time curve (AUC) and maximum concentration (Cmax) of chlorcycloguanil, while slow metabolisers had the lowest AUC and Cmax values. The difference between AUC and Cmax was significant. The trend of time to reach maximum drug concentration (Tmax) was not significant, but the trend was as expected.



## 5. Haplotype block of CYP2C19 and CYP2C9 alleles generated using MARKER

All the *CYP2C* alleles that we studied exhibit strong linkage disequilibrium.

## 6. Conclusions

- Slow and fast metabolising alleles have a frequency of 14% and 24% respectively in the Gambian population
- The allele frequencies are similar to those established in West African Yorubas and in Europeans
- The presence of fast metabolising alleles cause significant increases in AUC and Cmax of cycloguanil
- *CYP2C9* effects cannot be dismissed in this study because of the strong linkage disequilibrium between *CYP2C9* and *CYP2C19* alleles.

## 7. Future perspectives

- Work is underway to select more markers in the *CYP2C* cluster. In doing so, we are confirming the alleles that we have already genotyped and biochemically characterising the novel alleles
- We want to determine whether the genetic differences that we have established in this study in the pharmacokinetics of cycloguanil really translate into clinically effective antimalarial treatment in a randomised, control trial in over 400 children.

## 8. Discussion

One delegate referred to the genetic diversity and differences that have been shown with this new technology and asked to what extent this could be extrapolated to populations outside the Gambia. He also asked how the study's findings relate to the side effect profile of patients in whom these differences are seen. Finally, the delegate asked how the presenter foresaw transferring this new technology to the Gambia. The presenter responded by saying that these data are important in future clinical trials involving antimalarials like chlorproguanil, which would be needed to be taken into consideration in order to improve clinical trials or to prevent failures. Some of the alleles have an effect on chlorcycloguanil pharmacokinetics. Fast metabolisers tend to metabolise the drug so rapidly that they may not benefit much from treatment and may require high dosages. The data could be used to base dosages on an individual's genotype composition in order to prevent adverse events. In response to another question from the floor, the presenter

said that 400 subjects had parasite clearance following treatment with Lapdap. Work must now be done on data from adults and children to compare associations of *CYP2C* composition and parasite clearance.

The presenter answered another question by explaining how the study had looked at positive selection for *CYP2C19\*17* and *CYP2C19\*2*. It appeared that the \*2 allele was selected over the \*17 allele in the Gambian population. She thought that, since the \*17 allele causes rapid metabolism, it is rapidly excreted from the system and the person may not benefit much from it. One of the aims is that the data are used in future clinical trials involving chlorproguanil or its use in combination with other drugs.

Asked whether a dose escalation study had been done to find out the level at which a plateau is reached and whether it even matters, the presenter confirmed that no such study had been done.

## VI. General Discussion

While the gold standard for the detection of malarial parasites is microscopy, one delegate drew attention to the fact that Prof. D'Alessandro's study is using PCR and asked how the difference is drawn between gametocytes and asexual parasites. Prof. D'Alessandro stressed that this technique is not used for diagnosis but for distinguishing between new infection and recrudescence. The technique has its limits. In terms of data from an adjusted PCR, he went on to say that these are all recurrent parasitaemia observed during the follow-up period. The PCR cannot distinguish between gametocytes and asexual stages, but the PCR is done only on microscopically-positive samples.

Asked who is going to do the PCR, Prof. D'Alessandro confirmed that it would be done by his certified laboratory in Antwerp. In answer to a further question, Prof. D'Alessandro recited how, in a previous phase III trial for the registration of treatment with DHA-PPQ, a PCR analysis was done and results read by an independent person and 20% of the samples were redone. The same is intended to be done in the current study.

A question from the floor wondered why such a large study as Prof. D'Alessandro's is limited to *P. falciparum* mono-infection, since the inclusion of other species could

provide baseline efficacy data on *P. malariae* and *P. ovale*. Prof. D'Alessandro felt that this was a valid observation but explained that the study sponsors wanted a homogeneous population. A percentage of *P. malariae* and *P. ovale* is difficult to detect by microscopy, particularly in children suffering a clinical attack.

Another delegate highlighted the question of 'normal ranges' in Africa and asked Prof. D'Alessandro whether he applied them in his study. He also wanted to know whether data is first entered onto the eCRF and then onto paper, or vice versa, and how typing errors are detected. Prof. D'Alessandro said that each laboratory has its own normal range. Tests

cannot be interpreted without knowing about patients' histories, so there is no issue around adverse events. It is merely a clinical judgment within the framework of the clinical picture. In terms of data entry, data are entered from the source document into the eCRF. Site monitors have to check both, and additional, centralised consistency checks are able to generate queries.

Prof. D'Alessandro was congratulated on having established normal values in a series of trial sites and countries, which is a rare thing in many places. Prof. D'Alessandro clarified this point, saying that each laboratory has ranges, rather than normal values.

# Tuberculosis Clinical Trials in sub-Saharan Africa

**Facilitator: Joseph Odhiambo, (EDCTP PB)**  
**Rapporteur: Thomas Nyirenda (EDCTP SEC)**

## I. Determining the Optimal Doses of Antiretroviral and Anti-Tuberculous Medications When Used in Combination for the Treatment of HIV/TB in Co-infected Patients

**Dr Hellen McIlleron,**  
**University of Cape Town**

### I. Objectives

The study has several objectives that include:

- Describe and compare ARV (LPV, EFV, NVP) concentrations, in HIV-infected children and adults, with and without RIFAMPICIN-based TB treatment
- Identify risk factors in African populations for low of high ARV concentrations
- Association of efficacy and safety with concentrations of the ARVs
- Rifampicin and isoniazid concentrations
- WB, plasma, intracellular, free drug concentrations.
- Genetic polymorphisms
- Sample collection methods suitable for ARV concentration monitoring in resource-constrained settings
- Population pharmacokinetic (PK) and PK-PD models using NLME.

### 2. Methods

The study is composed of several sub-studies:

- 5 studies:
  - EFV PK in children (standard doses)
  - LPV/RTV PK in children (double dose Kaletra® during TB treatment)
  - LPV/RTV PK in adults (1,5 x and 2 x dose Kaletra® once established on rifampicin)
  - NVP PK in children

- NVP PK in adults
- Assay methods:
  - LC-MS/MS (accurate, ↓ volume samples)
  - Plasma, WB, intracellular, free
- Covariates:
  - Patient and treatment factors
  - Analysis
    - Trough concentrations, NCA, NLME
    - TB/HIV during- / after- TB treatment / controls / recommended ranges

### 3. Capacity building

The project has several capacity building components:

- PK study capacity at clinical sites
- GCP training and experience
- Assay methodology development
- Equipment: LC-MS/MS
- Technology transfer
  - NLME modeling
  - Assay methodology
- PhDs
  - scholarship in Kampala
  - students in Cape Town and Uppsala
- TDM service in Cape Town up and running

The project also has numerous partners working together.

### 4. Conclusions

- Pilot studies have demonstrated the importance of PK evaluation in the relevant patient populations
- Ongoing studies
  - ↑ sample size
  - covariate effects, safety and efficacy
  - adjusted dosing approaches
  - WB concentrations
  - exploration of intracellular and free drug concentrations.
- Challenges
  - changing environment of standard practices, treatment guidelines and available formulations
  - study population and design for optimizing NVP dose with TB treatment
  - translation of study findings into policy recommendations.

## II. Rapid Evaluation of Moxifloxacin in the Treatment of Sputum Smear Positive Tuberculosis: REMoxTB

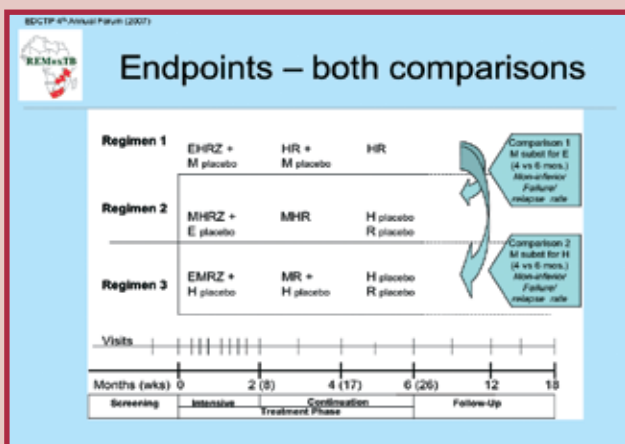
**Dr Kasha Singh**

### I. Sites

The REMoxTB trial included three sites in Tanzania, South Africa and Zambia. In June 2006 approval for a TB Alliance collaboration was sought. An amendment was made at this time, with the second phase III study included with the isoniazid substitution, as well as the original arm with an ethambutol substitution.

The arrow was brought in for support. The aim was to recruit all patients for the trial within 12 months, necessitating three new sites in Nairobi (Kenya), Cape Town and Stellenbosch (South Africa). Study evolution continued; regulatory approval and developments of drugs and packaging is mostly all done, with the development of a database at each site, site preparedness and recruitment to be done.

The trial has become complicated and multi-faceted, because we have a wide range of sites and different clinics involved. UCL in London and TB Alliance, based in New York are also involved.



### 2. Local development

There have been a lot of opportunities for training and development on site. At one of our clinics in Zambia we have been able to develop the facilities and all staff are GCP trained and have had training in clinical trials and protocol.

### 3. Staff

There are PIs at each site. Prof. Stephen Gillespie is the chief investigator, supported by Prof. Andrew Nunn at the MRC, and further PIs based in London. EDCTP and TB Alliance are also involved.

### 4. Conclusion

Hopefully the first patient will be enrolled by November 2007, with the first studies starting in Durban and Lusaka, and the other centres following within the next six months. I would like to thank all those involved.

### 5. Discussion

One participant congratulated the first presenter of the session on her project, commenting that it was similar to EDCTP's sponsored project that he had with colleagues in Tanzania and Ethiopia, focusing on the treatment of HIV and tuberculosis with rifampicin and efavirenz. The starting point was the genetic differences between the two countries, but he did not think that the presentation had included those genetic aspects in her study. Having not heard of this study until the conference, he felt that the trip had been worth it and could possibly lead to collaboration. The first presenter recommended they talk about collaborating, noting that they were also interested in the genetics of the other drugs, where it would be interesting to look at the possibility of genetic polymorphisms.

The second presenter of the session was asked whether new infections or relapse formed part of her study. She confirmed that they did, and that there were specific treatment paradigms for each situation. She said that re-treatment would occur for those patients that relapsed within 18 months, with standard TB treatment irrespective of which regimen they were on in the first place. If the relapse occurred while the patient was still undergoing initial treatment, particularly in the last two months, some patients would only be on placebo, but they would not know who those were. Any patient with a positive smear would be put onto an active drug until further results were obtained enabling individual adjustments to be made. One participant asked whether there was a place for DNA fingerprinting. She confirmed that the information would be collected. A participant asked the second presenter what dose of moxifloxacin she was using, how the optimal dose was decided, and whether the recent findings of a 27% reduction

in the concentrations of moxifloxacin when it was given with rifampicin in healthy volunteers would influence her approach or the results in the long-term. She replied that she was not familiar with the details of the study, but if further relevant information came up they would take it into account. The dose of moxifloxacin was 400mg. A member of the second presentation's team commented that the safety data on the 400mg dose of moxifloxacin per day showed that with increases in the dose the side-effect profile also increased. One participant asked whether there was a risk of cross-resistance when moxifloxacin was used for TB, and asked whether, if moxifloxacin and rifampicin were used together, there was a toxicity problem. The presenter thought that was a possibility, but as far as she knew to date, there had not been an extensive development of resistance to moxifloxacin. However, given that it had not been approved for TB she did not know whether there had been systematic surveillance. She said that she was unaware of evidence of increased toxicity where both moxifloxacin and rifampicin were used. One delegate asked what the cost issues were in connection with moxifloxacin and requested further indication of possible toxicity in contra-indications. The presenter said that in wider cost issues there were commitments to make moxifloxacin available. In terms of toxicity in contra-indications, allergy was not common, tendinopathy and arthropathy were a risk, but did not affect too many patients. Severe liver failure was a relative contra-indication, but those patients were excluded from the trial. As far as the presenter was aware there had not been instances of congenital malformations, but the drug had not been trialled properly in pregnancy and so pregnant patients were not included. A representative from the Global Alliance for TB Drug Development said that Bayer had undertaken to make moxifloxacin affordable and accessible. Bayer were also strongly considering incorporating it into a fixed dose combination, which would always be used with other compounds. One participant asked whether the panel would continue the use of moxifloxacin in children if the results were good. The presenter said that they would like to extent treatment, if the results were good, but she was unsure about using a quinolone in developing bones and joints.

### III. Two Interferon Gamma Release Assays and Tuberculin Skin Test in the diagnosis of Mycobacterium tuberculosis infection and disease in The Gambia

**Ifedayo Adetifa**

**Bacterial Diseases Programme, MRC (UK) Laboratories, The Gambia**

#### 1. Background

- The tuberculin skin test until recently was the only diagnostic test for latent TB infection (LTBI)
- In recent years, the interferon gamma release assays (IGRA) that measure interferon gamma released by sensitized T-cells, have been developed for the diagnosis of LTBI and provides a means of identifying and tracking short lived effector T-cells responding to specific TB antigens.
- IGRAs differ from each other mainly with respect to the technique of IFN- $\gamma$  detection (enzyme linked immunospot; ELISPOT vs. enzyme linked immunosorbent assay; ELISA) and the samples utilised (peripheral blood mononuclear cells vs. whole blood)
- Two interferon gamma release assays (IGRAs) are now licensed for the diagnosis of LTBI
- The T.SPOT.TB® is ELISPOT-based and uses PBMCs while QuantiFERON-TB Gold® is a whole-blood ELISA test
- The IGRAs, now available as standardised assays are being evaluated in a variety of settings leading to an increasing body of literature supporting their use
- But there remains insufficient data on test performance in high risk groups such as children
- We had previously compared an in-house IGRA to TST in children across a sleeping gradient of exposure to an index TB case and found it slightly less sensitive than TST in diagnosis of LTBI from recent exposure.

#### 2. Objectives

##### Hypothesis:

The diagnostic performance of two commercial IGRA assays compared to the TST across a TB exposure gradient is equivalent in Gambian adult and childhood TB contacts.



## Objectives:

- To evaluate the response of the TST, T-SPOT.TB and QuantiFERON TB Gold In Tube (QFT-GIT) tests in childhood TB contacts across a gradient of sleeping proximity to an index case
- To estimate the sensitivity of all tests in smear positive TB cases.

## 3. Methods

- Sputum smear positive TB cases aged  $\geq 15$  years were consecutively recruited
- Contacts aged 0.5-14 years who have lived for  $\geq 3$  months in the same compound as the case were also recruited
- They were excluded if they had been treated for TB in the past year or diagnosed with TB within a month of recruitment
- Written informed consent was obtained from all subjects
- Blood samples taken for both IGRAs, HIV testing and TST given
- Ascertainment of exposure
  - Tuberculosis contacts were categorized according to where they slept in:
    - the same bedroom as the case,
    - a different bedroom in the same house, or
    - a different house in the same compound.
- Procedures
  - TST was done with 2 TU PPD RT-23A TST, A 10mm cut off was used. Fieldworkers who gave this test were blinded to lab results
  - All commercial assays were performed and results interpreted according to the manufacturers instructions. Lab personnel were blinded to subjects status and TST results.

## 4. Preliminary results

- 385 subjects recruited, 100 cases and 285 contacts
- The sensitivities all tests in TB cases were
  - 82.8% [95%CI 81.5-94.9%] for T-SPOT.TB,
  - 85.4% [95%CI 81.4-95.8%] for QFT-GIT
  - 66.7% [95%CI 46.3-87.0%] for TST
- The prevalence of LTBI by
  - TST, 26.5% [95%CI 21.0-32.0%]
  - T-SPOT.TB 27.3% [95%CI 24.2-36.1%]
  - QFT-GIT 34.1% [95%CI 27.0-41.5%]

## 5. Agreement/Discordance Analysis

The agreement in contacts between

- T-SPOT.TB&QFT was 83% ( $\kappa=0.60$ , discordance  $p=0.05$ )
- TST&QFT-GIT 75.5% ( $\kappa=0.44$ , discordance  $p=0.006$ )
- TST&T-SPOT-TB 73.3% ( $\kappa=0.43$ , discordance  $p=0.0003$ ).

The agreement in index cases between

- T-SPOT.TB&QFT was 85.3% ( $\kappa=0.27$ , discordance  $p=0.76$ )
- TST&QFT-GIT 88.9% ( $\kappa=0.72$ , discordance  $p=0.37$ )
- TST&T-SPOT-TB 59.1% ( $\kappa=0.1$ , discordance  $p=0.09$ ).

Effect/influence of BCG vaccination

- T-SPOT.TB: OR 1.3 (0.7-2.4),  $p=0.43$
- QFT: OR 1.1 (0.6-2.2),  $p=0.77$
- TST: OR 0.7 (0.4-1.4),  $p=0.35$

Effect/influence of sputum smear grade in TB case

- T-SPOT.TB: OR 1.0 (0.5-2.2),  $p=0.97$
- QFT: OR 1.6 (0.7-3.9),  $p=0.28$
- TST: OR 0.9 (0.4-1.7),  $p=0.67$

## 6. Conclusions

- The detection of LTBI was similar with all 3 tests although the QFT tended towards more positive results
- All 3 tests responded to the *M. tuberculosis* exposure gradient but significantly so for TST and TSPOT compared to QFT
- There was good concordance between T-SPOT.TB and QFT but significant discordance between TST&T-SPOT-TB and between the TST&QFT-GIT
- The IGRAs have much better sensitivity in TB cases compared to TST but sensitivity in all tests remain suboptimal for the diagnosis of TB
- These results do not support the replacement of TST by IGRAs for diagnosis of LTBI in The Gambia.

## 7. Future perspectives

- Need to understand the nature and reason for discordance between IGRAs and TST
- Evaluate the utility of IGRAs as biomarkers for treatment or vaccine efficacy
- What is the value of IGRAs in predicting progression from LTBI to TB disease?
- To understand test and biologic variability.

## IV. RUTI: A New Therapeutic Vaccine to Shorten the Latent Tuberculosis Infection Treatment

**Dr Pere-Joan Cardona,  
Institut Germans Trias I Pujol Unitat de  
Tuberculosis Experimental, Spain**

### I. Rationale

Latent tuberculosis infection is a mixture of the latent bacilli made at the beginning of the infection, with an induction of necrosis, the induction of the specific immunity that made the latent bacilli, and then a constant reactivation of the bacilli. Treatment can stop this constant reactivation and allows the training of the bacilli from the host, stopping the risk of reactivation.

This is the core granuloma, this is the lymphatic ring, and these are the foamy macrophages that go through the available spaces. This slide shows one aspect of the foamy macrophages with some bacilli. At the chronic stage of the infection you are not going to see any acid-fast bacilli at inside the granuloma, but outside.

We have developed this vaccine RUTI, which is made by fragments of *M. tuberculosis* that have been cultured. That triggers a poly-antigenic response. When you do short-term treatment with chemotherapy you have a reduction in the foamy macrophages. When you stop treatment you have a reactivation from the latent bacilli that are still in the granulomas. When we inject RUTI we have a quick increase in the immunological response, which stops the reactivation of the bacilli.

This poly-antigenic response is against growing antigens related to growing bacilli and antigens related to the stationary phase of structural antigens. The three groups in black are all infected, the ones in red are those only treated by short-term chemotherapy, and the green group has been inoculated with RUTI after the chemotherapy. A lot of clinical experiments have been conducted. After the short-term treatment, and giving three shots of RUTI, we can see the effect. We could also see a lack of toxicity after the inoculation with RUTI in the guinea pig model.

### 2. Objectives

We want to demonstrate at the end of the clinical development that we can reduce the treatment from nine to six. We also use the short-term chemotherapy because it removes the foaming macrophages. You can see how after short-term chemotherapy the ring made by the foaming macrophages has disappeared. We have a paper comparing the infection between two strains of DBA. The susceptible DBA had increased bacilli account in the chronic phase, compared to the black one.

Looking at the granuloma, the chronic phase was mainly made by the foaming macrophages, which were in a higher proportion in the DBA case. It is therefore important to give short-term chemotherapy, because the vaccination will not be effective in the presence of foaming macrophages. You have a reduction of immune response, and with RUTI you avoid the possibility of reactivation by destroying the bacilli.

### 3. Methodology

We have already started a phase I trial in Europe. The methodology is within the usual parameters. We have increased the dose of RUTI in healthy volunteers, to 200 micrograms. We have also done a double-blind and controlled trial. We have been following these people for 168 days, and have also checked for neurological responses.

We started with groups of six people, checking for toxicity one week before the second inoculation. After three further weeks we decide whether to scale up the doses, and so on. So far we have injected the second dose of 100 micrograms.

### 4. Results

So far we have had really low toxic effects, with fever in one case. Unofficially the third dose has not resulted in any toxic effects. Two people received placebo, and we do not yet know who they are.

### 5. Future perspectives

We intend to run a European trial at the end of 2008 in HIV-negative and HIV-positive people. Trials in South Africa will start in the second half of 2009. A phase II trial will take place in Europe and South Africa in 2010.

## 6. Discussion

One participant asked what the exact composition of RUTI was and how it was made. The presenter said that it was made by MTB culture in stressful conditions.

One participant asked about the measurement of the immune responses, and asked at what point they were done. The presenter said that they had eight points, but that he had only shown the results from one week after inoculation. The measure was to look at whether the infection was going to reactivate or not. The participant asked whether they were going to take the trials to Africa, and whether exposure to mycobacteria would have any impact or would interact with the vaccine and, if so, how they intended to guide against harmful effects. The presenter said they were going to start with already infected people, both HIV-positive and HIV-negative, to see whether it was safe or not.

Another attendee asked what the role of RUTI would be in Africa. The occurrence of latent TB was very high, up to 95% in some place, and because of HIV and AIDS it was difficult to diagnose latent TB. A second attendee asked whether RUTI had been tested as a protective vaccine, and questioned the mice model of latency, because mice did not get a natural latency. In answer to the first question, the presenter said that the treatment of latent TB in Africa would only focus on HIV-positive people, who were the WHO's main target. The presenter explained that they had established that RUTI had a protective effect in mice, and were moving to test it in guinea-pigs. He said that they had started from the chronic model of TB in mice, but did not use chemotherapy as part of the model, because that meant losing the foamy macrophages. That was why they considered the model with six-week infected mice. The presenter explained that mice would never develop a cavitory lesion, which meant that mice had a weak response against *M tuberculosis*. Therefore, if something positive was seen in mice, it would be even better in humans. Working with mice and guinea-pigs also enabled them to establish whether there would be a toxic effect in larger animals.

One of the panellists responded to a question regarding the moxifloxacin regimen for children. He said that quinolones affected the growth plate in growing children, which had shown to be irreversible in animals. After five or 10 days of fluoroquinolones treatment children reported joint pain. Therefore, it would not be used on children in the future.

## V. Evaluation of Diagnostic Tools used for TB Diagnosis in Ibadan, Nigeria

**Dr Aderemi Kehinde,  
University of Ibadan, Nigeria**

### 1. Objectives

The main objective study is to evaluate the smear microscopy and culture as diagnostic tools for TB diagnosis, as well as to provide a baseline data on laboratory diagnosis of pulmonary tuberculosis (PTB) in Nigeria.

### 2. Methods

The study was laboratory based, carried out between April 2005 and May 2006. Three sputum samples were collected from new, confirmed PTB patients from various clinics in Ibadan. The samples were collected and processed for acid-fast bacilli (AFB) using the hot Ziehl-Neelsen (ZN) methods. The known AFB slide and the slide made of egg-albumin were used as positive and negative controls. The results were read according to the grading system of the International Union Against TB and Lung Diseases. One of the sputum samples was then cultured on Lowenstein-Jensen (L-J) slope incubated at 37 degrees centigrade for six to eight weeks. The microbacterium tuberculosis strain H37RV and sterile L-J slope were used as positive and negative controls respectively. Growth on L-J medium after eight weeks was identified as *M tuberculosis*.

### 3. Results

The results obtained were that for the period 1,120 sputum samples were processed, 80 of which were found to be AFB positive, with a lower percentage positive for culture on the L-J medium. The association between AFB positivity and culture positivity was not statistically significant. Sixteen of the specimens were found to be AFB negative, while positive on the L-J medium, while eight were screened AFB positive but culture negative. Only 40 were found to be positive by the two tests, while the majority, 1,056, were found to be negative by the two tests. Culture contamination was 8.8%, that is 99 out of 1,120, and they were discarded.

#### 4. Discussion and conclusions

Nigeria is fourth in the WHO list of TB high-burden countries, and the WHO recommends smear microscopy as a diagnostic tool for detecting TB in poor resourced countries. The study found that 16 of the specimens were AFB negative, but culture positive, which might be due to the low numbers of AFB in the sputum, not detected by smear microscopy. It is cumbersome and laborious to carry out culture, and it also requires specialist skills. It also takes time to diagnose the patient as TB positive, leading to a delay in starting therapy. The delay in diagnosis may lead to dissemination of the disease in the community, especially in settings where microscopy is the only available diagnostic tool. The high contamination rates observed in the study show a need to improve the standard of testing, through quality assessment and proficiency testing.

#### 5. Future perspectives

There is an urgent need to strengthen TB reference laboratories in Nigeria to perform quality assured smear microscopy, isolation of the organism in pure culture, and drug sensitivity testing. These improvements would be achieved through laboratory capacity strengthening planned by the National TB and Leprosy Control Programme of the Federal Ministry of Health. The initiative will be funded through accessed TB grants from the Global Fund for AIDS, TB and malaria. I strongly believe that this will go a long way to ensuring that we make accurate diagnoses at the correct time, so that we can initiate therapy and prevent the dissemination of the disease in the community. We hope that this study will stimulate collaboration between the stakeholders and the centre, in order to fight TB.

#### 6. Discussion

One participant asked whether the study indicated that AFB smear was more sensitive than culture. The presenter thought that the study did not show categorically that AFB smear was better than culture, but that the results had shown there was a strong need to ensure smear microscopy could be done correctly, and also that there were situations in which smear microscopy might fail, for example, where there were HIV and tuberculosis cross-infections. He was asked what the role of HIV infection was, because it had changed the whole diagnostic algorithm. Cross-infection had altered the accuracy of present diagnostic techniques, and the participant asked whether the presenter had examined how the diagnostic

methods had worked in the HIV-positive and HIV-negative groups. He explained that they were not aware whether the samples came from people with co-infections or not, because the study was purely laboratory based. He thought that in TB and HIV-positive cases diagnosis was a big dilemma, because of the low number of AFB in patients' sputum, which might not be detected using smear microscopy.

## VI. Recruiting Volunteers to Participate in a Community Wide Preventative Therapy Intervention – South Africa

**Dr Smangaliso Ntshela,  
Aurum Institute for Health Research,  
South Africa**

### 1. Objectives

Gold miners were recruited in three provinces in South Africa. Having spent their day 14,000 metres underground they were tired and testy, making it hard to recruit them. The miners live in a hostel near the mine, but it is also difficult to talk to them when they are resting, because they are sharing their own stories, being from diverse cultures.

### 2. Communication strategies

The existing communication systems in the mine were used, as well as educational programmes. The underground public announcement system, enabling communication with the miners, was utilised, as was the PA system in the hostel. Additional communication strategies were employed, including slots in organised labour meetings and presence at mining briefing sessions.

### 3. THIBELA TB ID card

Each participant was given an identity card at enrolment. They did not want it to be known that they were participating in the study, and the only way to identify them was to give them a different card from their clock card.

### 4. Various information leaflets and posters

Most of the miners lived in the hostel, where everything, including food and water, was free. When they enrolled they were given a t-shirt and, on their second visit, a cap.

Leaflets and posters were distributed in the hospital, giving information on research ethics and TB. An adherence calendar would be given to all participants, so that they could mark off the number of days they had been taking the medication.

### **5. Incentive events**

The miners were bored most of the time, repetitively going underground and back up again to the hostel. Incentive events were held to gain their interest, and the adherence calendars were used in draws for prizes of small value.

### **6. Participant follow up**

Specific numbers of participants with specific study numbers were block paraded. Those that are block paraded are told they need to attend the study centre, perhaps because they have missed a follow up. A follow up roadshow is held, comprising education on general TB and encouraging people to enrol on the TB studies. Some gifts were given to the participants, for example, a water bottle at visit three. It had also been found that people liked to receive rubber wristbands, and participants would receive different coloured wristbands at each month's completion.

### **7. Month nine**

At month nine, the final month, all participants are given a big umbrella, sports bag or blanket as a thank you.

### **8. Results: month 12**

Three community advisor groups have been established, and four participant advisory groups, with 306 peer educators trained on THIBELA TB. A further 6,000 volunteers have been recruited to participate in the BPS, and 7,000 volunteers have been screened for TB and offered IPT.

### **9. Discussion and conclusions**

We concluded that challenges included time investment, stakeholder management, management of perceptions. As the volunteers came from different cultural backgrounds, there were a lot of misconceptions as well as different language barriers and differing literacy levels.

### **10. Future perspectives**

Future initiatives included the emphasis of key messages in local languages, reinforcing individual contact, deploying leadership examples. We want to train the miners into

understanding TB, because advocacy around TB is very limited. Future plans were also made for using printed material in collaboration with the provincial and national government, electronic media, group communication and incentives. However, it was still the case that participants in trials were not being treated as equal partners.

## **II. Discussion**

One participant asked how the study justified the incentives given to the participants in terms of clinical research. The presenter said that they did not want to employ coercion and nor did they want to over-incentivise the participants. They wanted to give something practical, but not monetary, that the volunteers could use in their lives.

An attendee asked the presenter what he thought the real reason for the volunteers taking part in the study was, and how they set the limit as to what they used to incentivise the volunteers. He also asked how they handled negative rumours. She said that it was very difficult to handle rumours, because it was a highly politicised community, with a significant amount of illiteracy. Focus group discussions helped to determine ways in which to communicate.

Poster messages were used to answer misconceptions, slots were used in mass meetings, and they also attended the miners' induction meetings. The miners had a weekly newsletter in which THIBELA would write articles dispelling misconceptions. THIBELA's own newsletter, which was issued in the local language, would detail frequently asked questions. The presenter said that no coercion was employed to keep volunteers in the study, and if they had any ill feelings regarding the research, they could go to their health and safety representatives.

The presenter was asked whether the branding worked to make the trial more acceptable and encouraged people to participate. He thought that the branding had helped a lot. The participants were working in an industrial environment, where everything they were using was branded, and therefore they did not feel as if they belonged to things that were not branded. She felt that it helped, because it showed who was taking part in the trial, and others were encouraged to join when they saw the t-shirt and caps that were given out to participants.

One attendee asked whether a study could be undertaken to find out why people had decided to take part in the trial, and asked the presenter whether he could speculate on those reasons. She said that they had mandated another



organisation to conduct a study to understand why the miners were participating in THIBELA. Some said that they had seen their colleagues die and be taken out of work due to TB, and wanted to fight the disease, which they understood could be done through THIBELA.

One commentator expressed concern at rewards that were given to patients for reaching various stages, rather than merely compensating them for expenses. Another attendee commented that it was not considered unethical to pay people to take part in trials in the US or Europe, and did not see

why it should be considered unethical in the Gambia. It was commented that there was an important point around when compensation became paying somebody to take part in trials, especially in Africa. It was felt that participants had to be compensated, because otherwise people would not take part in trials, but that the main point was whether people were happy and not being exploited. The presenter commented that in giving people t-shirts showing their participation in the trial was helping to de-stigmatise the disease.



# Building Bridges – Networks of Excellence (Keynote Speeches)

**Chairs: Simon Agwale (EDCTP DCCC),  
Peter Smith (EDCTP PB)**

## An Update On African AIDS Vaccine Programme (AAVP)

**Dr Souleymane Mboup,  
CHU Aristide le Dantec, Senegal**

### I. Background

#### 1. Foundation

AAVP was initiated in June 2000 in Nairobi through a meeting of African researchers, via a declaration appealing for an African AIDS vaccine. This programme was later adapted during the Abuja summit and has now been endorsed by other organisations.

#### 2. Vision

The vision of the programme is to create an AIDS-free Africa through an effective vaccine. The stakeholders of this network are all committed to achieving this goal through research, advocacy, partnership, capacity strengthening and policy development – goals similar to EDCTP's.

#### 3. Objectives

The main objective is to develop advocacy strategy and communications tools for HIV vaccines. It also wants to develop a network of people and institutions, and promote candidate vaccines appropriate for Africa.

### II. Strategy

AAVP has been through some recent changes following successes in a number of areas and support for continued activity. There were also many opportunities for the African organisation to take a leadership role, and a need to restructure the organisation to make it more functional.

However, AAVP wanted to keep its identity – located in Africa and led by African scientists. AAVP is a central platform providing support, global representation and equal partnership in the vaccine area, contributing to creating a supportive, normative environment in which all phases of HIV vaccine trials can take place to the highest scientific and ethical standards in Africa.

### III. Partnership and Principles

The network partnership includes both internal and external stakeholders and involves all relevant development agencies, even non-HIV programmes, with open collaboration and complementarity. It will also share resources, capacity, experience and information, partnering with other initiatives for funding opportunities.

### IV. Structure

It is structured to allow several working groups to focus on specific areas, but it is now envisaged that the type of proposed AAVP work should influence the structure to give greater operational efficiency, and ensure transparency and accountability. The AAVP collaborating centre has been created to formalise the thematic groupings. The strategic plan divides activities into five areas, each of which include the same elements of our strategic direction.

### V. Biomedical Collaborating Centre

The biomedical centre has as its main objective to evaluate and identify needs and priorities, through assessment, information from partners and exchange of experiences. It can then develop networking between countries, institutions and initiatives, strengthening existing networks instead of creating new ones. We also want to strengthen capacity building through workshops and short-term training on current technologies, laboratory management and quality control. Another objective with EDCTP is to implement a database of clinical trials in the region. This is not a located centre; it is virtual, coordinated through Senegal, but already affiliated with two other centres in Uganda and South Africa.

## VI. Forums

AAVP also has different forums to bring together all our African partners and international scientists. We think there is more potential for collaboration through implementation of national vaccines, working together on advocacy and policy issues, capacity building, training and targeted research.

### ► Questions and Answers

#### I. Funding

A PB member from the UK enquired about the level of funding AAVP receives. The presenter explained that most of its funding came from CIDA and WHO, estimating this at around €10 million, which is used to involve many different centres through its networking efforts. He was also asked about current research opportunities, and answered that activities are limited until the next funding round in February 2008.

#### II. Collaboration

One participant had noticed many areas where AAVP overlaps with EDCTP's work. He asked how the presenter thought the two organisations should work together. The presenter thought this easy, as many of the same people were involved in both organisations, so were well aware of their specific activities. AAVP had the potential to help EDCTP access clinical trial sites in Africa. However, its secretariat was still based in Vienna. The Executive Director of EDCTP asked when it was coming to Africa. Souleymane explained that this programme was initiated by WHO with the plan for it to use existing potential. It now exists outside that construct, however, so can move within the next two years.

## Malaria Clinical Trials Alliance (MCTA)

**Dr Bernhards Ogutu,  
Kenya Medical Research Institute**

#### I. Background

MCTA as a programme has existed in the INDEPTH Network for a year and a half so far. It is a data platform to disseminate informed policies on population dynamics, from which one can evaluate interventions to generate required data in a short period of time in order to make the decisions necessary to inform policy.

#### II. Clinical Trials

##### 1. Challenges

The field sites that exist in Africa are not fully owned by the African community, which is where we are trying to bridge the gap. Needs for clinical trials are massive, for infrastructure, personnel, and to update them to meet ever-changing regulatory requirements. In Africa, you have to deal with many challenges, like setting up ethical review committees to support each trial you want to do. MCTA is trying to put in place an infrastructure to facilitate a major leap into phase III malaria studies.

##### 2. Requirements

We require 10 sites to support a study of 16,000 children next year. This needs much-wanted personnel and technology across seven different countries, and a lot of coordination. We have to upgrade and equip to ensure there are more resources available in the malaria vaccine and drug development fraternity. That is where MCTA is trying to bridge the gap.

#### III. Aims

##### 1. Capacity building

When MCTA was set up four years ago with funding from the BMGF, it aimed to develop short-term capacity for sites to facilitate the trials already going on. We work with sites

by reviewing their strategic plans and setting out where they want to be in the future.

## 2. Trial sites

Our main secretariat is based in Accra within the INDEPTH Network. We also have a satellite unit in Nairobi to map alliances across the continent. As we move on to phase III trials, we need to add more sites. We do not have much activity on drug trials, but expect more as products move on to phase II. We have currently been auditing sites to understand their development needs, and are trying to work on how we can make them more capable. We are also trying to ensure the ground personnel can meet the tasks ahead of them.

## 3. Training

We are involved in a range of training activities and have spent a lot of time on microscopy. AMANET has been leading this effort. No donor is willing to invest in the financial management of sites, so we also need to address training on how to manage money as well as clinical techniques. Sites should receive money directly into their African accounts, rather than being sent offshore to their partners. In the next two years, we hope that all sites have at least one certified clinical trials coordinator and certified investigator to ensure people talk the same language. We have an examination centre in Nairobi, where the first examinations took place in September 2007. Another area that has also been neglected is media training, which creates the link between the media and scientific communities.

## IV. Activities

### 1. Funding

In moving to phase III, we have to install digital X-ray machines to distinguish between deaths from pneumonia and malaria. This requires money. We have allocated funding to several sites, mainly focused on infrastructure development.

### 2. Workshops

We have organised several workshops to help provide accreditation at a lower cost for a number of sites with which we have been working. We have set up a training centre in Kisumu and aim to set up another in Ghana. We want our

microscopy centres to be housed in the African study sites, not somewhere unrelated. We are trying to use established sites to develop others by creating short-term attachments from one to the other.

## 3. Strategy

We have ensured that each site has a strategic plan spanning five to ten years, which will determine their funding stream so that they can achieve their ultimate goals. We are working with the WHO to start an accreditation system for microscopy as well, and want something similar for clinical research coordinators and database managers, too.

## 4. Partnership

We are asking senior scientists to partner with these sites to help them meet their strategic plans. Long-term, we want these sites to remain research centres for the future, which means they have to diversify beyond clinical trials and to other diseases for sustainability. We are still seeking more partners and building linkages with the industry and other members working within clinical trials. That is why I am here: to ensure our partnership with EDCTP moves on and we are supported in the future. MCTA needs your support to bridge the gap and ensure Africa becomes the hub for clinical trials in the next few years.

## ► Questions and Answers

### I. Evaluation

The presenter was asked what evaluation systems were used to assess clinical trial sites' performance. He said that site visits were carried out. If they are failing, they will be given new targets to meet; if these are not met, sites will be removed from the network and funding withdrawn.

### II. Funding Strategies

The next question was: what percentage of funding comes from African governments? The presenter explained that MCTA's ambition was to meet the head of state for each country where a new site opens to lobby on behalf of that site. One voice wanted to add a note of caution about how funding was obtained, believing that appealing directly to



heads of state was an unstable strategy as money could quickly be withdrawn. Various regional and institutional bodies have a better notion of their responsibility to promote sustainable trials. However, the presenter was hoping for closer engagement between sites and ministries of health in order to leverage funding.

## Microbicides Development Programme (MDP)

**Dr Sibongile Walaza**  
**Reproductive Health Research Unit,**  
**Johannesburg**

### I. Outline

The Microbicides Development Programme (MDP) is a collaboration between European and African partners to conduct phase III trials in microbicides across four African countries. It is funded by DfID and managed by the Clinical Trials Unit from the UK MRC.

### II. Partnership

#### I. Responsibilities

Our European partners include the London School of Hygiene and Tropical Medicine (LSHTM), the University of Southampton, which is doing community work and the University of Barcelona, which is responsible for social science. All partners have an input on scientific



decision-making. All African partners have been involved in protocol development, data management and analysis. They also have an impact on financial budget management, and sit on the programme management board executive committee, which meets to review progress on a quarterly basis.

#### 2. Local communities

As part of the feasibility study, the sites mapped their communities to decide who the stakeholders are, and involved them to explain what they were planning and ask them how to go about it.

#### 3. Oversight structure

The programme management board of institutional partners meets on an annual basis to review the programme's progress and assess financial returns. The programme liaison group reviews the scientific results of studies and allows questions to be put to different sites. The international scientific advisory group is formed from independent members to provide strategic advice to the management board. The data monitoring committee is responsible for participant safety and advising on the need for additional interim scientific analysis.

### III. Activities

#### I. Objectives

Our overall objective is to complete phase III efficacy trials into candidate microbicides in Africa by determining scientific mechanisms of action and conducting preclinical evaluations. We also carry out social science research into the acceptability of products questioning, for example, whether women should tell their partners about microbicide use. Capacity building between African researchers is another aim, as well as facilitating marketing and access of successful microbicides.

#### 2. Pre-studies

The programme engaged in pre-trial activities between 2001 and 2005. The different sites carried out feasibility studies to look at the incidence and prevalence of HIV and other STIs, as well as their ability to recruit and retain women in cohorts. All sites carried out a one-month pilot study, in which women were given a placebo gel to use to assess its acceptability and test the tools and activities for the phase III trial. The

feasibility studies allowed most sites to establish how many people they needed to recruit according to HIV prevalence rates. The programme decided on a nine-month endpoint for the main trial. Most sites have high HSV2 positivity, but this did not correlate with a history of ulcer reporting, except in one site where researchers were trained in soliciting answers from participants.

### 3. Phase III trial

We are currently conducting a phase III trial on one of the candidate microbicides, PRO2000, a naphthalene sulfonic acid polymer. We are recruiting close to 10,000 women in this placebo-controlled, double-blind study. The primary endpoints are HIV infection and safety. Secondary endpoints are other STIs. So far, we have recruited 6,000 women. The data monitoring team has met three times and identified no safety concerns so far. We are hoping to complete enrolment by July 2008 and produce our results by the end of 2009.

### 4. Progress

As I have mentioned, sites participated in the protocol-development process, but training is continuing. Studies into higher degrees are encouraged, and we have also developed a system of cross-site monitoring as a form of capacity building and training. We have received a grant from EDCTP for South-South networking to undertake a microbicide feasibility study in Mozambique and to improve the clinical infrastructure in Orange Farm. The Mozambique site is ready to start its study and training is taking place. As part of involving the community, we have set up ethics training for community advisory groups and also engaged them in research. The Johannesburg site has a weekly radio slot where we discuss issues of reproductive health, clinical research and medical ethics.

## IV. Summary

This is a comprehensive programme to develop, test and integrate an effective microbicide when it is available.

## ► Questions and Answers

### I. Sharing practice

A PB member from Sweden wanted to investigate what could be shared between the efficacy trials for HIV vaccines and microbicides. He asked what the cost of the PRO2000 trial was and what motivated MDP to move forward. The presenter believed the focus was different with microbicides, where the attraction was developing a woman-controlled preventive method. This meant that trials automatically had participants' support. She was unable to give a funding figure, but explained that pharmaceutical companies were not interested in supporting these trials because, in order to be successful, any microbicide would have to be accessible and cheap. The PB member added that vaccines were gender-controlled too: women can elect to vaccinate themselves.

## Research Capacity in Africa

### Dr Val Snewin, The Wellcome Trust

### I. Fellowships

The Wellcome Trust has a range of fellowship schemes for developing country scientists, covering all career stages. The award rate is relatively high, but the number of applications received remains low and geographically narrow in the countries and institutions applying. Not only fellowship schemes build capacity however; an attractive research environment, equipment and facilities create the energy and motivation to develop a research career. African universities need to be strengthened to provide this for African scientists.

### II. Health Research-Capacity Strengthening Initiative

#### I. Foundations

The Wellcome Trust formed a partnership with DfID to put £10 million each into a research-capacity strengthening initiative in Africa. We were joined by the International Development Research Centre (IDRC) of Canada. Following

a scoping mission, the team recommended setting up national task forces in Kenya and Malawi to develop programmes of work. These brought together quite fragmented and diverse communities and teams of researchers, involving the ministries of health and academic sector.

## 2. Aims

The aim of the initiative is to strengthen the generation and use of health research evidence, funding nationally developed plans through local organisations. The Kenyans are setting up a new NGO to undertake this, and Malawi is using its own national research council. The steering group is made up of funders and a secretariat, which give administrative support to the people developing the plans. The Wellcome Trust board of governors signed off the national plans in March, and is now monitoring and evaluating capacity-strengthening initiatives. We aim to share those evaluating and monitoring methods with other projects. After DfID approval, we can award funding based on agreed milestones and sign off the financial monitoring and reporting processes. We hope the initiative will also strengthen regulatory issues, coordination of the national research environment and facilitate key institutional academics working with government ministries.

## 3. Kilifi meeting

Developing this quite unusual initiative was a steep learning curve in listening more to what people in Africa were requesting. We aimed to take this more widely across the continent, so hosted a meeting in April 2007 to bring together a range of researchers who shared an interest in capacity strengthening in order to identify what was required within their own institutions. We wanted to hear their voices, and are grateful to our funders in working towards that aim. By the end of the meeting, we had agreed a menu of options and follow-up activities. This was nothing revolutionary, but an opportunity to bring activities together to work out how we could join up in a logical manner.

## III. Capacity Strengthening Aims

### 1. Menu of options

Feeding the pipeline of health researchers was key, as well as raising the profile of science and health research generally. Having a clear career path is also important. Supporting senior scientists was seen as a priority, as they act as role models and

bring in younger scientists. Grants and fellowship schemes could be locally devolved, as part of providing more support directly to African institutions, particularly universities, to develop themselves. Funders can drive change, providing it is in the right direction and led by African voices. Networks and partnerships are key to capacity strengthening.

## 2. Future activities

We agreed to meet again in Cape Town to assess progress, and also to map our research activities to share information about what researchers are doing. The Wellcome Trust has recently launched a call for proposals responding to the Kilifi meeting. Rather than focusing only on health research, we have broadened this to include administration, finance and leadership. We also hope to bring in expertise from other organisations, not just from the UK, but northern institutions where links already exist between partners around the globe. The call for proposals is launched and available on the Wellcome Trust website; the deadline is February 2008.

## 3. Complementarity

We hope this initiative will be complementary to EDCTP networks of excellence. It will mostly be focused on strengthening university research, although other areas are eligible to apply, whereas EDCTP is more focused on clinical trials. We hope a consortium of institutions will be developed, rather than bilateral links, acting as an incentive for research institutes to work with nearby universities. If you are interested in joining the consortium, please get in touch through the website, [www.wellcome.ac.uk/globalhealth](http://www.wellcome.ac.uk/globalhealth).

## ► Questions and Answers

### I. Collaboration

The Chair of the DCCC appreciated the synergy between the Wellcome Trust initiative and the EDCTP's call on networks of excellence. However, EDCTP also aimed to recruit universities to strengthen capacity. He wondered whether it was possible to pool resources, rather than have two parallel consortia forming in Africa, to expand on what existed. He also asked how much money was assigned to this activity. The presenter was unable to answer this question exactly, but saw this as a broad and diverse activity. In terms of pooling initiatives, funders are aiming for more clarity in the range

of activities available. The Wellcome Trust could join with EDCTP in marketing and explaining the range of possibilities for funding in order to avoid any confusion.

## II. Clarity

One participant was pleased at this opportunity to unite African institutions to discuss ways of building capacity. Africa needs indigenous institutions that focus on their own needs, are directed locally and only rely on external funding to a limited extent. It was agreed at Kilifi to build a forum to encourage such discussions and bring clarity to long-term research partnerships. A group of eight African researchers came together to help the Wellcome Trust develop its call for proposals and formulate the agenda of the Cape Town meeting, helping London ensure its aims are led by African researchers.

## III. Sustainable Funding

A concern about this sustainability came next, with a participant asking if the Wellcome Trust's initiative was fixed for the longer term. Without government funding it might not be viable. The presenter clarified that the call for proposals was for 10-year schemes, with funding released on a five-year basis, following approval. There have already been proposals put to African governments to increase the funding allocated to health research, but more pressure is required, perhaps best coming from development funders. The participant pointed out that the universities that the Wellcome Trust is working with already receive government support; it just needs to increase.

## IV. Networking

One participant asked why some African countries were not invited to the Wellcome Trust Kilifi meeting. The presenter explained that, before the wide involvement of African researchers, it had been difficult to establish who to invite. She was also aware at the Kilifi meeting that people in Africa did not necessarily know of research going on in their continent. There are activities to remedy this through the input of the Africa committee. She urged all listening to

engage more with the Wellcome Trust to ensure appropriate institutions were involved and their activities mapped.

## Africa Malaria Network Trust (AMANET)

**Dr Roma Chilengi,**  
**Clinical Trials Coordinator, AMANET**

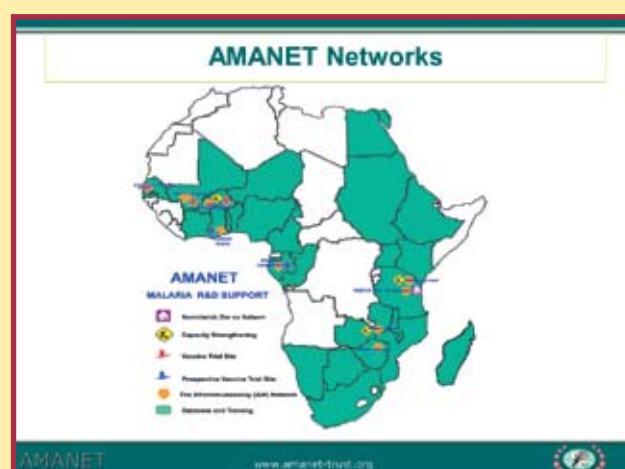
### I. Background

#### 1. Foundations

AMANET was established in 2002 as a network involved in capacity building and sponsoring clinical trials. It inherited the African Malaria Vaccine Testing Network, which had a much more restricted mandate. AMANET is registered as a not-for-profit organisation. It is run by a board of trustees and supported by a scientific coordinating committee, while a secretariat undertakes oversight activities. Our key activity is to build capacity to support institutions that were previously considered too weak to participate in trials. Our niche is in our ability to take responsibility to sponsor clinical trials, too.

#### 2. Networks

This is a network of institutions involved in malaria research across the African continent. We have sites for which we have provided capacity-strengthening grants, done vaccine trials or worked on immunoassays. From an inventory conducted at the outset, it was clear that only a select few institutions were able to meet international standards for conducting malaria



trials, and that these centres traditionally had strong links with the North. In the view of AMANET, this was problematic and did not meet the demand for trial sites caused by increasing pressure for malaria research. AMANET wanted to break this cycle by deliberately building capacity in centres that were qualified as incapable. To do this, we have to deal with issues of infrastructure, equipment and human resources.

## II. Capacity Development

### 1. Example

A key example is the CNRFP site in Burkina Faso, which was deliberately and directly supported by AMANET to the stage that they are now able to do vaccine trials. We supported infrastructure development there, refurbished the labs, bought equipment and trained staff.

### 2. Training

Besides the targeted capacity-building programme, we also embarked on a mission for short-term training in workshops to support clinical trials, where we perceived there were gaps in university teaching. These included issues of design and methodology of trials, data management, molecular biology and immunology on vaccine development, as well as trial sites' needs assessment and research ethics. We are proud to say we have contributed substantially to training over 1,000 African scientists. We also support long-term training, by enrolling staff from our centres in Masters degree programmes or PhDs.

### 3. Clinical trials

One of the key achievements of our programme is taking up the challenge of conducting and sponsoring clinical trials that meet international requirements. At the moment, we have four clinical trials for candidate malaria vaccines ongoing.

### 4. Ownership and sustainability

Another key aspect to our approach is developing self-sustainable centres, which requires sufficient technology transfer. Assays should not be sent out of Africa. We have tried strongly to reverse such an approach and establish enough capacity for centres to process the assays and ensure the quality of their results is acceptable. We also adopted a programme with the European Malaria Vaccine Initiative

to share immunological findings, and transfer findings and technology, across the continents. We are slowly working towards South-South mentorship and training, so the sites being developed now will take up opportunities to be attached to other African sites.

## III. Centralisation

### 1. The Afro-immunoassay network

AIA involved six laboratories in an effort to harmonise assays that evaluate responses to potential candidate malaria vaccines. We recently received support from Europe to bring this to the second phase of activities to expand and improve the work we have done, in the hope of establishing and harmonising our own assays.

### 2. Ethics committees

With the support of BMGF, we recently embarked on another activity for health research ethics capacity strengthening in support of malaria R&D. This started with a programme surveying institutions' ethics committees across Africa, some of which will receive direct support. We will provide formal training through workshops to ensure every member of these committees can work to develop harmonised operations and ethics procedures in Africa. Other activities include encouraging ethicists to make networks among themselves to exchange their ideas and debate case studies. There is a forum for individuals to access ethicists to help resolve their particular dilemmas. Another project we have started is a web-based health research ethics course, funded by EDCTP, which provides researchers with the opportunity for remote training. We are happy with our progress over the past year, and look forward to the next phase of this activity to expand web-based training for French-speaking colleagues and create courses in other areas.

### 3. Communications

Other activities are related to advocacy and the publication of our malaria-related trials. We circulate a newsletter biannually and hold scientific conferences. We are working on the African Malaria Research and Control Forum, which is a publication intended to bridge the gap between researchers and people who use the fruits of their research, by translating scientific findings in a way that allows more users access to them.



# Pan-African Bioethics Network (PABIN)

**Dr Abraham Aseffa,  
PABIN Secretariat**

## I. Background

### 1. Foundations

PABIN was founded at a pan-African conference by a group of health researchers in January 2001 and the forerunning organisation of AMANET. It is the African arm of the Strategic Initiative for Developing Capacity for Ethical Review (SIDCER).

### 2. Aims

One big activity in our strategic plan is for an overview of the existing situation regarding ethical committees. Other objectives are to develop competent in-country ethical review systems, to create a concerted African voice in international ethics discussions, to assist national authorities to establish national review systems and to contribute to the sustainability of such capacity by introducing ethical principles into university curricula. In general, we want to set up an interface between African and international researchers, and between African researchers themselves.

### 3. Membership

PABIN is composed of voluntary members who join as individuals. We have 324 members across 26 African countries. We are currently trying to establish national chapters composed of these individuals to strengthen local ethical review committees. PABIN's executive committee is composed of senior members from different countries. The active national chapters support local ethical review systems and try to generate their own support through establishing local links. One such activity is to translate WHO guidelines into local languages, and to host meetings that are relevant to national health issues.

## II. Activities

### 1. Meetings

Another major activity of PABIN is building forums. Our annual conferences have different themes, such as contemporary problems or the Millennium Development Goals. The forum in Yaoundé met at the National Assembly there and sat with parliamentarians.

### 2. International recognition

One other relevant activity is what we are doing in the SIDCER recognition programme, which aims to strengthen ethical review committees to such a level that they are internationally recognised and acceptable. Monitors are sent from outside to look at ethics committees' activities. If we are accepted, we will be added to the SIDCER homepage, which currently does not feature any African countries.

### 3. Training

Another aim of PABIN is to develop capacity in ethical review by sending African researchers for hands-on training at the Western Institutional Review Board.

## III. Challenges

### 1. Funding

Fundraising has been challenging, but EDCTP has recently added their support, as has BMGF. We have been trying to leverage support through brokerage activities. The challenge is still funds.

### 2. Constitutional matters

National chapters are not proceeding as much as we had hoped, as we still need to stimulate people to register them through voluntary organisations. The constitution of PABIN is composed of regulations or bylaws that give rights to general assembly members, but it has been very difficult to bring all members to one assembly, so the constitution has to be revised to give powers to national chapters rather than individual members. This has created some difficulties recently.

### 3. Independence

Another major challenge is the dedication and commitment we hope to receive from African members. We need to keep

stimulating those grassroots voices as we strive to remain totally independent. PABIN seeks the support of granting agencies that are interested in building independent ethics initiatives.

#### IV. Next Steps

The next general assembly is scheduled for October 2008. The call is out to bring together more members, modify the constitution and make more progress for PABIN.

### ► Questions and Answers

#### I. Achievements

The first question addressed PABIN's achievements so far. Where, for example, had it been able to integrate ethical teaching into university curricula? The major focus of PABIN's activities is encouraging universities to work on this themselves, answered the presenter. In Ethiopia, a bioethics unit has been established within the medical faculty, and other universities are starting to do the same. Generally, however, PABIN has not achieved much and still has more to do, as it works to define where it should most focus. The structure is not rooted strongly enough to facilitate implementation. Activities are growing faster in Ethiopia and Cameroon, because of their cohesive local chapters. They bring together engaged and interested individuals to contribute to local capacity. Once activities start rolling, more funding becomes available and motivation stays high.

#### II. Social Connections

Next the presenter was asked to clarify how the initiative involved non-medical partners interested in human rights, like the clergy, lawyers and human rights campaigners. He agreed that local capacity building had to include social science elements; however, he was focused on ethical review for health research, not general ethics. The continental/national structure aims to involve local governments to support ethics activities. In meeting that aim, members of parliament are involved in PABIN's conferences and forums are held in government buildings.

### III. Francophone Involvement

The Executive Director of EDCTP noticed that PABIN's membership did not include many Francophone countries. The presenter said the executive committee would be the first to admit this weakness, although this committee itself included some Francophone members. It is not that there was no inclusion, but that the mechanisms for communication meant that not everything was translated. Abraham hoped this could quickly be solved by recruiting a bilingual coordinator to the secretariat. However, he also cautioned against dividing Africa according to language or region; ethics discussions must be pan-continental. The emphasis of the initiative is for diverse, independent, grassroots activities bringing together a cohesive African voice. There are multiple players in the ethics field, but PABIN, as an umbrella organisation, can facilitate their networking.

### The Vienna School of Clinical Research

**Dr Christa Janko,  
The Vienna School of Clinical Research (VSCR)**

#### I. What Change?

I will share thoughts and ideas about training, education and networking, with reference to the experience the VSCR has had in collaboration with African experts and researchers in the context of EDCTP. A precondition and the key to success in medical progress is investment in people skills. It is time to make a change here. Who has been involved in clinical trials over the past decade?

[Show of hands]

Almost everyone here has been involved in clinical trials.

What was the process of your training? Did you know from the very beginning what it was about or, like in many cases, did you learn by doing, depending on the commitment of supervisors and co-workers to do things right? That was the past; we now have to embark on new approaches to make clinical research a real discipline.

## II. Principles

### 1. Research

What is the right approach to training our clinical researchers most effectively? I believe it is about ethics. Clinical research is a very complex area and involves different methods, procedures and goals across many stakeholders. 'Ethical' to me means that any research project first of all must consider patient protection. They must be based on evidence, and the research question must be built on what is already known in order not to waste resources and patients' time. Clinical research must be delivered by qualified people capable of good scientific practices, who can formulate, design and initiate clinical trials that follow these principles. Quality is another issue, as the most promising idea may fail if a study is not carried out reliably. Another issue of importance is making your findings public, so that future studies can benefit from your results. We have to stop research that is not based on these principles and focus our limited resources on doing these things right.

### 2. Training

What is the best approach to training? Who do we want to train, when and how often? What are the most suitable training topics? Where should this take place and how should it be delivered? Discussions are ongoing about whether classrooms are the best approach or whether distance learning is preferable. We hope to train people before their involvement in research starts, but we also recognise that continuous training should be part of research. How do we certify those who have had the required training from those who have not? My institution is still considering all these concepts.

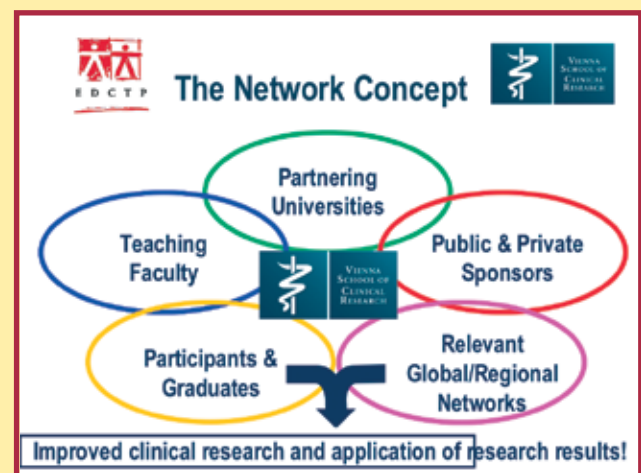
### 3. Knowledge transfer

We see our mission as promoting exchange and the transfer of knowledge across countries and disciplines. We are trying to disseminate common principles to follow, irrespective of where the trial is conducted. However, we also consider the unique qualities of different settings. In the context of EDCTP's goal for sustainable capacity building, we are trying to look for strong local partners and to build sites on a long-term basis. Our ultimate goal is to build clinical capacity to the extent that the VSCR is no longer needed.

## III. Methods

### 1. Networking

We aim to be a public-private-academic partnership, with faculties built by academia with participants and funders from all sites. We focus on our principles to initiate dialogues, and put these into the context of particular trials, countries or ethical review systems. We also take the 'inter' approach: we want to be international, interdisciplinary and use an interactive training style. Whenever we go into a country as an institution we look for strong local experts to maintain the high levels of expertise necessary to do advanced research.



### 2. Partnership

We partner with numerous universities, which advise us on content and recommend speakers and trainers. At the same time, part of our mission is fundraising, which we use to grant scholarships to academics, clinicians and physicians to access our courses. Our teaching faculty is open and can be adjusted to the audience and the topic. We network to keep up to date with what relevant organisations are discussing, including African bodies. We have been using speakers from AMANET, for example. We want to see our graduates come back as teachers and trainers, within and outside VSCR, to disseminate their learnings and knowledge. The educational programme consists of a number of short courses and is meant for people in full-time jobs. These short courses are standalone and may be taken based on need. At the same time, packages of these courses can be put together to qualify

as diploma programmes. As of next year, we will offer a Master of science medical research degree.

### 3. Future aims

With EDCTP, we have had some activities in African countries as well as African experts visiting Europe to run courses. Overall, more than 300 clinical research experts from sub-Saharan Africa have attended courses at the VSCR. We are interested in participants becoming and remaining members of an international network of clinical researchers, and want to build and strengthen clinical research sites, seeing our graduates as multipliers of knowledge. By building a strong network and an elite group of researchers, with shared understanding, we may spread across sites, countries and research institutes to fight the diseases that are such a burden to the people of Africa. A new generation of clinical researchers will take us forward.

## ► Questions and Answers

### I. Local Needs

#### 1. Training

The PB member from Senegal backed the need to transfer expertise to ensure sustainability. The presenter explained how local trainers were used in research institutions, which VSCR would sponsor in order to install processes that were maintained and controlled by local people. However, she hoped a certain amount of exchange would remain between the North and South, through trainers visiting one another's locations.

#### 2. Support

The MIM coordinator asked what weak institutions had to do to gain VSCR's help. The presenter thought that strength came more from people and their enthusiasm, than from any institution itself. Her approach was to develop people to make them aware of their local needs and able to fight for them. Training centres can thus gain VSCR's support when there are sufficient numbers of people capable of turning their centre into a hub for excellence.

### II. Networks

In concluding, PB member from the UK emphasised that the linkages between many of the networks discussed need to be carefully coordinated and strengthened.

[Electronic Poster Sessions]









# HIV/AIDS Capacity Building in Africa

**Facilitator: Michel Klein (EDCTP PB)**

**Rapporteur: Walter Jaoko (EDCTP DCCC)**

## I. Development and Evaluation of an Affordable HIV Viral Load Assay for Use in Resource-limited Settings

**Dr Abraham Alabi,  
Viral Diseases Programme,  
MRC Laboratories, the Gambia**

### 1. Background

Due to increased resources in recent years, more people in resource-poor settings now have access to ART, but despite this improvement there are treatment challenges. One of these is the high cost of treatment monitoring, trained personnel, and lack of infrastructure, resulting in inadequate immunological and virological monitoring of patients on ART. We have to meet that need. Direct virological monitoring is achieved by measuring HIV viral load. However, there are limitations of commercial viral load assays. Firstly they have a high cost; secondly, we need adequate infrastructure and expertise, and thirdly, there are subtype variations, and both HIV-1 and HIV-2 are prevalent in South Africa, and there is currently no commercial VL assay for HIV-2. There is a need to develop robust and cheap VL assays to monitor viral control in clinical trials and intervention programmes.

### 2. Assay development

I received funding from EDCTP by responding to an open call in 2004. My project commenced in February 2005. With the money from EDCTP I was able to develop a colorimetric format of an RT-PCR assay for quantifying HIV RNA in human plasma. This assay is a quantitative reverse-transcribed PCR of the long terminal repeat sequence of HIV in which test samples are quantified by comparison with a standard curve.

### 3. Basic procedures

First of all RNA was extracted from the patients' plasma, which is a routine procedure, before reverse transcribing the RNA to cDNA. You then set up a PCR with specific HTL primers, before detecting the DNA product by a process called Elona, a technique similar to Eliza. We have tried to improve on this assay so that it is adaptable to different situations. We have concluded an internal calibrator, which goes through the different stages of the assay. The use of this internal calibrator has made the assay resistant to some of the forces felt in normal PCR reactions, for example inhibition, RNA loss, and makes the assay more competitive. It is a simple technique using basic equipment already available in laboratories, which makes it affordable. The cost analysis has put the direct cost of the test at about £5 per test, which is cheaper than any other test currently available.

### 4. Assay validation

We have to validate the assay by comparing it to other known assays. Our test compared the differences between RNA copies per millilitre as determined by our assay and against the international standards from NIBSC, which are PWS-1, PWS-2 and PWS-3 and 97/656. We quantified samples with our assay and quantified the international standard with our assay, producing the expected variables from the reference centre. The mean log difference for these four standards was 0.13. This is saying that our assay competes favourably. For HIV-2 there is no commercial assay, so we did a limiting dilution analysis, testing 15 HIV-2 positive samples, which were quantifiable by limiting dilution and also by colorimetric assay, and a good correlation between the two was found. We tried to compare our HIV-1 assay with the commercially available Roche amplicor assay, which is the most popular commercial assay and very similar to ours. We found a good correlation.

We also tested this assay for specificity, including some RNA viruses, for example, HTLV, HIV-2, Hepatitis B and HIV-samples. We could not detect any copies from any of these samples. We also included a non-positive control, and we were able to detect that, which ensured the assay was very specific.

Our standards and reference points were as follows; that the negative control was detected as negative, that we know the

number of copies in the positive control, and that reduction between the two points were at least 0.9. If any of the points failed, then it would be less than 0.9, making the criteria very strict.

## 5. Assay implementation

When patients are not on treatment they have more HIV and fewer immune cells, but if the drug is working there is less HIV and more immune cells. We have established that higher viral load correlates with higher transmission rates in the absence of treatment, and a high baseline VL correlates with poor prognosis in the absence of treatment. We have a long-term study looking at viral load dynamics in HIV-1 and HIV-2. We are also using this in treatment monitoring, initiating and modifying antiviral treatment, testing the efficacy of treatment regimens and early detection of resistance development.

## 6. HAART in Gambia

HAART is a treatment programme that became available in the Gambia in October 2004 through the Global Fund for AIDS, TB and Malaria. The MRC is one of the main centres in the Gambia. AZT or D4T, with 3TC, and NVP are being used for HIV-1. For HIV-2 we are using AZT or D4T with 3TC and Kaletra.

We have used the assay to monitor patients on treatment. The viral decay after the commencement of treatment is measured at 12, 24 and 48 weeks. The HIV-1 viral load became undetected after 12 weeks, and HIV-2 became undetected after 24 weeks. People have now been on treatment for two years, and most of them still have an undetectable viral load.

## 7. Capacity building / training

As part of my involvement with this project we have incorporated some capacity building and training in viral load. Through EDCTP funding we have trained scientists from the West African sub-region, with 10 participants from several countries. Again this year another training scheme was conducted for scientists from the southern African regions, held in Kenya. There were nine participants, four of whom came from outside of Kenya. Our goal was to train more people, but we were limited by budget.

## 8. Existing and proposed networks

We are part of a North-South collaboration on HIV-2 infection

in Europe, which is a multi-centre project comprising nine laboratories. Ours is the only laboratory in Africa. The project is attempting to evaluate in house viral load assays that are being used to monitor HIV-2. Therefore samples are sent to the different laboratories and measured independently. Our performance, compared to laboratories in Europe, has been very good.

We are also part of a South-South collaboration with the Gambia's National AIDS Programme, and with the scientists that participated in the workshop that took place in 2006. We are hoping that the participants in the 2007 workshop will take part in the evaluation.

## 9. Conclusions

We have developed a high-throughput assay for HIV viral load monitoring. There have been a lot of successes, particularly some published works, and we are now using that assay to monitor all patients on treatment. We are looking for potential companies that would help us market our product, but the competition is very high and there are a lot of big companies producing assays for HIV-1. Our assay is low cost compared to other assays and is also user-friendly.

## 10. Future prospects

As I have said, we are planning a multi-centre evaluation, and we also want to evaluate the assay for HIV sub-types. It has been developed against sub-type A, and we are expecting some participants from eastern and southern Africa to send us samples of other sub-types, which we will then evaluate. We are also looking into the possible commercialisation of this assay, and would welcome any input from attendees who might know how to go about this.

Lastly I would like to acknowledge the people in the Gambia who have contributed to what I am discussing today, especially my director Professor Tumani Corrah, the NIBSC in London, and EDCTP.

Finally, much is known about HIV transmission, but every 14 seconds, a person between 15 and 24 years old is infected with the disease, accounting for half of all new cases of the disease. This means we really need to spread the message of prevention further.

## 11. Discussion

One participant wished to clarify whether two assays had been presented by the presenter, one for HIV-1 and the other for HIV-2, and speculated that this assay might be used

by many resource-limited countries in their laboratories. She also asked whether the presenter had heard of any international quality assurance programmes. The presenter said there were two different primers, one for HIV-1 and one for HIV-2. With a dual-infected patient you would quantify the sample for HIV-1 first and then for HIV-2. The only difference in the assay for HIV-1 and HIV-2 was the differing primers. In terms of quality assurance, the presenter said they had not conducted a direct programme, but had undertaken one that was similar as part of the European study that the laboratory was part of. The same set of samples is sent to all laboratories, and quantified badly. The presenter said that no laboratory had reported any positive samples in the negative sample that he had taken, and the viral loads were found to be similar.

## II. Preventing Per-Partum Transmission of HIV-1 in Africa: Tenofovir Based Alternatives to Single Dose Nevirapine in the Light of Future Treatment Options

**Dr Didier Ekouevi,  
EDCTP Senior Fellow**

### 1. Background

I would like to share with you the first data on the combination of tenofovir-emtricitabine, a new ARV regimen for the prevention of mother-to-child transmission of HIV-1 (PMTCT). There is a limited number of ARV drug regimens used for PMTCT in Africa. Currently zidovudine, lamivudine, and nevirapine are being used. Among those single-dose nevirapine is the most common ARV regimen used for PMTCT. The data reported by the HIVNET012 trial in Uganda showed that one 200mg tablet given at the onset of labour, before one dose of syrup on day two, resulted in a reduction of 47% of the rate of transmission in comparison with the single dose of zidovudine. The absolute rate of transmission at week six was 11.9%.

### 2. Viral resistance

Viral resistance is the most worrisome problem with the single-dose nevirapine regimen. Many studies have found a

high rate of occurrence of NVP resistance mutations in the four weeks after exposure, with the rate of NVP resistance mutation between 25 and 50%, and in children of between 20 and 87%. If you have nevirapine resistance, you are resistant to all non nucleoside reverse transcriptase inhibitors (NNRTIs), which has a poor impact on the future treatment options.

One important question today is whether there is an alternative to the single-dose nevirapine PMTCT regimen. Our hypothesis is that tenofovir-emtricitabine could be a complement or alternative to the single-dose nevirapine. We therefore planned the Tenofovir Emtricitabine in Africa and Asia (TemAA) trial.

### 3. Truvada

Truvada is the combination of two antiretroviral drugs – tenofovir disoproxil fumarate (TDF), a nucleotidic analogue, and emtricitabine (FTC), which is similar to 3TC. Second, the pharmacokinetic data was interesting, with a half-life value of between 12 and 18 hours for TDF and 10 hours for FTC. There is just one tablet per day for adults. Animal studies with tenofovir have shown it is effective in protecting newborn macaques against SIV infection, and that no major toxicity was found in animals with high doses of TDF.

### 4. Objectives

The objective of the trial was to study the pharmacokinetic properties of TDF and FTC in pregnant women and their newborns. The secondary objective was to study the safety and toxicity of the two drugs, to estimate the frequency of the occurrence of TDF and FTC resistance mutation at four weeks postpartum, and to determine the frequency of peripartum mother-to-child transmission of HIV-1 after the use of these ARV regimens.

### 5. Method

It was a phase II clinical trial taking place across three centres. The first site selected for the study was Abidjan, Côte d'Ivoire, which was supported by EDCTP, and the other sites were in Soweto and Cambodia. The three sites were selected for having a large representation of the HIV strain. The first step was the initiation of Truvada only in the mother, and the second step in the mother and also in the infant. The following inclusion criteria included HIV infected pregnant woman aged 18 or above, meeting haemoglobin and creatinine clearance criteria. The women did not make the



criteria for ARV treatment for her own health, only women who did not need ARV for treatment were included in the study. They must be naïve for ARV treatment, and informed consent must be gained from both the mother and father of the unborn child. Finally, the mother must consent to a three-day stay in hospital after giving birth.

The mother was given one ZDV tablet twice a day at the prepartum stage, two tablets of Truvada, 600 mg of TDF and 400 mg of FTC, and one tablet of NVP at intrapartum stage, and one Truvada tablet once a day for seven days postpartum. The newborn received ZDV syrup for seven days.

We collected a total of 12 blood samples from the mother and three samples from the infant for the pharmacokinetic study. For the genotypic resistance mutation study one blood sample was collected at four weeks in the infant and mother, and for the HIV transmission, to know the timing of HIV infection, we collected the blood sample on week three, week four and week six from the infant.

## 6. Results

A total of 19 women were enrolled, with a median age of 27 years. The pharmacokinetic parameters were estimated. The time to reach the maximum concentration is  $T_{max}$ , the maximum concentration  $C_{max}$ , and the minimal concentration  $C_{min}$ . After the 400 mg of FTC administration in the women, the area under the curve is 14.5, and you reach  $T_{max}$  three hours after the administration of the drugs, the  $C_{max}$  is 1.6 mg per litre, and the  $C_{min}$  concentration is 0.1. The maternal FTC concentration was slightly higher during the first five hours than the infant concentration, but it was similar after that. At delivery the median FTC maternal concentration was 1.0 and it varied from between 0.03 to 1.4. The median concentration was 0.7.

There were no important clinical manifestations in the mothers. We found just grade three and four biological events, one case of anaemia was reported, three women presented neutropenia associated to leucopenia, and two women presented only isolated neutropenia. Four serious adverse events took place, with three deaths. One twin died of gastroenteritis related to formula feeding, one presented HIV infection and intestinal conclusion, and one presented severe neurological symptoms at birth. Two other infants presented with anaemia. The community in charge of the validation of the adverse events concluded that all biological or clinical events were not related to the administration of tenofovir or emtricitabine.

## 7. Rate of HIV transmission

One case of HIV transmission was identified among the 20 infants tested. It was in utero infection with a positive test on day three, which was confirmed at week four. No cases of intrapartum transmissions were reported. The HIV infected child died on day 26, before the initiation of ART, due to gastrointestinal symptomatology.

The slide shows the maternal kinetics of maternal plasma viral load over time, which was measured at baseline 48 hours after delivery. The median viral load of 4.0 was recorded.

## 8. Viral resistance after exposures to ARVs for PMTCT

The genotyping resistance test was available for 18 out of 19 women at four weeks postpartum. No viral resistance to ZDV, NVP, FTC or TDF were detected. The phylogenetic analysis revealed the predominant strain in Abidjan is CRF02-AG.

## 9. Conclusion

FTC was shown to have a good placental transfer. Based on the data available, the initiation of 2 mg / kg 12 hours after birth, or 1mg / kg six hours after birth, should produce neonatal concentrations comparable to those observed in adults. The analysis will be available at the end of this October 2007.

The TDF/FTC combination for PMTCT was well tolerated in women and exposed newborns with no intrapartum HIV transmission reported. The adverse events reported were not related to TDF or FTC.

From the preliminary results we can say that the use of TDF/FTC in the seven days after delivery, immediately after delivery, after a single dose of NVP and two doses of TDF/FTC, extended the suppression of viral replication, plus avoiding postpartum exposure to NVP alone.

Next, we are preparing for step 2 of the trial, administering TDF and FTC to neonates. Our goal is to prepare for the phase III trial as soon as possible.

## 10. Discussion

The first question addressed the design of the study, asking whether an AZT was given to the mothers first, before the Truvada, and then postpartum there was NVP. The presenter said that the strategy was to take into account the WHO recommendation and to add just the tenofovir-emtricitabine at the beginning of labour, and continue until after delivery.



### III. Killer Immunoglobulin-like Receptors (KIR) Frequencies in a Rural Community in Northwestern Guinea-Bissau

**Louis Marie Yindom,  
MRC, the Gambia**

#### 1. Overview

I will be touching mostly on killer immunoglobulin-like receptor cluster genes and natural killer (NK) cells. NK cells are the body's first line of defence against invading particles. Most importantly we now know that they have some receptors on their surfaces that control their antiviral activity. These are KIR in humans.

#### 2. What are KIR?

KIR are encoded by a set of genes from human chromosome 19. They can be defined as glycoproteins with two to three extracellular domains. They can be called specific HLA class I sensors because they survey other cell surfaces looking to make contact with their specific ligands. Upon binding to those ligands, series of biochemical events take place that will eventually modulate NK cell activities.

#### 3. KIR structure

Functionally KIR molecules can be classified in two classes, as inhibitory or activating KIR based on the number of extracellular domains. Those with three extracellular domains are called KIR3D while those with two are KIR2Ds. The latter can further be subdivided into type 1 or 2 based on whether they carry D1 (type 1) or D2 (type 2) in addition to the common D2 domain. The tail length and the number of ITIMs for those with the same tail length can further discriminate them functionally. Those with 3Ds can only be differentiated based on their tail length and the number of ITIMs on the tail.

#### 4. KIR genes

The genes classification is similar to that of the proteins they encode. Ideally a KIR should have nine exons, but you have some with eight or less due to deletions.

#### 5. KIR haplotypes

KIR haplotypes are KIR gene combinations at the individual host level as opposed to the usual haplotypes that are genes

on the same chromosomes that are inherited together. To harmonise the huge amount of KIR haplotypes described by various investigators, they have been grouped in two broad categories as A and B. A are mainly constituted of inhibitory genes, while B are constituted of both active and inhibited genes. A haplotypes are highly polymorphic and usually contain no activating gene except 2DS4. On the other hand, B haplotypes are highly polygenic and are a mixture of both activating and inhibitory genes.

#### 6. KIR and NK cell function

On the surface on NK cells, KIR molecules are constantly surveying other cells surfaces for the presence or absence of HLA class I molecules that serve as their ligand. In the presence of the corresponding ligands for both activating and inhibitory receptors, the inhibitory signal predominates over the activating signal and the target cell is not destroyed. In the absence of the ligand for the inhibitory receptor, as is the case in most viral infection where there is downregulation of MHC class I molecules, the activating signal will activate the NK cell to kill the target. This takes place very early post infection.

#### 7. KIR3DS1/Bw4-801 in HIV infection

A good study has been conducted linking KIR genes with other diseases, but we are interested in the association between KIR-HLA and HIV infection. The most intriguing finding has been that associating 3DS1 and a subset of HLA B Bw4 alleles with protection against rapid progression to AIDS in HIV-1 infected individuals. This same combination has been associated with protection against OIs and lower VL set point. Other HLA molecules have also individually been associated with a lower viral onset point.

#### 8. Why this project?

We all know that the niche of HIV infection rests in sub-Saharan Africa, which harbours two thirds of all affected people. The world population has been crying for a vaccine to stop the spread of the virus, but up until now the hope of an effective vaccine remains a dream. The barrier to the realisation of this dream is the lack of understanding of the mechanisms of protective immunity despite great effort from the research community.

In West Africa we have HIV-2, which is less virulent and less pathogenic than HIV-1. Unfortunately the HIV-2 has not received as much attention from the global community as

HIV-1 has. Despite much effort from MRC the Gambia and other research institutes in the sub region, little is known as to why this other form of HIV, which shares up to 60% homology with the HIV-1, is much less pathogenic and why it remains confined in West Africa.

## 9. Specific objectives

Our specific objectives for this part of the study were: to determine the KIR gene pool in a community based cohort in Caio, which is in Guinea-Bissau, to study the effect of individual KIR genes and haplotypes on susceptibility or resistance to HIV-2 infection, and to determine the haplotype diversity and its role in long-term non-progression status observed in HIV-2 infection.

## 10. Method

We extracted DNA from 150 HIV-2 individuals, 35 HIV 1 and 2 individuals, and 328 unaffected subjects. We used KIR specific primers to design a phototype to detect the presence or absence of KIR genes.

## 11. Results

We succeeded in typing 513 individuals. 150 were HIV-2 and out of that 74, almost half, were diagnosed with HIV-2 since 1989. From this, only seven deceased. We do not know when they were infected. Out of the 328 negative individuals 219 had participated in the first survey in Caio, and out of that almost 14% became infected with HIV-2 by 2006. Only one has deceased since then. This shows the benign nature of HIV-2. In 17 years there was one death, which makes it possible to do several studies on these subjects before they deacease. We detected 15 KIR genes in this population, but only two showed some kind of protective difference against susceptibility to HIV infection, because the frequency of the genes was higher in the unaffected group than the affected group.

The most frequent gene in this population was KIR3DS1, which was present in almost all the samples, which is an inhibitory KIR gene. The activating KIR genes were very low, and only present in about 30% of the sample. We compared our data with what had been published before, particularly with data from the Senegalese population published in 2005, where the frequency was similar. Moving to a cohort in South Africa the frequency in the group was far lower. The most striking difference between the Senegalese and the Manjago community was KIR3DS1, which was found in 19% of the cohort, and 4% in the Senegalese population.

## 12. Summary

We found 15 KIR genes in our study population, and an HIV-2 incidence of 14% in 17 years compares with only 0.5% death, compared to 5.5% among the persistently unaffected individuals since 1989. Activating genes were least frequent in this population. The KIR2DS2 and KIR2DL2 were showed a significantly protective value in the cohort. KIR3DS1 was more frequent in our study compared to other African studies, and other activating gene frequencies, apart from the 3DS1 that were lower if you compared this to the genetically different South African population. 79 distinct haplotypes were found, 5A and 74B, with YA1 predominating. Three out of five of the A haplotypes were absent among cases.

## 13. Future direction

In the future, we plan to conduct a detailed analysis of this Caio cohort. I have just presented the preliminary data, and we are planning to do KIR and HLA sequencing to confirm what we have seen in the results. We want to repeat this process with another cohort in Fajara in the Gambia, since this cohort is almost homogeneous. We want to be able to do some functional assays to check the level of expression of genes of interest, and we want to develop some new HLA and KIR typing techniques based on the new SNPlex platform.

## 14. Discussion

One attendee asked whether the presenter was proposing the association of KIR2, DS2 and DL2 with resistance to the infection. The presenter said that the preclinical findings were proposing protection against susceptibility to HIV-2. The attendee thought that one of the major differences between HIV-1 and HIV-2 was that in HIV-1 you had a ligand that was not present in HIV-2, which could explain the different evolution of the two diseases. The Chair of the PB noted that the presenter had talked about understanding the pathogenesis of HIV-2, which would help in designing vaccines. He asked whether they were intending to design therapy treatment or preventative vaccines. The PB Chair asked whether it was ethical to deny people with HIV-2 treatment in order that they could be studied for such trials. The presenter said that that would not be ethical, but they did have the opportunity to conduct greater studies into HIV-2. He said that one problem worldwide was lack of knowledge of the mechanism for protective immunity. Some people were resistant to infections, others were resistant to progression, but the system that was controlling that was unknown.

Therefore, doing immunogenetic studies such as this one in a multi-ethnic and homogenous populations might lead to something that could be explored.

## IV. Understanding the Informed-consent Undertaken by Research Participants in a Vaccine Trial in Misisi Township in Lusaka, Zambia

**Bornwell Sikateyo,**  
**Ministry of Health, Zambia**

### I. HIV vaccine trial

There are two corrections. Firstly, I was refused permission to enter the trial site by MDP UK, and so the focus changed to another site. Secondly, this is not a presentation about viral loads, but a social science presentation looking at ethics in biomedical research. The vaccine trial that I will be examining in the next 12 months is a three-year multi-site trial controlled from London, which has other sites in Zambia and Europe. The focus is on the first year, which is looking at the assessments that are going to be done for the four vaccines, and how they are being done. The trial is testing whether micronutrients can enhance innate immunity in response to colonisation by live, attenuated oral vaccines. In the last study they found that supplementing HIV patients with micronutrients reduced morbidity and mortality. Four vaccines were used: orochol, vivotif, rotarix, and ACAM2010 and ACAM 2017.

The first part will only involve helminth-negative patients. Each of the vaccines will be tested in a different trial in order to determine the time course of any effects on antimicrobial peptide and cytokine expression. They will do some endoscopies, which include the taking of some tissue for biopsy. The procedures that are going to be undertaken in the vaccine trial are very laborious, and have to be staggered. The study wants to pick one member of each household to be vaccinated at a time to detect unexpected secondary transmission effects in the community. Despite not being given the vaccine, other household members were asked to give stool samples. For the four vaccines there will be a total of 160 endoscopies on 80 volunteers, which means that each volunteer will be subjected to two endoscopies. There

are 20 participants for each of the four vaccines, and each group of 20 will be split into four, with those groups of four undergoing their second endoscopies at staggered intervals.

### 2. Location and study population

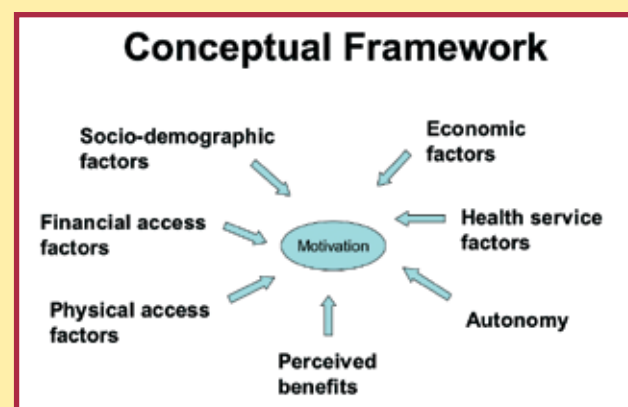
The trial location for the vaccine is Misisi, one of Lusaka's poorest townships. The research team has been working in this area for over 10 years, so there are issues arising from the long-term relationship between the research team and the subjects. They have targeted both sexes, aged between 18 and 78 years, 35% of which are HIV seropositive. There is one vaccine that is being targeted for infants in that cohort, and the idea is they will gain consent from the parents or guardians of those children.

### 3. Ethical concerns

This is a resource-poor setting, which makes its selection an ethical issue. Access to health care is also problematic, raising further issues. Targeting an area of high HIV prevalence is another issue, as is the justification for research on infants, and their safety. The target study population is the one that will bear the burden of the trials, but are unlikely to be able to access the products after the trial. The study population is one that has relatively low literacy, and there is an issue of how they will understand the procedures conducted in the trial. I also want to look at the long-term affect of the relationships between the study team and the cohort, while also focusing on issues of trust and mistrust in situations of poverty and exploitation, also given the complexity of the trial.

### 4. Critical components of consent

There are three broad critical components when considering informed consent. The first is disclosure of information, which entails resolving therapeutic misconceptions of the



trial by making it clear that it is research and not medical treatment, how long they will be on the trial, what procedures will be done and what inconveniences they will be subjected to, and what dangers they face. The second is understanding, and addresses what procedures would be carried out in a language that participants can understand. The third, trust, is also needed in the healthcare system.

## 5. Social relations

A lot has been written about issues of information, understanding and trust, whereas issues of social relations have not been adequately addressed. Therefore, I want to examine the special grounding of consent in the research process by looking at the social relations that make the research function. I will be looking at how gender affects one's decision to go into trial, what effect the lack of health and medical benefits has on those issues, how to look at relations of trust and mistrust, the economic and medical situation of those taking part. Autonomy is only one of many components of decision-making; there are other factors that affect one's decision to participate in a study. I intend to look at interactions as ongoing activities throughout the trial, elicit a range of viewpoints from various actors, and understand what elucidates successful negotiations in the everyday interactions. Normally, what we say is that documentation of consent happens after a series of events over time. I know of situations where that does not happen, usually we tend to be in a hurry to get a signature so that we can progress with the trial. I want to see what happens in this trial.

## 6. Actual consent practices

Social, economic and healthcare contexts influence our understanding of the research and the agreement to take part in research. That is why critics have questioned whether such participation can be voluntary and ethically sound. I want to address consent as a socially grounded agreement between agents, rather than an individual choice. I will take the ethical nature of the interchange to become more grounded in the social interactions between participants. Consent is supposed to be an evolving, processual relationship that develops over time, and not a moment of information exchange. In that way I believe we can make consent more robust.

## 7. My approach to informed consent

The aim of my study is to assess the understanding of informed consent for participation undertaken by

HIV-positive participants in what the research team acknowledges is a complex and challenging vaccine trial. I want to see what makes the participants go into this process. I have three objectives; to determine and explore the factors that motivate people to enrol into the vaccine trial, as well as determine and explore factors that stop them from enrolling in the trial, and assess how the consent relationships evolve and change over the course of time.

I am going to use the framework that was developed by Kruger that is used for evaluating health seeking behaviour in poor or resource-poor communities, and will try to look at some sub-factors. I propose to approach consent as a broad social consensual agreement between agents. I will examine person-to-person interactions in the process during the procedures, by looking at both the complexity and invasiveness of procedures. I will then use those interactions to look at the long-term relationships, what expectations the participants have, and whether they have any rights. In medical anthropology the distinction between data collection and analysis is not very distinct, because the minute you start collecting data you also build up an analysis. I will triangulate interdisciplinary tools, conduct case studies and ethnography, as well as in-depth interviews, field notes, transcripts and a narrative analysis. I will also do some literature and document review.

## 8. Limitations / bias

My affiliation to the Ministry of Health may be a potential bias in this study, as is my gender when approaching mothers, research bias, location of study, length of inquiry and other factors. There is no risk to participants in this study.

I hope this study will generate some data on the application of ethical guidelines for consent in the course of research, to better inform academia, policy makers and the public. Hopefully that will inform national policy on the development of vaccine trials in Zambia and sub-Saharan Africa.

## 9. Discussion

One attendee questioned the prevalence of HIV infection in the study. The presenter said that the national infection rate in Zambia was 16%, whereas in the area of study it was about 35%. The presenter said that the ethical basis of research in areas where the HIV prevalence was high was something that he wanted to examine.

## V. Preparations for HIV Vaccine Research at Zambia-Emory HIV Research Project (ZEHRP)

**Dr William Kilembe,  
Zambia Emory HIV Research Project**

### I. Overview

ZEHRP was established in 1994 with the aim of providing couples voluntary counselling and testing (VCT). Currently we have three sites in Lusaka and others sites on the Copper-belt Province. The study focuses on HIV discordant couples, because we realise that HIV negative partners in a discordant couple are at the highest risk of contracting HIV. The couples are followed up at least quarterly and provided with risk-reduction counselling and supplied with condoms to prevent HIV transmission to the negative partner. In the event that the negative partner contracts HIV, we also want to study the virologic and immunologic correlates of HIV transmission.



### 2. Objectives

Our main objective has been to carry out research aimed at prevention of HIV infection and development of a safe and efficacious HIV vaccine. To do this, we need to adequately train staff and prepare the trial sites for clinical trials. Another objective is to establish baseline characteristics of normal individuals in the populations that we will be dealing with. We will also endeavour to provide accurate information to trial participants, and recruit and retain vaccine trial participants. Finally, we want to expand the cohort of HIV-negative discordant couples for future vaccine trials in at risk individuals.

### 3. Training of staff

It is an international requirement for everyone participating in clinical trials to undergo Good Clinical Practice (GCP) and Good Laboratory Practice (GLC) training. All staff must complete a Collaboration IRB Training Initiative (CITI), which each person has to renew every two years, that deals with human rights protection. Staff also undergo DAIDS policy training, which includes the Expedited Adverse Event (EAE) training. Part time and full time staff are enrolled at the London School of Hygiene and Tropical Medicine studying elements related to clinical trials. Clinical staff are also trained on basic life support. We have monthly training days on site, where staff are taught about basic life support training, and they also go through protocols.

### 4. Infrastructure development

In order to carry out trials successfully, we have developed a new site aimed at coordination of the vaccine trials. We have internationally accepted laboratories and pharmacies, which have been externally audited, and have undergone accreditation by the GCLP.

### 5. Protocol D

Protocol D was a cross-sectional observational study to establish clinical laboratory references values. We enrolled 400 healthy HIV-negative individuals from 2005 to 2006, aged between 18 and 60 years of age, mostly from the couples VCT in Protocol D. This study closed in March 2007. Mainly we enrol couples from those in the VCT, and we also have a mobile couples VCT programme. They are enrolled in a discordant couples cohort, which is called the Heterosexual Transmission Study. For the vaccine trial that we have just finished, we enrolled our volunteers from Protocol D. We gave information sessions to 93 individuals, screened 47 and enrolled 16. We give information sessions to couples in terms of basic clinical research, information on HIV vaccines and effective contraception and risk reduction.

Other planned studies include the V002, which is a phase II randomised placebo-controlled double blind trial to evaluate the safety and immunogenicity of a multi-clade HIV-1 DNA placement vaccine. A similar study is the PAVE 100, which focuses more on the efficacy side.

### 6. Lessons learned

We realise that enrolling participants from existing cohorts into vaccine trials is a good strategy to improve retention and



follow-up rates. Even before we enrol these people in vaccine trials, we will have followed them up for about a year, created a rapport with them and built up trust. We lose a lot of people in the first three months of follow-up, but this reduces significantly in those couples that stay in the study for one year. We have collected and updated locator information, which has greatly assisted in the follow-up of participants. The experience gained here will help us in upcoming larger vaccine trials. The information sessions given in the focus group discussions have facilitated the informed consent process. The information sessions have also allowed us to take time over the informed consent process, and plan for focus group discussions in advance of the consent date. They have also helped us identify and emphasise certain trial concepts. The involvement of a community advisory board has helped us to ensure that we have the required cooperation from participants.

### **7. Future perspectives**

We intend to spread out activities to the two new sites on the Cooper-belt, and ramp up our couples VCT activities to increase the cohort of discordant couples, by increasing the activity of our mobile units, expanding our activities to district clinics within Lusaka, and by reverting to the old system of 6-day-week testing. We also intend to train community-working people to encourage more people to participate in the VCT, to eventually join the cohort.

### **8. Discussion**

The presenter was asked about the reference ranges and parameters he had used, and the possibility of borrowing the reference ranges for work in Zimbabwe. He explained he had looked at epidemiological and biochemistry data, as well as CD4 and CD8. One attendee asked whether the recruitment staff were salaried or were volunteers. The presenter thought that they were given a small incentive.

## **VI. Challenges of Expediting the Conduct of Ethically Approved Phase II and III Clinical Trials on Herbal Medications in Africa**

**Dr Modest Mulenga,  
TDR, Ndola, Zambia**

### **1. Overview**

There is a serious debate going on in my country about herbal medication and the application of research funds to herbal medicine. I understand other countries are in the same predicament. However, few people have guidance on which way to go. I will highlight some factors driving the demand for use of herbal remedies, before outlining ethical, regulatory, and methodological issues in the conduct of clinical trials with herbal medication for HIV/AIDS and malaria, before coming to some conclusions.

### **2. Background**

In many African countries, there is an increasing demand to explore the possibility of integrating traditional medicine into the conventional healthcare system. There is mounting political pressure in some countries for R&D institutions to explore the possibility of testing herbal medication in humans. Some people claim we already have herbs that are being used in human beings, whereas modern science cannot accept the herbs until they have been tested in each respect. The urgency of this matter is dividing opinion as to the understanding of traditional medicine itself and the best way of evaluating it to make it widely accessible. We should distinguish traditional medicine and herbal medication. I am leaning towards what has been termed phytotherapy, because I do not want to be drawn into discussions about the definition of traditional medicine as given by the WHO.

### **3. Introduction**

Humans have always looked to biodiversity to meet their health needs, an activity that transcends all cultures. It is argued that Africa's biodiversity constitutes a major resource that remains to be fully exploited for the socio-economic benefit of its peoples. This rich resource may provide the necessary leads to effective therapies for health problems, including HIV/AIDS, TB and malaria. Herbal medication is

the mother of conventional medications, and to date the only sources of drugs remain the natural ones, semisynthetic and synthetic.

#### **4. Traditional herbal medication in revival?**

Traditional herbal medication may not be in revival, but it is certainly beginning to receive more attention. Policymakers in the Ministry of Health, particularly in Zambia, are considering directing scientists to look at what we already have. In some African countries it is said that 80% of patients will have previously received traditional medication, either in their home or from traditional healers. This is a divisive figure. Some are positive, stating that if 80% of people are going to traditional healers many have accepted that traditional medication is the way to go. However, some are negative, stating that if 80% of patients seeking formal healthcare have already attended a traditional healer, then the traditional medication has failed.

In South Asia, traditional medicine has been integrated into the formal health system. In developed countries, traditional medicine is termed 'alternative' or 'complementary' medicine, and is increasing in popularity. It has been accepted and runs parallel to the conventional healthcare system. In Africa, despite the demand, there is an unequalled policy response to embrace traditional medicine into the conventional healthcare system, and in the recent past traditional medicines were even illegal.

#### **5. Approaches**

My approach was to take the literature at national level and the international guidelines for ethical conduct of trials on herbal medication, and then review available legislation governing the use of herbal medication, and review guidelines for identifying suitable preparations for clinical trials, review reports of ethical and methodological issues in trials of herbal medication. Then I took some time to talk with medical practitioners and herbalists on their perceptions in an informal way. I did not get consensus on this issue, because some senior physicians in my country have embraced traditional herbal medication, and others have not. For some, herbal medicine addresses many issues they do not believe modern medicine can, that is, the neglected spiritual and mental elements.

#### **6. What drives people to consult traditional healers?**

People are driven to consult traditional healers because of the prohibitive costs of conventional healthcare. Traditional medicine is easily accessible, these people cannot travel to conventional services, and they like the privacy. There is a stigma around modern diseases, problems around personal and cultural beliefs and worry about the problems themselves. People often trust the healer because they are authoritative in their local community, and they can offer something other than just giving medication. Some people believe the rituals that go with traditional medication help them in some manner, although this situation can differ across countries and continents.

#### **7. What is driving the demand for use of traditional medication by governments?**

Perhaps the demand for use by governments reflects their acknowledgement that traditional medicine is being used by large numbers of the population. Other factors might include the associated difficulties of controlling emerging and re-emerging diseases with limited therapeutic options; the prohibitive cost of drugs for common health problems, which are beyond national health budgets; reducing dependency on conventional medications to reduce the cost of healthcare; and the view that advanced technologies and improved research methodologies have created a platform for better understanding and harnessing of indigenous knowledge. There is also the need to document claims by traditional healers before some of the plant species become extinct.

#### **8. What is the international response to increasing demand for traditional herbal medicine usage in Africa?**

The disparity between governments and international responses to traditional medication is staggering. There are WHO guidelines already in existence to try to validate some of the known plants for the purpose of treating HIV and other infections. At country level there is serious opposition as to how they can absorb traditional medication into their healthcare system, let alone acknowledging there can be parallel health systems.

## 9. Specific responses from regional and international bodies

Specific responses from regional and international bodies include setting a framework for integrating traditional medication into the healthcare systems; putting up mechanisms to protect intellectual property rights; advocacy to promote traditional medicines at all levels; providing guidelines and technical support to strengthen national policies on traditional medicines; and trying to promote collaboration and consultation among partisan partners to promote traditional medicine. Specific guidelines and methodologies of clinical trials are being developed by these bodies to try to help governments to harness traditional medication.

## 10. Definition of traditional medication

The WHO's definition of traditional medicine is a long one. Many of the people I interviewed did not agree with it, and some even wanted to develop their own definition. Some people believe that traditional medication should be about herbs, rather than rituals. I will stick with the definition as herbal medication.

## 11. Regulatory issues

Herbal medication is mentioned in legal documents and guidelines, but the guidance information is scant for those who have something they would like to register, and hard to enforce. One study shows that 74% of countries do not have pharmacopoeia on herbal medication, and if they do, it is rarely legally binding. Furthermore, 78% of countries do not have herbs on the essential drug list. Pharmacovigilance systems in many countries do exist, particularly in Africa, but they are not applied.

## 12. Methodological issues

The crux of the matter is taking herbal materials to test on humans through the fastest route. Much depends on the strength of the evidence available to support the claims of traditional medication. People are worried about herbal medicine being dragged back by scientists advocating animal testing when these products have already been given to humans. How do we prove the claims that a herb is doing what it is supposed to be doing? Some people do not think that we should go back to the bench. The WHO guidelines outline a procedure for doing this in complementary medicine.

There are certain methodological issues that have to be considered, for example, whether to conduct observational studies when we might get more information from comparative or equivalency studies.

## 13. Ethical issues

There are also ethical issues to consider – to distinguish between the needs of treatment and/or research, providing adequate information on herbal products, particularly those that have only been used in undocumented ways or are only documented by oral evidence. There are also issues about making information available about the conventional health systems; for example, if you are dealing with malaria how do you give someone herbal medication when you know that efficacious drugs are there.

## 14. Other important issues

Other important issues include the infrastructure we need to use to handle traditional medicine, how to maintain surveillance and reporting mechanisms. We need to identify partners in R&D and to meet educational and training needs.

## 15. Summary

The conclusion was that human rights, socio-economic and political pressure were also giving impetus to the demand for clinical trials on herbal medicine. However, the appropriate ethical guidelines concerning clinical trial on herbal medications are needed in order to address the increasing demand. The appropriate regulatory and legal framework is necessary, and it is clear that it is absent or vague in many countries.

## 16. Discussion

One participant thought that the first step with traditional medicine was to prove it was inoffensive. In his experience some treatments were more detrimental than helpful, therefore the imperative was at least to prove that it was not harmful. It should not be marketed as the cheap alternative to standard care. He thought that it could not be considered an approach alternative to those that were too poor to afford conventional medicine. Therefore traditional medicine faced an uphill struggle. He also thought that herbal medicine should go through the regular procedures, including the laboratory stages. Many other drugs, like quinine, started as a herbal medicine, but went through the normal trials before being standardised.

## VII. General Discussion

The Chair of the session asked if the group had some general recommendations to take back to the Forum. The first suggestion was to devise a standard protocol to help individuals interested in developing potential herbal medicines. Although it was difficult to imagine if you were not African, many people lived so far from conventional health centres and had been brought up on traditional remedies. Even politicians and learned people sought traditional medicines or followed natural remedies. Alternative remedies were also a growing business in Europe and the US. However, it was felt that Africa needed sanitation, to determine how some of the herbs could be packaged and used in a sanitary matter.

One participant questioned whether the EDCTP should fund such a project. It was commented that secrecy in herbal medicines should be discouraged. The only way to get traditional medicine into the mainstream was through proper clinical trials, supported by appropriate collaboration. One attendee thought that EDCTP should look at the promising areas. For example, he did not think that blocked fallopian tubes could be cured with herbs, but perhaps diarrhoea would respond to herbal medication. However, the safety of the patient as paramount was emphasised.

It was interesting to note governments' interest in these medicines. One participant thought the chances of being funded to undertake clinical trials in non-traditional ways were very slim, which was now a challenge to government. It was felt that governments were only promoting traditional medicines because they could not afford to buy conventional drugs. Therefore governments had to find the resources to encourage the conducting of clinical trials of herbal medicines.

One attendee commented on the issue of informed consent, which she felt was something that should be promoted. There was a need for the work studying informed consent, particularly what it reflected in terms of developments in behavioural science and establishing what was of benefit to communities.

Returning to the unifying theme of this session: capacity building in Africa, the Chair of the session asked each of the presenters how their work had contributed to capacity building in Africa, whether the system had worked, and what needed to be done to strengthen and improve on what had been done in the past. To begin, the first presenter thought that his programme had trained people to use new techniques in assessing HIV-2, who were now ready to try the techniques out in their facilities, but needed help and funding to do so.

The second presenter highlighted his contribution towards educating people from the ground up, stressing the need for trained expertise and scholarships to sponsor relevant programmes on sites. In addition, better laboratory equipment would reduce the need for samples to be sent for analysis at given times. He felt that EDCTP's participation in this specific programme was low.

The following speaker thought that the training of young scientists had to be one of EDCTP's primary goals to strengthen the sites currently being used. He also thought there was a need to facilitate the transfer of techniques and technologies from where they were now to where they were really needed, across Africa. There was much groundwork still to be done on how to receive vaccines and follow up what happened post-vaccination, which could only be achieved through locally available, qualified scientists. Alongside this, institutions need to be strengthened to retain staff that had been trained. The first priority was to train young scientists through targeted EDCTP funding, and communication should take place between the training institutions and EDCTP. It was hoped that EDCTP could also help to encourage people to come to Africa from other countries to build careers.

The last presenter thought EDCTP needed to increase the behavioural science capacity to support vaccine trials. Another participant took a different perspective, and wanted to generate a team to absorb best practices from other studies, as well as getting people to lend facilities. EDCTP had also helped in identifying people to work on such projects, enabling them to gain qualifications.

# Malaria Capacity Building in Africa

**Facilitator: Peter Klemsner (EDCTP PB)**  
**Rapporteur: Mathieu Ndounga (EDCTP DCCC)**

## I. Assessment of the Public Health Benefit of ACTs for Uncomplicated Malaria Treatment in Mali

**Dr Abdoulaye Djimde,**  
**University of Bamako, Mali**

### I. Objectives of the projects

- To test the hypothesis that repeated administration of AS-AQ, AS-SP and AL for the treatment of consecutive episodes of uncomplicated malaria reduces the incidence of falciparum malaria and malaria attributable to anaemia
- To measure the impact of this repeated administration on antimalarial immunity and malaria transmission
- To measure the efficacy and safety of the three prospective candidate ACTs in this context of repeated administration.

### 2. Methods

The study began in July 2005. We conducted a randomised, controlled trial in Bougoula-Hameau, a rural village of about 5,000 people in the south of Mali, where malaria is hyperendemic with seasonal transmission.

The drugs used were AS-AQ, AS-SP and AL.

Once patients were randomised, they remained in the same group and subsequent episodes of malaria were treated with the same drug.

We have two years of follow-up data. Active follow-up was performed at 28 days, followed by passive follow-up with 24-hour availability of physicians in the village for the full two years.

We looked at clinical symptoms, as well as biological parameters such as Hb, liver and kidney enzymes, and blood toxicity.

The protocol was approved by the ethics committee of the Faculté de Médecine, de Pharmacie et d'Odonto-Stomatologie (FMPOS) of the University of Bamako.

Written consent was obtained prior to enrolment.

The study was sponsored and monitored by Sanofi Aventis, which always provided the AS-AQ drug.

### 3. Descriptive results

- We screened 4,000 patients and 260 patients were enrolled in three treatment arms
- The 780 patients enrolled experienced a total of 2,019 episodes of uncomplicated malaria during the study period
- We had a successful follow-up rate of over 95%
- The treatment arms were comparable at base line for age, sex, parasitaemia, gametocyte carriage and anaemia.

### 4. Efficacy

At day 28, efficacy was 55%, 80% and 91% for AL, AS-AQ and AS-SP respectively. Following molecular correction, all three rose to almost 99%.

- With AS-SP, efficacy remains fairly stable throughout the year
- With AS-AQ, there is a peak during the dry season but this is not statistically significant
- With AL, efficacy is lowest during the peak of malaria transmission.

### 5. Evolution of anaemia during follow-up

There was a mean incidence of 2.6 episodes of malaria in the different study groups, with a maximum of eight, 12 and nine in the AL, AS-AQ and AS-SP groups respectively.

During the first 28 days of follow-up, we saw a significant decrease in anaemia in all three treatment groups.

### 6. Evolution of gametocyte carriage by treatment arm on follow-up days

Gametocyte carriage decreased sharply following ACT treatment.

### 7. Transmission

#### a. Methods

During the course of the efficacy study, we screened for gametocyte carriers and included those aged between 6 and 18. We performed direct feeding using an F1 generation of *An. gambiae* that had been starved for at least 12 hours. These mosquitoes were then kept in insectaries for eight days, after which they were dissected and observed for the presence of oocysts. We then compared the infectivity of base line gametocytes to those obtained after drug treatment.



### **b. Infectivity of post-ACT gametocytes**

At base line, 12% of mosquitoes were oocyst-positive.

Between days seven and 28, 34%, 28% and 8% of mosquitoes were infectious following treatment with AS-AQ, AL and AS-SP. The decrease in effectiveness with AS-SP is not statistically significant.

## **8. Ongoing analyses and studies**

We plan to undertake a detailed analysis of the incidence density of clinical malaria and compare it with data prior to this study.

We will perform cytokine kinetic and antibody response analysis on each drug treatment arm.

The clinical and biological safety analysis is also ongoing.

## **9. Summary and conclusion**

- All three regimens are comparable in terms of molecular-corrected efficacy over one year of follow-up
- In terms of delay in re-infection, AS-SP was superior to AS-SQ, which in turn was superior to AL
- All ACTs significantly decreased malaria-attributable anaemia
- ACTs decreased gametocyte carriage, although the reduction in malaria transmission may be questionable.

## **10. Discussion**

Answering a question from the floor, the presenter explained that gametocytaemia density did not correlate with effectiveness outcomes. Another delegate asked what the ethical committee's view was of direct feeding. He reiterated that the study was fully approved by the ethical committee, his centre has a long history of direct feeding, and volunteers are not presented with any risks. In response to a further question, the presenter confirmed that the reduction in gametocyte carriage correlates with the monotherapy figures. The peak is day seven; by day 28, there is a considerable decrease to almost normal levels.

In response to a question from a participant from Tropical Diseases Institute of Antwerp the presenter restated that base line infectivity is measured in asymptomatic carriers. The participant then asked whether the differences between treatments are the first signs of resistance to the artemisinin derivatives. The presenter replied that a decrease in infectivity is seen with AS-SP, but could not explain the effects seen with AS-AQ and AL. Resistance to monotherapy is less than 5%.

Returning to the presenter's point about the peak in gametocytaemia being at day seven, one delegate felt that those gametocytes would not be infectious. He asked how homogeneous the groups were on feeding days and what their ages were. The presenter replied that these experiments are done only in children aged six and older. He could not agree that day seven was too early for the gametocytes to be infectious.

Asked whether there might be differences in naturally-acquired immunity to malaria between the different regimes, the presenter suggested that the use of a drug with a long half life tends to influence immunity. A further question asked what a good marker of antimalarial immunity might be, but the presenter felt that there were none. The most used proxies are antibodies against known antigens. Another theory is that cytokines play a role in immunity.

## **II. The Potential of Anti-Cancer Methotrexate for the Treatment of Malaria**

**Dr Alexis Nzila,  
Kenya Medical Research Institute (KEMRI)/  
The Wellcome Trust**

### **1. Work on Antifolate/Folate Biochemistry**

While working on antifolate/folate biochemistry in malaria, I became interested in other uses of antifolate. Much had already been done with methotrexate in the treatment of cancer. Methotrexate is the first anti-cancer antifolate and I decided to try to tap into the information available from research into cancer in order to better understand the malaria foliate pathway.

### **2. Discovery of methotrexate as an antimalarial**

While testing the Kisliuk effect, I discovered that methotrexate is potent against malaria parasites and multi-drug-resistant isolates, with IC<sub>50</sub>s of 25-35nM. Methotrexate is an old drug whose pharmacokinetics and pharmacodynamics are well understood. I learned that a low and safe dose of methotrexate can yield a concentration of more than 250nM, which can kill malaria parasites.

### 3. Problems with methotrexate

- Methotrexate is toxic
- It cannot be used in pregnancy.

It cannot be developed as a tablet for mass treatment, but it may be possible to produce a specific syrup formulation for children, or to restrict it to specific interventions such as intermittent preventive treatment in infants (IPTi) or severe malaria. We have now agreed to conduct a clinical trial for further evaluation.

### 4. Toxicity

While the drug is toxic, its toxicity has to be contextualised. Methotrexate is used at high doses and for several months in the treatment of cancer, which is associated with life-threatening toxicity. At the same time, methotrexate is used at low doses for up to five years in the treatment of rheumatoid arthritis in adults and of juvenile arthritis in children. We have 30 years' experience of the use of low-dose methotrexate and we know that it is safe and well-tolerated. It is better tolerated by children than adults.

### 5. Common side effects

- In cancer patients, the major side effect is bone marrow suppression
- In rheumatoid arthritis, the major side effects are oral ulcer and diarrhoea.

This toxicity is the result of use on a chronic basis for several years and of dose increases. In the treatment of malaria, we propose just one three-day course of methotrexate treatment, with no increase in dose.

### 6. Discussion with rheumatologists

After discussions with colleagues in Kenya and Germany, I learned about the dosing patterns used in rheumatoid arthritis. Folic acid is given alongside methotrexate to counteract its methotrexate.

### 7. Safety

Low-dose methotrexate is used also for the treatment of other immune diseases like inflammatory bowel disease, psoriasis and multiple sclerosis (MS). In MS, the dose is not increased and no folic acid is added. Metanalysis clearly shows that a weekly 7.5 mg dose of methotrexate for up to two years is safe and produces no side effects. For the treatment of malaria, we propose a dose of 2.5-5 mg, which will yield a concentration that kills malaria parasites.

### 8. Proof of concept

Two small clinical trials in the 1970s showed that 2.5 mg a day of methotrexate for three to five days was efficacious and safe in the treatment of malaria. However, the results were taken no further, due to concerns over toxicity. The use of methotrexate in the treatment of rheumatoid arthritis began only in the 1980s.

### 9. Time to revisit the potential of methotrexate

Early next year, we plan to repeat the first clinical trial in which methotrexate was proven to be safe and efficacious. Every week, up to a million adults worldwide receive low-dose methotrexate for the treatment of rheumatoid arthritis. In Europe, up to 50,000 children a week receive methotrexate for the treatment of juvenile arthritis. The number of people being given methotrexate is increasing, and methotrexate is the safest and best tolerated anti-rheumatoid arthritis drug.

### 10. Collaborative work

After a meeting with colleagues in Mali and Nigeria, we plan to wait for the results of their Kilifi trial. Colleagues in Thailand are also supportive of the concept of a clinical trial there.

### 11. Conclusion

There is a lot to learn from cancer research:

- Probenecid increases not only the anti-folate activity in the treatment of cancer, but also the efficacy of antimalarial drugs like Fansidar.
- The same drug also reverses chloroquine (CQ) resistance.

### 12. Discussion

A question was asked about the cost of methotrexate. The presenter confirmed that it is cheaply available in Kenya: a 5 mg tablet costs roughly 50 US dollar cents. Another delegate asked the presenter to elaborate on the point about children tolerating methotrexate better than adults and on the mechanism of methotrexate on malaria. The presenter was unable to give a firm explanation of the mechanism of action. In terms of the kinetics, the theory is that the rate of cell division and multiplication is higher in children than in adults.

### III. Understanding the Mechanisms of Piperaquine (PQ) and Lumefantrine (LM) Resistance in *P. Falciparum*

**Dr Leah Mwai,**  
**KEMRI, The Wellcome Trust**

#### 1. The Project

The overall goal is to identify molecular markers that can be used to monitor PQ and LM resistance.

#### 2. The hypothesis

There are mismatched pharmacokinetics between artemisinins and PQ and LM in their combination. In combination with artemisinins, PQ and LM have a longer elimination half life and may provide strong selective pressure for resistance.

PQ is a bisnoquinoline and LM is an amino-alcohol. We think that the impact of CQ molecular markers may have a bearing on resistance to these two drugs. We have been using CQ resistance as a framework to start studying PQ/LM resistance.

#### 3. Objectives

- To assess the PQ and LM activity in Kilifi for the duration of the project it is important to establish the base line activity of Coartem and Artekin in order to monitor for efficacy
- To assess selective pressure for resistance: is selective pressure for Coartem or Artekin resistance exerted by PQ and LM?
- To search for molecular markers that can be used to predict Coartem and Artekin efficacy
- To assess the effect of artemisinin derivatives on auditory function.

#### 4. Clinical trial

A trial looking at the efficacy of Artekin versus Coartem in Kilifi followed 223 children – 149 in the Artekin arm and 74 in the Coartem arm. Samples were collected before and after treatment. Isolates were adapted *in vitro* and assessed for the activity of CQ, LM, PQ and DHA using the hypoxanthine incorporation assay. Most isolates were classified as sensitive to CQ.

#### 5. Assessment of LM and PQ selective pressure

We found that isolates that occurred following treatment were considerably less sensitive to LM, with an IC<sub>50</sub> to LM of 90.32 versus 54.33 before treatment. The same figures for CQ were 38.99 and 58.52 respectively.

#### 6. CQ activity in Kilifi

We found that 88% of isolates had IC<sub>50</sub>s of less than 100nM and only 17% were resistant. We then went on to do pfcr-76 genotyping, which is a marker for CQ resistance *in vitro* and *in vivo*. Wild-type, mixed and mutant pfcr isolates had a mean IC<sub>50</sub> of 13nM, 24nM and 63nM respectively. This led us to choose 25nM as an appropriate cut-off point for Kilifi.

#### 7. CQ resistance before and after its withdrawal in Kenya

In 1998, Kenya changed its treatment of choice policy from CQ to SP, due to resistance. We have analysed the frequency of CQ-resistant genotypes in Kilifi from 1993 to 2006 and compared those data with what has been observed in Malawi, which was the first country to report a reversal of CQ resistance a decade after withdrawing the drug from clinical use. We found a reversal of CQ resistance in Kilifi, but at a much slower pace than that reported in Malawi. We predict that it will take another 10 years to see complete reversal in Kilifi, to the point where it can be used once more.

#### 8. Search for molecular markers of LM and PQ resistance

Although there is evidence that LM and PQ resistance can be rapidly selected, we have no established isolates that are resistant to LM and PQ. We are using three approaches to resolve this:

- Assessing the *in vitro* activity of LM and PQ in isolates and identifying those that have decreased susceptibility to LM and PQ
- Selection of resistance *in vitro*
- Selection of resistance *in vivo*.

#### 9. Work in progress

- Pfmrd1 copy number analysis, which may be important in LM resistance
- Sequencing of genes associated with quinoline resistance
- Continued adaptation of field isolates, drug assays and assessment of selective pressure

- Sampling of V<sub>I</sub>/S LM and V<sub>I</sub>/S PQ for whole genome analysis and expression profiling using DNA microarrays
- Continued selection of resistance in vitro and in vivo
- Characterising isolates with reduced sensitivity to LM.

## 10. Summary

- CQ and PQ are active against field isolates although some have reduced sensitivity to LM
- There is a reversal of CQ resistance in Kilifi, but at a slower pace than that observed in Malawi
- We have established isolates with transient resistance to PQ and LM.

## IV. Research Management Strengthening in an Emerging Medical Education Institution: Experience of the Research Support Centre, College of Medicine, Malawi

**Dr Exnevia Gomo,  
University of Malawi**

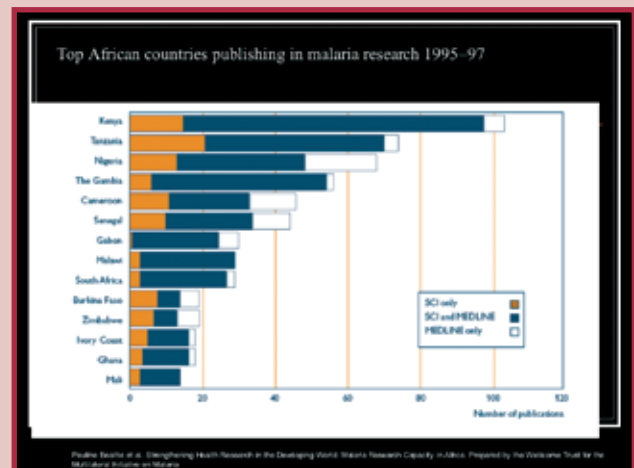
### 1. Background

- The College of Medicine was established in 1991 and now has 100 academic staff, 67% of whom are local staff
- Its main output is medical doctors, so most of the College's work is in clinical research
- Graduate courses include degrees in medicine, medical laboratory technology and pharmacy. Postgraduate courses on offer are MPH and MMed
- The College has produced high quality research with research affiliates in the field of malaria.

Most of the research is from expatriate investigators.

### 2. Highest publishing African countries and malaria research centres 1995-97

Malawi ranks number eight in Africa, with about 30 publications, and the College of Medicine number eight, with about 20 publications.



### 3. Malaria research publications from Malawi in Medline 1973-2007

292 publications were published in which malaria was mentioned, with an increasing trend over the period. Only 17% of publications were authored by African investigators, leading to questions around where our trained professionals are.

### 4. Research strengthening initiatives at College of Medicine

We face serious challenges in terms of a 'brain drain', so the college put in place various strategies:

- 43% of graduates underwent postgraduate training in various fields between 1991 and 2000
- In collaboration with the Gates Malaria Partnership for research capacity strengthening in malaria, since 2001, nine PhDs and six MScs have been completed in various fields, leading to an increased level of publication and a positive impact on healthcare delivery.

### 5. Lessons learned

We have focused on the development of individual skills as a contribution to the building of institutional capacity. Researcher-driven efforts are often fragmented and do not necessarily address institutional needs. There is no institutional recognition of achievements and, hence, no career enhancement. There is limited utilisation of the skills developed in applying results due to a lack of an institutionally-backed communication system with policy makers. Skills are not used to create an appropriate or

conducive environment for the conduct of research, leading to an inability to reproduce local capacity. All of this leads to the phenomenon known as ‘brain drain’.

Institutionally-driven and coordinated research capability strengthening programmes address issues of sustainability of scientist motivation and local capacity reproduction. We need to create an enabling and supportive research environment for the development of local research capacity.

## 6. Institutionalisation of research management at the College of Medicine

The College of Medicine has established a research management function in the Office of Postgraduate Studies and Research, the overall function of which is to coordinate the research efforts within the College of Medicine, looking at the issue of research capability strengthening.

A Research Support Centre was established in 2006 with a mandate of putting structures in place while trying to provide individualised research support, introducing GCP standards and providing a non-commercial clinical trial monitoring service, research information services, grants administration and data management services. We are trying to create an environment that helps scientists through the grants application process once they have set their ideas out.

## 7. Achievements

There is an increasing trend towards the coordination of research activities: because information is now flowing into a central hub, it is easily redirected to specific individuals who need it.

## 8. Challenges

- Researcher apathy
- Fear of change
- Fear of responsibility
- Perceived increase in bureaucracy
- Fear of loss of position and income
- Fear of the unknown.

## 9. Conclusions

- Institutionalising research management provides a more comprehensive research training and support programme, ensures sustainability through institutional commitment and support, and enhances institutional capacity to attract more money

- Capacity building depends on a supportive framework established at home. We need to build individual skills alongside building institutional capacity to retain those skills
- Building bridges between individual and institutional efforts in order to strengthen research in Africa is key to sustainability.

## 10. Discussion

In response to a question from the floor, the presenter confirmed that the College is a government-funded public institution with a key goal of producing doctors. The only way that we in Africa can move forward is to transform research into an enterprise. The challenge is how to encourage the government to consider funding research management positions.

One delegate stressed the need to define what ‘a critical mass of scientists’ and ‘African leadership’ means. The presenter added that, while the situation has improved, work remains to be done. Another question asked what steps are being taken to make funding sustainable. He reiterated the need for a comprehensive research governance framework to improve the chances of survival for institutions. The greatest challenge is convincing governments that research is a critical component of teaching and training.

Another issue raised was around the brain drain, leaving behind newly-qualified PhD graduates, none of whom had yet published any publications. The brain drain is being driven by a search for higher salaries elsewhere. Funding agencies repeat the need for capacity building in Africa yet provide no salary element in their grants. Most African PhD graduates leave the continent within 5 or 10 years for an international position. The presenter agreed, but stressed the need for individuals to contribute to bringing in the money from funding agencies.



# Tuberculosis Capacity Building in Africa

**Facilitator: Thomas Nyirenda (EDCTP SEC)**  
**Rapporteur: Michael Makanga (EDCTP SEC)**

## I. Characterisation of TB Clinical Trial Site in Eastern Sudan

**Prof. Maowia Mukthar,**  
**Institute of Endemic Diseases, Sudan**

### 1. Background / rationale

In Eastern Sudan at least 50% of the hospital admissions were due to pulmonary TB. We wanted to understand the epidemiology in preparation for a trial for a TB vaccine or diagnostics.

### 2. Ethical clearance

Ethical approval was obtained from the Institute Ethical Committee and from the National Ethical Committee in the Federal Ministry of Health. All diagnosed TB patients were referred to the National TB control programme for free treatment.

### 3. Objectives

To identify a new site in Sudan for future TB clinical trials, as well as to determine the real burden of TB in this area, and to improve the Ministry of Health's plans for TB.

### 4. Specific aims

The specific aims were divided into three subgroups. Firstly, TB disease related: estimating the frequency of pulmonary TB in patients with a cough for more than three weeks, to determine the burden of TB at village level, and to document the health seeking behaviour of TB patients. Secondly, health system related: evaluating the health system and its accessibility to TB patients. Thirdly, infection related: studying the incidence of TB in selected areas, mapping the frequency of Mycobacterium drug resistance in enrolled patients, determining the diversity of Mycobacterium isolates, and studying the risk factors for TB.

### 5. Methods

The study was completed through cross sectional surveys, looking at the cough rate at village level. Those who had a cough for longer than three weeks were subjected to clinical and bacteriological surveys for identification of TB patients.

### 6. Study population

The area was divided into strata based on population density, and random villages were selected from each state, 50 from Gadarif and 30 from Kassala, and 100 households were randomly selected from each village. They were divided into male and female, subjected to a cough rate questionnaire, and sputum samples were taken from those who had a persistent cough. Some patients had already been reported to the TB control programme.

Kassala has a population of 1.4 million individuals, most of whom are nomadic, with 17 different tribes inhabiting the state. Gadarif has a population of 1.7 million, mostly settled communities. In Kassala we studied 16,763 individuals; in Gadarif we studied 41,180 individuals. Both tribes live in huts that do not allow good ventilation, making them conducive to the spread of infection.

We asked about death rates for five years prior to the study. We found that 1% of the population of Kassala died in that period, compared to 6% in Gadarif. Looking at gender there was a 4% death rate in males and 3% death rate in females, in the two states. We found that 13% of the deceased people of Kassala died because of TB, compared to 5% in Gadarif. Therefore TB kills more people in Kassala, despite the higher death rate in Gadarif. There were a lot of children dying of other causes than TB in Gadarif. Of those being treated for TB at the time of their death, about 10% of the people in Kassala were under treatment and not responding, whereas 2% of those who died in Gadarif were receiving TB treatment.

### 7. Cough rates

The cough rate in the Kassala population was 1%, compared to 2% in Gadarif. The cough rate varied between villages from between 0% to 8%. Coughing was equally split between genders.

### 8. TB diagnosis

In Kassala 0.66% of the population were diagnosed with TB, compared to 0.5822% from Gadarif state. That translated into between 9,000 and 10,000 patients in each state. All had typical microbacterium TB. More than 60% of those

questioned said they would seek treatment within 6 months of experiencing coughing, and about 60% would seek traditional medicine first, mostly due to the stigma of the disease. Less than 20% of those attending hospital seek free diagnosis and treatment, and there is a 30% drop out rate from the treatment due to inaccessibility of treatment centres and the stigma of the disease.

## 9. Discussion and conclusions

We concluded there were two epidemiological patterns between nomads and the settled population. Although there were similar TB endemicity rates, the TB infection was more fatal in Kassala than Gadarif. The rate of TB infection was still low compared to other countries, but only 10% of the real TB rates were being detected in the study. Therefore more surveillance was needed, as well as a need to improve the accessibility of both diagnosis and treatment. We believe that it could serve as a suitable TB clinical trial site.

The presenter was asked whether he found any incidents of bovine TB and asked for clarification on the gender mortality rates. He said that there were no differences between the genders on mortality, and that they did not find any bovine TB during the study. One participant asked what the primary diagnosis for the persistent cough was, after TB, and asked about the burden of extra-pulmonary TB. The presenter said that the burden of extra-pulmonary TB was high, but it had not been included in the study. Those who displayed a persistent cough were subjected to smear tests, but they were often inaccurate. The laboratories conducting the studies required upgrading, and a lot of patients were missed. One attendee asked why the mortality was lower in Kassala, speculating that perhaps it was because they were nomadic and as a result their records were not as accurate, and also asked about the death rates during treatment. The presenter said that there was a 10% death rate during treatment for Kassala people, and commented that many of them came to treatment very late. There was also severe malnutrition in Kassala, with many people relying on coffee for survival. When they were given food through aid programmes, they would sell it to buy coffee, which was unhelpful to their nutrition.

It was asked whether genetic variation explained the different death rates between the groups. The presenter said that they did not know, but speculated that it was related to the behaviour and culture of the tribes involved, and their lifestyle. A further question asked for advice in dealing with

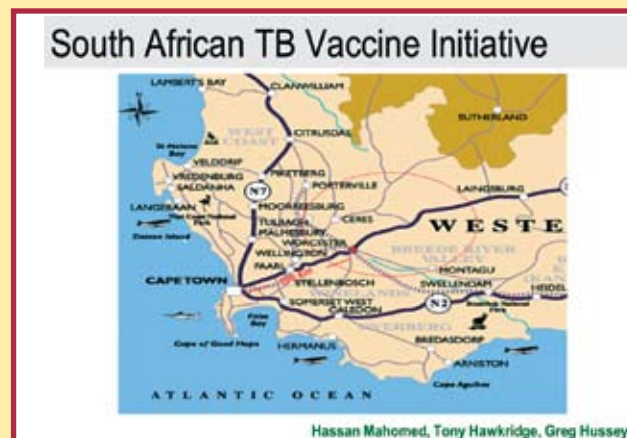
nomadic people. The presenter said that the most important factor was getting people to trust you. In addition, knowing the migration routes, the government had been able to set up some places where the tribes could gather and obtain water.

## II. BCG-induced Immune Correlates of Protection against TB

**Dr Brian Abel,  
University of Cape Town**

### I. Objective

We know that BCG vaccination has variable efficacy. One of the main thrusts of the study is trying to understand why BCG vaccination is so variable, and why some infants are still susceptible after vaccination, and others are protected. In 2000 Greg Hussey set up a clinical site in Worcester, 100 km from Cape Town. The first TB hospital was set up there 50 years ago, and there is an incredibly high instance of TB on site.



### 2. Study design

Looking at the study design, 5,675 infants were enrolled at birth, and were vaccinated with BCG. Ten weeks later blood was collected and stored, and the infants were followed up for two years, and beyond. At a later stage two groups were identified, one consists of 77 infants protected against TB, and 38 that were susceptible to TB, shown by sputum positivity. The two groups were also known to have exposure to TB index cases in their households. We are currently

looking at several parameters 10 weeks after vaccination and are interested in finding biomarkers or new correlates of protection, which may enable us to discern differences between protected and susceptible groups after BCG vaccination.

### 3. Outcomes

There are several outcomes; soluble cytokines can be measured in the plasma, T cell-associated cytokines by intracellular cytokine assays, T cell proliferations can look at the antigenic repertoire, antibody responses specific for mycobacteria, and gene expression and innate immune cells.

### 4. T cell-associated cytokines

Throughout the study a whole blood assay was used that was developed five years ago. Tubes are prepared with the antigen in the lab, transported to the clinic where blood is drawn from the infants, the antigen added, before the tubes are put into an incubator to view the changes. The portable incubator is then plugged into a car cigarette lighter so that it can be transported at the correct temperature, which is critical as delayed incubation can affect the outcome drastically. Upon reaching the lab the plasma is harvested and Brefeldin A is added to block transporter proteins. After another 12 hours the water bath switches off, and the samples are processed.

On the next slide you can see a BCG-induced T cell cytokine expression. You can also identify BCG specific T cell subsets. A more complex analysis can be done by looking at five cytokines intracellularly through multi-parameter flow cytometry. The immune correlates study analysis can be conducted, leading to approximately 136 different outcomes.

### 5. Soluble cytokines

Looking at soluble cytokines in infants, 10 weeks after vaccination, we see one example looking at interfering gamma levels. When you look at it as a new correlate of protection, you find that there is no difference between the protected and non-protected group. With the technology that we had, we could measure 29 different factors in the plasma simultaneously. Looking at univariate analysis, MIP1a was the most specific thing in terms of a BCG-specific stimulated factor. The protected group had higher levels of MIP1a compared to the non-protected group. When looking at unstimulated growth, you see that epidermal growth factor is higher in the non-protected group than the protected group, although we cannot yet say whether this is biologically important.

### 6. Differences between stimulated and unstimulated samples

Using univariate analysis in unstimulated plasma we found three significant factors: IL-13, epidermal growth factor and fractalkine. In this case we found there were 10 factors included from the unstimulated results that were then put into a model to try to determine a difference between the protected and unprotected group. We found a sensitivity of 84%, a specificity of 79% and correct classification of 81%, but the data still requires validation. Looking at BCG stimulated blood; the model was not that strong. Three factors were taken into account: MIP1a, fractalkine, and IL-12p70. The sensitivity is only 66%, specificity is 71%, and correct classification is 69%.

### 7. Conclusions

IFN- $\gamma$  alone measured at 7 hours in a WBA is not a BCG-induced immune correlate of protection against TB. Combined analysis of multiple measures, as shown, may allow differentiation of the two groups in question. Also, analysis of unstimulated blood might yield answers. Importantly, critical determinants of protection such as interfering gamma, is not necessarily an immune correlative protection.

### 8. Discussion

One participant noted it was interesting that the evidence of TB in unstimulated blood became very obvious when analysing cytokines. It was asked whether it was always reliable that children could produce smear positive results. The presenter said that the children were subjected to two induced sputa, and it was a very carefully carried out study. He also commented that it was interesting finding the differences in the plasma. One attendee asked what the take-up of BCG was in the study area, speculating that they could perhaps be used as controls. The presenter said that there was a delayed vaccination study, where vaccination had been delayed for 14 weeks, following the group. However, normally it was imperative that the children were BCG vaccinated. It was asked how the BCG immunity differentially affected HIV-positive and HIV-negative children. The presenter said that it was a concern giving a live BCG vaccine to potentially immunosuppressed infants. A study was ongoing, looking at BCG specific responses in HIV-positive infants. One attendee highlighted the importance of the timing sample measurement. The presenter agreed that it was critical, and

when dealing with infant blood a limited sample was gained, so time points had to be decided carefully. One participant commented that it was interesting to see that there was no difference between the profiles of the gamma between the two groups, and asked whether there were any quantitative differences. The presenter said that it had been a quantitative measurement. He also stated that the intracellular T cell analysis would also yield interesting answers.

It was asked what the other determinants of protection were, asking about socioeconomic factors and whether exposure was assumed to be uniform among all infants. The presenter said that all infants came from the same area, and although identical exposure could not be addressed all 115 infants from the two groups had confirmed TB index cases in their household.

### **III. Safety Tolerability and Monitoring of Combined Anti-tuberculosis and Antiretroviral Therapy**

**Ms Thuli Mthiyane,  
MRC, Durban**

#### **1. 6-Arm pharmacokinetic study**

This study is for my PhD, and investigates the bioavailability of rifampicin, isoniazid, zidovudine, lamivudine and efavirenz. The pharmacokinetic study has six arms, studying different levels of immunosuppression. The groups of 20 patients included:

- HIV-positive without TB
- HIV / TB co-infected patients with a CD4 count lower than 200 receiving anti-TB treatment and ARVs
- HIV / TB co-infected patients with a CD4 count of 350 to 500 receiving TB treatment only
- HIV / TB co-infected patients with a CD4 count of 350 to 500 receiving TB and ARV treatment
- HIV / TB co-infected with a CD4 count of 220 to 349 treated with TB treatment only HIV / TB co-infected patients with a CD4 count of 220 to 349 treated with TB treatment and HAART.

Therefore, one group receives both chemotherapy for TB and HAART, and the other receives only chemotherapy.

#### **2. Aims**

The purpose of the study is to compare side effects of participants receiving both treatments for HIV and TB, and compare it with patients receiving treatment for TB only. One aim was to determine the effects of polymorphism in N-acetyltransferase and cytochrome P350 on toxicity and pharmacokinetics of combined TB and HIV therapy. We are conducting a Health Related Quality of Life questionnaire between the two groups, and also investigating the utility of IFN- $\gamma$  release assay in the monitoring of immune reconstitution and outcome of therapy in patients treated with TB and HIV therapy.

#### **3. Study objectives and methods**

We looked at all serious adverse events from both groups, hepatotoxicity of grade one to four, and comparing this between patients who have hepatitis B and C, to patients that have hepatotoxicity without hepatitis B and C. We also looked at immune reconstitution syndrome in both groups. We also looked at patients' quality of life when treated with TB treatment as compared to TB and HIV treatment. We are also looking at the kinetics of mycobacterial cellular immune responses in patients treated with HIV and TB drugs, using an INF- $\gamma$  release assay.

#### **4. Study design**

We are looking at 120 patients, began recruitment in March 2007, and have currently recruited 59 patients. Of those 40 have a CD4 count of below 200, 20 have HIV infection without TB and 20 have HIV / TB co-infection. We have collected samples for Hepatitis B and C and IFN- $\gamma$ .

#### **5. Challenges**

One challenge is recruiting patients in the higher CD4 count group. The area has a big HIV / TB co-infection, but unfortunately most patients come with a CD4 count below 200. In those patients with a CD4 count between 220 and 500, if they are nearer 220 they tend to drop below 200, which means they qualify for ARV therapy; or if they are closer to a 500 limit, they go over, which means the patient should not have been treated with ARVs as yet. Therefore this creates a big dilemma for the study.

## 6. Responses to challenges

We used to be able to find all the volunteers in TB clinics. Since South Africa has moved towards a comprehensive healthcare system, the TB patients are now in all clinics, making the search harder. More staff are needed to assess the additional sites.

## 7. Discussion

It was commented that there were schools of thought regarding people with a CD4 count of lower than 200, although there was no answer as to why ARVs should be started at less than 200. Some believed it was a political or financial issue. The presenter agreed there were no scientific reasons for starting ARVs at a CD4 count of less than 200, although a main study was being conducted to determine the best time to start ARV therapy. They were also looking at starting patients with a CD4 count of between 220 and 500 on ARVs to see what the drug interactions were. One participant said that rifampicin was not mainly metabolised by cytochrome P450. The presenter thought that there was literature that said that it was. It was asked what instances of hepatitis B and C were expected in those that suffered from HIV and TB. The presenter thought they were looking at 10% of hepatitis B cases, but was unsure about the projected rates of hepatitis C.

## IV. Anti-retroviral-drug-induced Hepatotoxicity and Introduction of these Drugs at the Level of CYP450 Metabolism

**Dr Getnet Yimer Ali,  
Addis Ababa University, Ethiopia**

### 1. Introduction

Ethiopia ranks eighth among the 22 high burden countries, with a TB incidence rate of over 353 per 100k. In Ethiopia TB / HIV co-infection ranges from 6.6% to 58%. The DOTS coverage in Ethiopia is 70%. Although effective therapy is available for both TB and HIV there are major treatment problems. One of the main problems is a high pill burden, with patients taking up to 20 tablets a day, and there are also problems with adherence and immune reconstitution

reactions. The main areas of our interest are overlapping drug toxicities and drug-drug interactions.

The major area of our interest is in addressing adverse drug reactions, and we have only got a small amount of published data in cases where patients are taking TB medication and ARVs. When we see drug-drug interaction, the ARVs interact at different levels, and we believe the level of PIs and NNRTIs is significant when taken with rifamycins. There are also interactions between INH and ARVs, where there are only a few studies showing how INH inhibits liver function.

### 2. Significance of the study

We believe the study will allow us to identify the prevalence of hepatotoxicity and try to identify the possible risk factors for level of hepatotoxicity. We will try to identify the drug-drug interaction between ARVs and anti-TB drugs, as well as the genetic profile of different drug metabolising enzymes in Ethiopians.

### 3. Phase I: objectives

The objective of the first phase was to assess the prevalence, severity and prognosis of hepatitis induced by first-line anti-TB drugs in Ethiopian HIV-positive patients and identify associated risk factors.

### 4. Methods

The sample size contained 103 HIV-positive patients and 94 HIV-negative patients. All patients gave consent and were screened for HIV. Relevant demographic, clinical and laboratory data were collected from the patients. They were followed every week in the first month, and every two weeks in the second month for development of hepatotoxicity.

### 5. Definition of DIH

Drug induced hepatotoxicity (DIH) will be diagnosed based on a standardised toxicity grade scale, which classifies severity based on change of the serum AST or ALT levels relative to the upper limit of normal.

### 6. Results

The results of the phase I study indicated the different demographics of those who participated in the study, showing the more dominant individuals being under 35 years of age, with a lower BMI in most of the study participants. The HIV positivity and negativity was also proportional. We identified a significant association between being female



and being DIH, those with a lower CD<sub>4</sub> count were also at risk of DIH. We did not find that older people were more at risk of hepatotoxicity, but a relation to malnutrition was detected. The development of hepatotoxicity in individuals with hepatitis B and C could not be compared in the study, because the sample was small. Those with slow acetylators are at a higher risk of developing hepatotoxicity.

## 7. Phase II

We extended our study to include a phase II, where we have included only HIV-positive patients. This phase has two projects. The first is to see the prevalence, severity and prognosis of hepatotoxicity in HIV-positive and HIV / TB co-infected patients. The second project is to determine the pharmacokinetics of these individuals, where we will be looking into CYP 450 and NAT<sub>2</sub>, and will try to see whether the polymorphism in this gene will affect development of hepatotoxicity or not.

We need to recruit a further 134 patients in this group, and will follow them for development of hepatotoxicity, as we did in the previous study. The study period will be between August 2006 and August 2009, with the diagnosis and treatment of HIV/TB according to Ethiopian National Guidelines. Those conducting the study have taken part in the relevant courses and training.

## 8. Progress

So far we have been able to screen 250 patients, but we were only able to enrol 26 patients. The reasons for the gap between screening and enrolment was due to a high rate of HIV negativity, patients with extra pulmonary TB, patients already on ARVs, previous anti-TB treatment, a high CD<sub>4</sub> count, refusal of PIHCT, and residence outside Addis Ababa. Two patients have already developed hepatotoxicity, but only one patient has discontinued his anti-TB medication.

## 9. Challenges

One of the major challenges has been the low enrolment rate. This has been exacerbated by the other clinical trials being conducted in Addis Ababa as well as the very tight inclusion criteria.

## 10. Discussion

One participant asked what the TB regimen in Ethiopia was. The presenter said that the Ethiopian treatment for TB was two months of intensive and six months of continuation,

where they used rifampicin, ethambutol and pyrazinamide in the intensive phase, and ethambutol and INH in the continuation phase. The presenter was asked whether he was studying other types of toxicity alongside hepatotoxicity, for example, peripheral neuropathy and the potential interaction of that with nutrition. The presenter explained that he felt it was a known factor that the nutritional status of the patient did affect the level of hepatotoxicity. As the drugs were carried by plasma proteins nutritional status had a direct impact on the level of albumin and other drug transporting proteins in the body.

One attendee asked whether the hepatotoxicity was mainly dose dependent or idiosyncratic, and whether the answer to that question had a bearing on the sample size of the study. The presenter said that so far the study had shown that the dose did not matter, and they had not tried to coordinate the dose with the development of hepatotoxicity, because they were giving the same dose to all participants.

## V. Assessment of 21 Clinical Trial Sites in Africa to Measure their Readiness to Conduct GCP/GLP-compliant Trials for new TB Therapies

**Dr Christo van Niekerk,  
Global Alliance for TB Drug Development,  
Pretoria, South Africa**

### 1. Objectives

We developed a user-friendly database as part of the project, where the assessed clinical trial sites and associate laboratories are housed. This is for utilisation by a broader audience.

### 2. Assessing and building infrastructure

First of all we developed a very comprehensive site and laboratory evaluation form, looking at different aspects of clinical sites. We looked at primary clinical site facilities, the pharmacy, the information systems, communication and data management, the microbacterium and safety laboratory from a quality control and quality assurance aspect, the regulatory and ethics committee environment, the requirements for importation of unregistered compounds into a country,

whether there were any satellite sites working with the primary site, and the TB and HIV specific information. This questionnaire was geared towards GCP and GLP registration standard compliance at a particular site. We then conducted the assessments for the clinical sites and the laboratories. The report comes to 120 per clinical site.

In order to do this we contracted two CROs, PPD who assess sites in South America, and Quintiles, who assess sites in Africa, North America and Europe. We also hired two internationally recognised microbacterium laboratory experts, to ensure the quality of the TB laboratory evaluations:

Dr Kathleen Eisenach from the University of Arkansas and Dr Frederick Sirgel from the MRC in South Africa.

### **3. Distribution of sites**

We have assessed 51 sites in 25 countries and 5 continents. We had one tool, the questionnaire, to ensure the consistency and integrity of the information that we obtained. In Africa we assessed 21 sites in 10 countries in west, southern and east Africa.

### **4. Per site summaries**

We tried to summarise our findings, and estimate the time required to ready sites for participation in a registration trials. We rated laboratories that would be ready in under six months, six to 12 months, one to two years, and over two years. In some instances we made recommendations about capacity building.

### **5. Clinical sites**

Looking at clinical sites and the time required to ready them for participation in registration trials, we can see there a total of 21. Of the sites, 20 would be ready to participate in trials at a GCP/GLP registration level within six to 12 months. One site would take between one and two years to be ready.

### **6. Laboratories**

In total, only 17 laboratories were tested, because some sites used the same laboratories. Only four laboratories were deemed to need six months to be ready, and another four would take 12 months. Therefore, almost half of the laboratories would take six to 12 months, but nine would take longer than that, with seven taking one to two years, and two laboratories taking more than two years before they were ready to participate in registration compliant trials.

### **7. Time required to ready site and laboratory**

Of the 21 sites, four would be ready in under six months and seven in six to 12 months. That leaves more than half of the sites ready within 12 months, but eight that would take one to two years to be ready. Two sites would take over two years.

### **8. Reasons for delays**

We looked at whether the laboratories were accredited and whether they had a quality assurance system and / or a quality manual. Only two African laboratories were accredited, only four had a quality assurance system, and only two had a quality manual.

We also looked at whether SOPs were in place in laboratories, and how comprehensive they were. We found that SOPs were available in almost all laboratories, but they were only comprehensive in 17 laboratories. In the others there were large gaps in SOPs. Only ten of 17 laboratories implemented their SOPs, for the remainder the SOPs were in the lab manager's office, or could not be found. It was also worrying to discover that in only five cases the SOPs were regularly reviewed, in other cases they were written up to five years ago and had not been updated.

We looked at the laboratories' capability of performing drug sensitivity testing, and one can see that 12 of the 17 laboratories could perform drug sensitivity testing, and 11 of the 17 could do TB strain typing.

### **9. User-friendly database**

Many of the reports have been captured in a database that is open to relevant stakeholders through our website.

### **10. Summary**

Overall clinical sites are in a more advanced state of readiness than laboratories. Many laboratories were not certified or accredited, they did not have quality control systems or manuals in place, and although SOPs were in place in many of the laboratories, they did not cover all laboratory areas and are not reviewed annually.

### **11. Conclusion**

The conclusion is that we need to develop adequate clinical trial sites and laboratory capacity in many of the high burden countries to meet the global registration of new, improved treatment therapies in appropriately diverse populations.

## 12. Discussion

One attendee asked what parameters and tools were used to determine how far SOPs were implemented, because he had personally found the process difficult. The presenter agreed that it was difficult to do, because while the SOPs existed they often were not implemented, and in some cases were not available. The presenter was asked how he ensured his recommendations were implemented, because his study did not have that mandate. He explained that the assessments were general, focusing on many aspects. Anyone wanting to conduct a clinical trial would be subject to different protocols, and they would need to run a protocol-specific assessment. He said that it was also not in the study mandate to conduct capacity building.

An aspiration to be able to treat TB in ten days was held by the TB Alliance, but one participant questioned where this optimism came from when there had been no new TB drugs in the last 40 years, the BCG had been around for 100 years, and HIV was now confusing all aspects of TB treatment. The presenter explained that when the TB Alliance was founded in 2000 it thought there would be many molecules on the shelves of big pharmaceutical companies, but in fact there was only one compound. There were now 17 compounds in the TB Alliance portfolio, and probably about 30 or 40 compounds being studied by other organisations. Therefore, the presenter thought that he would not see the 10-day TB treatment, but perhaps the younger scientists would.

## VI. An Alternative Consenting Process: is it Appropriate for Developing Countries?

**Dr Ashley Veldsman,  
University of Cape Town, South Africa**

### I. Background

Informed consent is the cornerstone of clinical research, and researchers are constantly looking and striving for ways to improve the informed consent process. The South African TB Vaccine Initiative was launched in 2000, with a mission of developing new and effective TB vaccines. The sponsor for the study is the Aeras Global TB Vaccine Foundation, and the clinical field site referred to is based in Worcester, 100km outside of Cape Town. The site is essentially a mountainous

region inhabited by a farming community, with smear positive TB rates between 0.5 and 1% per annum, and HIV rates at around 10% in pregnant women.

### 2. Current phase I TB vaccine study

The informed consent process that we are referring to involves the current Phase I TB vaccine study. The participants are largely drawn from packaging industries and from municipal offices. The picture will change, because the Phase III trials will focus on poor, rural and predominantly Afrikaans and Xhosa speaking participants.

### 3. Description of informed consent process

In 2005 Aeras approached SATVI to implement an alternative consenting process, using DVDs and audio taping. The DVD describes the elements of the study and informed consent in three languages: English, Afrikaans and Xhosa. We used staff members to record the DVD. The potential participants were given the informed consent documents 24 hours prior to the consent discussion. In addition they were given a copy of the DVD. The DVD was screened in the waiting room, followed by a question and answer session. Permission was sought from the participants to audiotape the process and the discussion, and the entire process went through our UTC ethics committee for approval. Participants were consented individually and privately, using the standard oral written approach. The nurse went through the details with the participant, and they signed the consent form when they were happy. The process was audio taped.

### 4. Potential benefits

The potential benefits of this technology for the consentor are that they can review the audiotape and identify possible shortcomings in terms of the informed consent process, they can identify frequently asked questions, and can enhance the way that they are conducting or informing the process itself. For the participant the information is being reinforced on a continuous basis, it is being screened in the waiting room and they have a copy at home, so they have an opportunity to review the information on a regular basis, they can then also listen to the audiotape. For the sponsor, the information to the participant is consistent and more comprehensive, and there is tangible proof of the informed consent process itself.

## 5. Potential disadvantages

There are numerous potential disadvantages on the technology side, including access to power supply, access to TV, DVD players and costs. The cost to us was \$650, which was for the costs of getting the audio and videotape done. In the clinic waiting room you would need a DVD player and TV, and the participants themselves also need to have that technology.

There are questions over whether this is appropriate for rural and urban settings, and the fact that lack of technology creates unequal access to information. There are questions over whether the participants themselves, the community and the culture, approve of this approach. Questions arise around the storing of a copy of the audiotape in the home environment, which could potentially result in the loss of confidentiality, and whether audio taping is appropriate when gathering sensitive information. The participant is at liberty to disclose anything, but might be inhibited by the audiotape.

## 6. Points to consider

Our research staff said they found the DVD particularly useful. The fact that information was reinforced resulted in the participants being particularly forthcoming. Whether it is cost effective would be site specific. In terms of being feasible and acceptable, we would probably need to approach our community advisory boards site by site, and consult with them. Is there another way? We have been looking at mobile phones and the way the technology is advancing, and whether there is something that we can do around that.

## 7. Future perspectives

I am hoping that discussion will be generated here, but it is for you to decide whether other sites should explore this technology.

## 8. Discussion

One participant commented that in Africa it was not common to find DVDs in villages, which would be a problem. The presenter concurred, stating that the participants that they had used in the Phase I study had had access to such technology, but with Phase III studies problems were anticipated. One attendee had already been using video consent for the past 10 years, and had found it very useful. However, showing the video once was not enough, and they had found they had had to show it three times, because the

consent forms were so long and complicated. Dr Veldsman said that on participant visits the video was played constantly in the waiting room, so that the message was constantly reinforced.

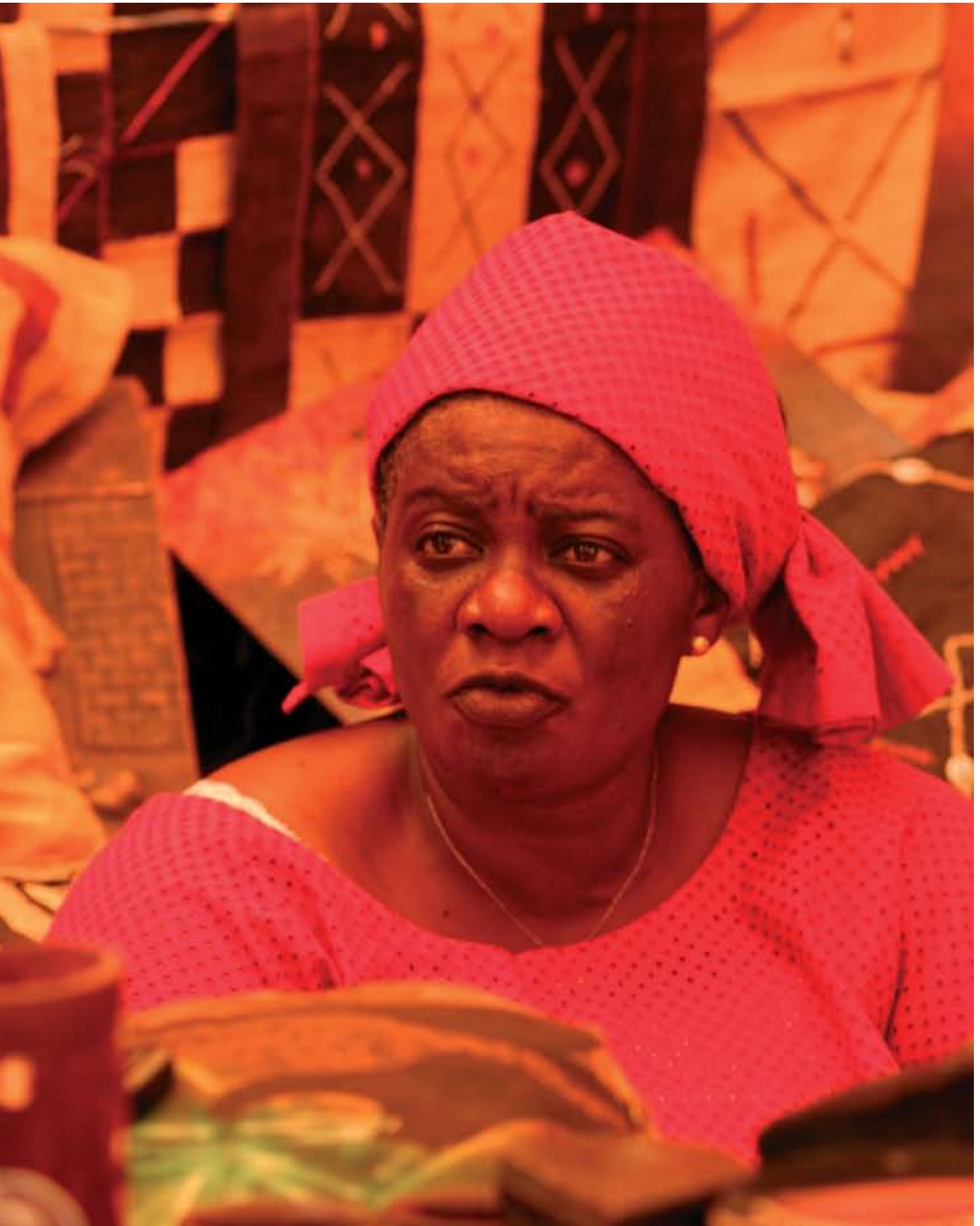
The presenter was asked how she bridged the gap between making an interesting video, which would encourage people to take part in trials, and a more objective video, asking whether the ethics committee had seen the video. It was also conjectured whether participants, when viewing the video in groups, might feel pressure to consent if others did. She said that the ethics committee were just given the transcript of the video, but that making it more exciting would incur a cost factor. She explained that participants were called to a confidential setting to agree or refuse to take part in the trials, therefore nobody else would be aware of their decision.

One attendee asked whether participants signed a piece of paper or whether they just said 'yes' or 'no' on the recording, and also raised the question that an independent monitor might not be able to understand what had gone on if proceedings were being conducted in local languages. The presenter said that the participants signed the informed consent document, were also asked to give permission for the informed consent process to be recorded, and were provided with a copy of the audio tape to take home. The monitors would essentially monitor the document. One participant stressed the need to have the hard copies of the consent, not just the tape. She explained that they had not yet evaluated the strategy, and stated that she was personally concerned about confidentiality. She explained that the trial also kept a copy of the tape, and would keep it to bolster the informed consent document.

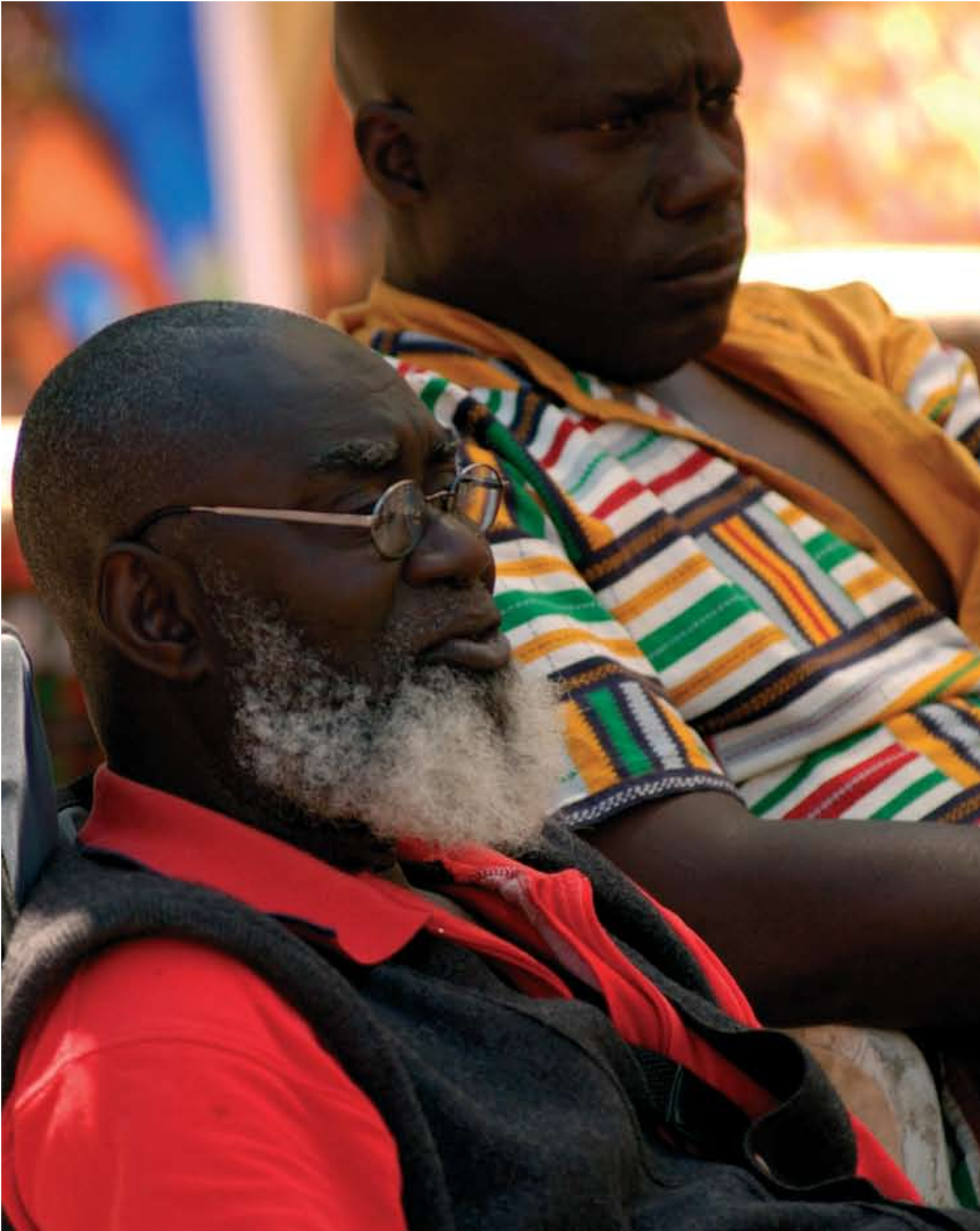
## VII. General Discussion

The Capacity Building Manager of EDCTP requested suggestions for future research areas into TB from the attendees. One commentator stated that it was crucial to identify people that you wanted to treat and manage. Quality management in clinical trials was also mentioned, to include data management and statistical support. He thanked the speakers, who had presented a wide range of science, and all of the participants.









# EDCTP Future and Perspectives (Keynote speeches)

**Chair: Diana Dunstan (EDCTP GA Chair)**

## Building Bridges into the Future

**Prof. Charles Mgone,  
EDCTP Executive Director**

### I. Your Ideas

I want to get ideas from you rather than your questions. I am still listening to find out where best to send EDCTP.

### II. My Dream

About two months ago, after the close of the review, EDCTP decided on its goal. During this process, one question consistently put to me was: what are my dreams? I am going to present my dream but, like many good dreams, when I woke up I found it incomplete, and also found that I was able to amend and improve it. I discussed this matter with the steering committee, incorporated ideas from the review committee and added some of the suggestions you have given me this week. After today's discussions, we can fine-tune what is now a wish list into a working mechanism.

### III. The Platform

#### 1. Goal

The goal of EDCTP is to alleviate poverty, through control of its three major diseases in developing countries, and through interaction between European and African programmes working in partnership.

#### 2. Governance

I am thankful to those going before me in EDCTP, to its past directors and workers. Making the structure what it is

explains why EDCTP took so long to take off but I can now say, proudly, that we have strengthened our partnership between European and African countries, making Africans joint owners of this programme.

### 3. Consolidation

These structures are put together to kill that Goliath: poverty in Africa. Can we alleviate poverty with phase III clinical trials only? David had divine intervention to help him. We are consolidating our activities putting clinical trials at the centre. North-South networking builds the exchange of technology into its development, but EDCTP also has to develop capacity, ensuring that everything we do has an essential purpose. If you utilise capacity immediately, you must ensure that that capacity is retained and that the approach taken is to the benefit of the local community.

### IV. The Future

#### 1. Expansion

We now have the instruments and are beginning to consolidate, but can we down this Goliath in one stroke? Something that has come out clearly from listening to you is that we need to expand our activities; instead of focusing on phase II and III trials, why do we not look from phases I to IV? Is traditional medicine one of the options that we should pursue? Another problem noted is the diagnostic detection of diseases. Then there is the question of assessment tools and whether we need standardised assays. This is a wish list, but there are some things our partners can do and some things we can fight together. Another suggestion has been to broaden our scope beyond the three diseases of HIV, TB and malaria. Why do we not also look at filariasis and schistosomiasis? Should we also broaden our coverage beyond sub-Saharan Africa?

#### 2. Goals and plans

To do all these things, we need a framework and a mechanism that works. The aim of this project is to have a joint programme addressing all responsibilities in which we are active – administrative, scientific, financial and supervisory. We should take a phased approach to this, progressively evolving from a realistic baseline, and guarding against over-ambition.

### 3. Governance

We need to sit down and plan our medium- and long-term goals with our partners, collaborating with other agencies and like-minded organisations to formulate clear strategies that will unite this industry. My vision is for every clinical trial to be part of a commercial product development plan.

### 4. Appeal

My appeal to you, as part of this dream, is to use our heads to think together, and to use our hearts to commit to this partnership.

## EDCTP: Past, Present and Future

**Dr Manuel Romarís,**  
**Directorate for Health Research, European Commission**

### I. Budget and Organisation

Why EDCTP and what has happened in the past years?

The EC organises its research activities into framework programmes. The seventh framework programme (FP7) runs from 2007-13 and has dramatically increased its budget compared to previous years. The EC has a substantial budget, but manages only 5% of the total public research budget of member countries, which is why we need to pool together the capabilities of all states. How can we do this? Typically the EC finances calls to action and networks of different researchers. We have to find new and easier ways of doing this.

### II. Funding Programmes

#### 1. ERA-NET and article 169

We created two instruments. ERA-NET coordinates national programmes and funding agencies, while Article 169 aims for a full integration, rather than just coordination, of national funding programmes. ERA-NET Plus again coordinates national programmes, but the EC tops up funding levels by one-third.

### 2. Creation of EDCTP

In 2003, we created EDCTP with the specific aim of coordinating national programmes employing Article 169 of the Treaty for the first time. We asked ourselves what we were willing to coordinate and decided to focus on poverty-related diseases. In Europe, poverty is not our main priority. It would be more obvious to us to build networks on cancer, for instance. But, in 2001, the EC created a programme of action to fight against poverty-related diseases responding to the UN's Millennium Development Goals. It had four original pillars:

- reducing the price of pharmaceuticals in developing countries
- health-related interventions
- health policies for neighbouring countries
- new interventions against HIV/AIDS, malaria and TB.

This last arm was a response to the envisaged pandemics of these diseases.

### 3. Focus

Why have we focused on phase II and III clinical trials?

The EC typically funds small- and large-scale projects that demonstrate innovative approaches, but there was a gap in support at phases III and IV. We knew we needed additional money from member countries to finance trials and so created EDCTP.

### III. Performance

#### 1. External review

In the past four years, the performance of EDCTP has been lower than expected so that, by the middle of 2006, we began to have our doubts. We had had four executive directors and there were calls for an external independent review. The EC always carries out mid-term reviews of important projects, and so appointed five experts – Adetokunbo Lucas, Allyson Pollock, Fernand Sauer, Jean Stéphenne and Wim Van Velzen.

#### 2. Key recommendations

They produced a document submitted to the EC in July 2007 containing some very specific recommendations. Nobody was saved; everybody had to improve. One of these, directed towards the EC, was to submit a new funding proposal to the Council and Parliament, conditional upon several changes

to EDCTP's targets, governance and commitments. This was the review board's recognition that EDCTP was necessary. They also advised on ways of integrating with Article 169 initiatives. Main recommendations directed to EDCTP were for it to comply strictly with its mandate, for member states to provide their promised levels of financial support and to improve governance performance. If, by the end of 2008, EDCTP had not improved significantly, the board would not recommend its renewal.

### 3. Progress

Are we on the right track? If we take 2007 and the end of 2006, we can see that we have a new executive director, a roadmap to 2010, a scientific strategy, stakeholder meetings bringing 11 calls for proposals and support from BMGF. Member states are starting to commit themselves and integrating EDCTP within their national programmes. In July 2007, the partner members agreed that EDCTP was performing much better than before and gave EDCTP a two-year extension until 2010 and additional funding of €40 million.

### 4. Renewal

In 2008, we will have to decide whether or not to extend EDCTP. We are not as concerned by the secretariat's performance as we are by the financial commitment of member states. If we go ahead, the EC will also have to start its procedures for defining EDCTP 2 in 2010-14.

## IV. Scope

Do you want a broader scope for EDCTP? Should we extend it to other continents and expand it to tackle other, neglected, infectious diseases? Member states have to be involved in these decisions, as their financial commitment is required. For the EDCTP of 2010-14, we want to see EU national programmes for poverty-related diseases in place, and member countries working for their full integration. We need this to become a real public-private partnership, where private funding makes EDCTP the instrument for pharmaceutical companies to conduct clinical trials in Africa. We also envisage full ownership of member states by 2014, so that there is no longer a need for EC funding at all.

## Dr Diana Dunstan

The review was a painful experience, but a positive one in the end, because it underlined the path we had set ourselves and showed that we have begun to achieve some of our objectives already.

## The Role of the East, Central and Southern African Health Community in Health Research

### Dr Steven Shongwe, Executive Secretary, East, Central and Southern African Health Community (ECSA-HC)

#### I. Outline

##### 1. Foundations

ECSA-HC is based in Tanzania and currently has 10 active member states in sub-Saharan Africa. Our convention binds these countries together to fund the organisation, but we also receive support from partners, ministers and policymakers, the largest of which is United States Agency for International Development (USAID).

##### 2. Goals

Our focus is on strengthening technical programmes and our core mandate is to 'promote and encourage efficiency and relevance in the provision of health services in the region'. Our mission is to promote the attainment of the highest standard of individuals, families and communities in our region, which we do through advocacy, coordination and brokerage. Some of our objectives are to promote cooperation, undertake activities that contribute to the highest possible standards of health, bring greater accessibility to health services, and encourage and facilitate the exchange of information among member states. More relevant to this Forum, we aim to encourage and facilitate the conduct of research and dissemination of health research findings.

## II. Role

Our main role is capacity building and training in health research, both operations and clinical, although we have tended to focus more on health systems. We are also involved in facilitation and collection of research, bringing people together to develop proposals across different institutions. An important part of our work is advocating the use of evidence-based research to support policy and programme development.

## III. Research Activities

### I. Highlights

We have been involved in reviewing the voluntary and counselling policies, looking for a new approach whereby we promote provider-initiated counselling and testing. We have been assessing programmes to prevent MTCT and looking at the impact of HIV/AIDS on the health workforce. We have also been involved in evaluating the prevention and treatment of malaria in pregnancy in the ECSA region.

### 2. Dissemination

We provided several forums for researchers to present their findings. Again, this includes both clinical and health systems research. The Health Ministers' Conference (HMC) brings together ministers, senior officials, researchers, regional and international organisations to review research and see how it might be applied to improve systems and develop new policies and programmes. We also hold annual regional forums on best practices and expert committee meetings on HIV, TB and malaria.

## IV. Conclusions

ECSA-HR promotes and supports health research in member countries across sub-Saharan Africa, uniting ministries, universities and research forums. Most activities involve operations research, but we are also keen to participate in clinical research. Forums such as HMC can be used to disseminate your findings and advocate changes in policy. We are very keen to forge a partnership with EDCTP and thank the team for their leadership and collaboration.



## Panel Discussion

### I. Awareness Raising

#### 1. Communications mechanisms

The Chair of the session asked his colleagues for their ideas about how to build EDCTP for the future. The Chair of the PB started by stating that the dream of the Executive Director of EDCTP was reliant on fulfilling the recommendations presented by Manuel Romarís. To have a proper joint programme, better communication was needed between EU member states and EDCTP. Some headway has been made in this direction, for example by using stakeholder meetings to explore partners' interests. Another instrument is Networks of Excellence, which would oblige European countries to collaborate. Also needed is a shared strategic vision particularly between European countries. The ERA-NET mechanism could help them define their own strategy as the first step to harmonising a European vision. It must be the responsibility of each member state to do that.

#### 2. Advocacy

The PB member from Botswana had surveyed member state awareness of EDCTP, from which she concluded that more advocacy work was needed. She recommended that bilateral health organisations support programmes within the individual countries, too. All knew that better research was needed for better-informed funding and capacity development. She supported ECSA as a means to support and to sell EDCTP in the African region – something she defined as a 'make-or-break' issue in the coming year. The Executive Director of EDCTP acknowledged that awareness of EDCTP was low among some policymakers, but stressed that it was everybody's duty to work towards correcting this. The Executive Secretary of ECSA hoped some of the ECSA forums could be better applied to promoting awareness of EDCTP, as could individuals' own interactions with ministers. The group was also reminded that one core function of EDCTP was perhaps to remind the world that the

ever-present threat of poverty-related diseases meant that a solution must continually be sought.

### II. EDCTP's Ambitions

#### 1. Ambitions

Although the call to expand EDCTP's coverage was appreciated, one participant reminded the group that over-extension has often been the downfall of empires. Another voice from Senegal backed the need for all new programmes to clarify their criteria and aims from the outset before thinking about expansion.

#### 2. Phased approach

Any changes of the types envisaged must be carried out step by step, ensuring that the clinical-trials focus is not lost. Perhaps the first step forward would be towards phase IV trials, bringing tested technologies into wider-scale development. In response, EDCTP's Executive Director explained that he had divided his goals into the medium- and long-term in order to ensure such expansion plans did not overstretch the organisation. However, he was eager to hear members' views on what should be done and when.

### III. Funding Mechanisms

#### 1. Centralisation

A member of the Partnership Board was able to inform the audience that funding for any programme required 50% commitment from EDCTP with the other 50% made up of contributions from at least two member states. Many participants thought that in the past there had been contradictory messages about how this funding mechanism worked, which had made it difficult for researchers to access support. One proposal was for European members to place ear-marked money into a centralised pot, which would then allocate funding to the best-performing programmes.

#### 2. Mandate

##### a. Flexibility

The EC representative explained that EDCTP's abilities were restricted by the EC mandate and Article 169 preconditions, although some flexibility is permitted. Phase II and III trials,

for instance, might be broadened to phase I or II, and III or IV. In this way, the organisation might plan its gradual expansion. However, this text would certainly require more overt revision if EDCTP was to actively target other diseases. He was reluctant to suggest such changes before additional funding was secured. He agreed the ideal position was for this common pot that had been suggested, which would sideline the objections of individual member states, but national programmes would still need to be followed and may conflict with many projects envisaged by EDCTP. The task of the organisation therefore returned to one of integration, with the reminder that EDCTP was created to reflect a more strategic approach to all of Africa.

#### **b. Segmentation**

An idea from the PB member from Sweden, which might bring greater clarity to funding mechanisms, was for EDCTP to fund phase II trials, but then recruit member states' support when it came to phase III.

#### **3. Member states' participation**

The EDCTP Assembly member from Spain then asked to speak on the view that member states were not participating enough. There was this dream to integrate national programmes, yet this was difficult when many individual countries have never required defined approaches to TB, HIV and malaria, and have even less history of attacking these diseases in Africa. It was also seldom made clear to EU countries how they should contribute. Although the idea of a common pot was supported, she urged everyone to appreciate how difficult it might be for nations to sign over money to an area for which financing had not previously been allocated. The EC representative explained that every member country already contributes 1% of their GDP to a central EU account. As additional money is needed to conduct clinical trials, EDCTP asks that states contribute more, but many refuse because they feel they are already contributing.

### **IV. Product Development**

#### **1. Capacity building**

The audience was asked to reflect on the progress the medical sector has made in finding drugs to treat TB. The global portfolio is growing, with 17 compounds now being proposed for clinical development. To bring these compounds

to patients, trials will need to take place that meet the requirements of regulatory authorities, which demand strict population profiles. Africa is ideally situated as the base for such studies. Capacity must be developed now, so that we can be ready when many of these compounds reach phase III or further.

#### **2. African empowerment**

The PB member from the UK stated that the main remit of EDCTP was specified as product development, but there were other players in this field, many with more money than EDCTP has. Perhaps its specific function here was partnership to support funding, and a core responsibility within that was empowering African scientists. He hoped that that could be seen as EDCTP's main agenda, but questioned whether the current structure allowed the organisation to best achieve that. The make-up of the GA was 0% African; he urged that that be reconsidered. Here EDCTP's Executive Director pointed out that there was no way of ensuring fair representation of each African country when so many nations were involved in EDCTP. Structures like PABIN and ECSA exist for that very reason: African countries are wary of any central continental body.

#### **3. Sustainability**

An ex-PB member from Canada seconded the UK PB member's view. As the cost of product development was far from the realm of EDCTP's capabilities, to be useful EDCTP had to be focused to show it could help private industry achieve its goals, with the infrastructure and competence to retain the best scientists and sustain the most advanced sites. A representative of MCTA agreed; there is no point making good food if it never reaches the table. Systems are needed in developing countries to bring products to the people that need them.

#### **4. Ethical review**

A participant from Austria hoped EDCTP could also use its influence to develop an ethical review scheme for the entire continent, rather than a series of smaller schemes, in order to build the foundations of sustainable African ownership.

#### **5. Restrictions**

Although speakers were broadly united in recommending a louder voice for African medical interests, there was a legal barrier here in that the GA is a European Economic

Interest Group, so there might be problems in allowing African participants to have a role. If the definition 'product development for poverty-related diseases through clinical trials' could be changed in EDCTP's mandate, it might be able to broaden its scope to more operational research.

## **V. Conclusions**

The Chair of the session summarised that having discussed their dreams, the group now needed to work on putting them into effect. The Chair of the EDCTP-EEIG Assembly thanked all participants for their suggestions, which showed that, as well as sharing a vision, Africa and Europe are willing to share ownership of this partnership, between funders, scientists and, in particular, politicians, united in their commitment to ensure a bright future for EDCTP.



# Enhancing Capacity in Africa: Difficulties, Solutions and Challenges

**Facilitator: Fabio Zicker (TDR Switzerland)**  
**Rapporteur: Michael Makanga (EDCTP SEC)**

## I. TDR's Research and Capacity Development Strategy

**Dr Fabio Zicker,**  
**TDR Portfolio Policy and Development**

### I. Overview

This morning's discussion was very important for addressing several key issues with which we have struggled – the dream, the mandate, the strategy and the rationale for change. All those are common features of TDR, too.

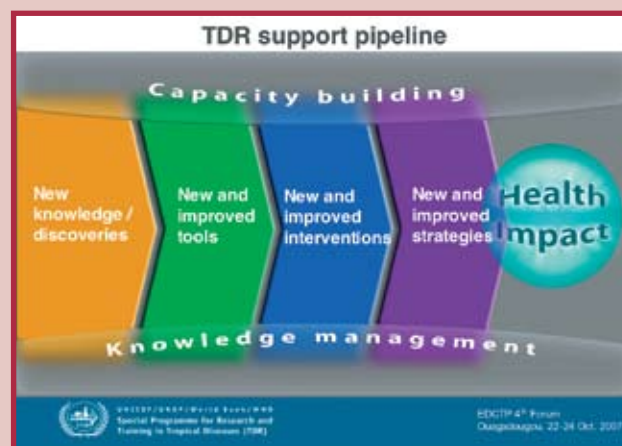
### 2. Evolution

TDR was established 30 years ago with a twin-track objective: to build research capacity, and to produce tools, interventions and strategies to fight disease. Those two tracks are still present and relevant, but we have been changing our programme and framework according to changes and opportunities in the environment. We have opened our scope over the years, and are including analysis of neglected infectious diseases. We have had four independent, external reviews and can now present the final shape of the programme, following this transition period. TDR is still relevant in this new environment, whatever its funding level, due to its constituency, convening power, membership endorsements and analytical skills. We have a core group of scientists in Geneva, but every year mobilise around 300 consultants to review and give direction to our programme.

### 3. Support pipeline

We support activities from the very basic research and discovery, through to the development of drugs and diagnostics, interventions and policy. Capacity building includes the support of institutions, training, networks of various activities, knowledge management and the

production of research documents. We are moving into another phase whereby we are structured according to working packages of business-like activities. We have activities in several countries, focused on development, evaluation and implementation, plus connections with WHO to establish policies and facilitate procurement of products for public health use.



### 4. Competition and partnership

Thirty years ago, TDR was the single major global player in research and training in tropical diseases. Now we are one tree in a forest of comparable organisations. How can we remain relevant in such an environment? Like EDCTP, we need to define our niche, according to our focus, vision and strategy.

### 5. Trends in the infectious disease research environment

Private-sector money is engaging more and more but, at the same time, there is increasing fragmentation. We can see a tremendous increase in research and capacity in developing countries, although there are regional variations. Perhaps what is still missing is an active role for developing countries in priority-setting. In terms of diseases, there have been epidemiological changes as some come close to elimination, while others grow more resistant or start to transmit in different ways. The burden is still high.

### 6. What is needed?

We need an effective – concerted, coordinated, harmonised – global research effort on infectious diseases of poverty in which disease-endemic countries play a pivotal role.



This is our dream. We want to be able to contribute to that global effort by bridging identified gaps and helping to establish priorities on the relevance of treatment methods. The first gap we saw was in the transitioning of new knowledge into product development. There is a second big gap in the real-life evaluation of products, interventions and strategies. There is a need to evaluate the best way to deliver new interventions, in terms of social acceptability, cost-effectiveness and so on. This involves the stewardship of the global effort and empowerment of developing countries. This is how we have reinvented TDR's role in this new environment.

## 7. Empowerment and stewardship

We are promoting innovation in product research and development, as well as interventions in real-life settings through very close integration with control programmes. Our three strategic functions are a new way of seeing this programme: stewardship, empowerment and research on neglected priorities.

## 8. Framework

### a. Business lines

One important point is that this new strategy is organised according to business lines, which are focused, well-defined lines of research on specific priorities. To be productive with a very small budget, you need to operate as a business, and know your metrics and deliverables. The business lines we have established are: basic research, discovery, product development, interventions, real-life evaluations and research for access. Everything else is built as self-contained, time-limited research areas. Each of these business lines has its own budget and advisory group.

### b. Research on neglected priorities

We are looking at innovation, interventions and research for access on priorities not adequately addressed by other partners. This does not include product development, which EDCTP is funding.

### c. Stewardship

When we talk about stewardship, we are aiming to bring partners and governments together to provide consensus in terms of direction, coherence, harmonisation, collaboration and sharing health research. There are several instruments

we can use to do this, by convening disease-based and thematic review groups. A portal to be launched on our website will provide a range of information and analytical research.

### d. Empowerment

We are looking for more capacity, engagement, quality, negotiation skills, decision-making and leadership, and have ways of promoting those concepts. This is about having a voice in terms of what to do and when to do it.

## 9. Research leadership

We have several mechanisms of support – individual, institutions, regional partnerships and global networks. We bring out quality accreditation and best practice in all the research we fund.

## 10. Expansion of scope

Most of our activities are in Africa, but we also cover Latin America and south Asia. In some ways, these activities are an expansion of our scope. At the same time, there is focus on what we are trying to do. We have to balance those concepts within our mandate. Other organisations operate more at the individual or institutional level, some at the national or supra-national level. TDR expects to touch different points in the area of health research.



## 11. Impact dashboard

We have various metrics to assess our performance and portfolio monitoring to see how well we are progressing against our strategic activities, using milestones and deliverables. We are putting together TropIKA.net as a

means to have access to comprehensive information on tropical disease research, analytical reviews and journalism. In addition, we have recently published a 30-year history of TDR. Our experience of TDR has shown that, if you want truly to understand something, try to change it.

## II. Capacity Development in the Conduct of Clinical Trials in Africa

**Dr Nicolas Nagot,  
University of Montpellier, France**

### I. Evidence-based medicine

I would like to focus on the need for all interventions to stem from evidence-based medicine, not beliefs or weak concepts. Evidence-based medicine is about clinical trials – the gold standard of this concept – which require high-quality standards for their results to be trusted and therefore implemented. Such standards have been formalised into Good Laboratory and Clinical Practices (GLCP). There is a clear need for development of research capacities in Africa to meet these needs. We have different levels from where we can build capacities – structures, systems and roles, staff and facilities, skills and tools. This project addresses skills and tools. Another aim, and an EDCTP desire, is to strengthen the networking between Anglophone and Francophone institutions in Africa and in Europe.

### 2. Objectives

The main objective of this project is to develop the capacities of universities and research institutions in Africa to conduct clinical trials in general, but particularly on HIV, malaria and TB. More specifically, we will provide materials and skills for the implementation of practical and theoretical courses on clinical trials in African universities.

### 3. Methods

#### a. Core modules

This project builds on an existing and very popular distance-learning Masters on clinical trials that is currently running at the LSHTM. The first step going forward is to translate the core material into French. The core modules

address the fundamentals of clinical trials, which encompass a wide range of different specialities. We have a focus on practice and all the different aspects of how to implement trials on the field. One module also addresses issues of reporting and review.

#### b. Capacity building

The second step is to conduct two workshops, one in the University of Wits and the other in Burkina Faso, to develop the capacities of institutions to teach materials for face-to-face, rather than by using distance learning. We aim to use 10-15 experienced staff members, and will use the experience of people from the University of Wits, who have already done this exercise for other courses.

#### c. Advanced modules

The third step is to focus on three additional advanced modules addressing the practical aspects of conducting trials, addressing ethics issues, community involvement and field organisation. Hands-on learning will give students experience of real-life challenges.

#### d. Additional courses

The final step is to provide two new Masters courses in clinical trials in Ghana and Burkina Faso.

### 4. Results

This project is ongoing. Step one is half-complete and validation is in process. The first workshop will be held later this year, and the second in 2008. A task force that includes all institutions has been put in place and the project is expected to begin by mid-2009.

### 5. Discussion

We believe this to be an innovative collaboration work between Franco- and Anglophone institutions. It is not easy to work with different languages, but this is succeeding. These Masters courses aim to provide students all the skills needed for a theoretical and practical understanding of the design, conduct, analysis and interpretation of RCTs for different health interventions.

### 6. Future perspectives

This project should be considered the first step for future intervention and capacity-building projects. It is hoped that eventually we can offer the distance-learning Masters course

at the University of Montpellier, so that African researchers can take it from their job or institution in Africa. We also plan to develop South-South university networking. Finally, we hope to move from the individual to the institutional level of capacity building through this network of institutions.

### III. A Bioethics Study of Clinical Research in Malawi

**Matilda Mkunthi,  
The Wellcome Trust Bio-ethics Research  
Study, University of Malawi**

#### 1. Rationale

Our main activities are training and research on ethics. I will present the results of activities carried out as a result of funding from the Wellcome Trust, and show you the training we are doing as capacity building.

#### 2. Objectives

The objectives of this study are to improve understanding of cultural attitudes and perceptions to research, community consultation and the informed-consent process in both urban and rural settings. With that understanding, we hope to provide a base for informing and reforming the informed-consent policy and, through these findings, assess the validity of the Western concepts of informed consent and autonomy in an African setting. We are now seeing a wide spread of clinical research in African countries, but little information has come out from empirical research. Our study is based on the belief that we cannot continue to copy ready-made answers from the West, but need to apply our own answers to the African context.

#### 3. Methods

This study was divided into three phases:

- Phase 1 was a qualitative study where we conducted discussions with 494 participants, whether they had participated in research before, were local leaders or health researchers.
- In phase 2 we were more quantitative, designing a questionnaire from the focus group discussions to give to current trial participants by interview. We only recruited 318 participants because study leaders were reluctant to let us

use their volunteers.

- The third phase, on which we have just embarked, will be more descriptive, involving comparisons between the first and second phases, and other studies too. Similar studies are being carried out in Kenya, Zambia and elsewhere in Africa.

Approval for the study was sought from and given by the College of Medicine Research Ethics Committee. Informed consent was given by individuals at both stages so far.

#### 4. Results

##### a. Discussions

In the group discussions, we wanted an understanding of what would motivate participants to enter research studies. Most participants thought such activities were associated with preventive health measures such as community assessment and health education. 94.6% of the interviewees said they understood the study objectives, but only 21.8% were able to recite them accurately. Most people gave good quality of healthcare as the main motivating factor in their involvement; they believed people were examined better when they participated in research.

##### b. Interviews

In the second phase, 30% of those who perceived benefits through participation also mentioned the high quality of care, which they equated to being in a private hospital. The majority said it was necessary for individuals to give informed consent, and were able to explain why it was necessary. Interestingly, 17% acknowledged there might be risks to their participation, but still chose to take part because of the higher quality of healthcare.

#### 5. Preliminary conclusions

People who refuse to take part in health research do so with an impaired understanding of its meaning and objectives, usually because of superstitious rumours associated with it. Most participants understand their voluntary participation in research, and appreciate that informed consent is sought alongside community consultation.

#### 6. Future perspectives

We want to promote dissemination of research findings to communities to enhance their engagement. We also want to develop public sensitisation programmes to increase

understanding, issuing material in the local language for investigators to use. Workshops on ethics and Good Clinical Practice are also desirable.

## 7. Capacity building

The Bioethics Research Unit has developed modules to teach undergraduates and postgraduates at the College of Medicine, introduced from the first year of medical training. We have also introduced a Masters degree on public health with a specialty on bioethics, offered in conjunction with Michigan State University for the eastern and central African regions. EDCTP has given us some funding, which we will use to strengthen the capacity of the two ethics research committees in Malawi.

## IV. General Discussion

### I. Education

#### a. Translation

The first point came from a participant from Belgium, who explained that at the Institute of Tropical Medicine in Antwerp they ran Masters courses in both French and English. However, they had found that students taking the French course had a lot of problems understanding research, the majority of which was published in English. The presenter from France agreed with the principle behind these points; however, there is such a great need to develop research capacities and skills in Africa that a step has to be taken to start training, while being clear with researchers that eventually they will have to improve their English language skills.

#### b. Distance learning

One speaker threw doubt on the prospect of offering distance-learning clinical courses to Africa-based students, when internet access was often not very reliable. At the moment, as the presenter from France explained, this remained a future prospect, but he believed that internet access would have to improve in the continent. Another participant stated that there were many good institutions in Africa that lacked constant online access, yet still produced high-quality scientists.

#### c. Masters courses

Another more general question was around what organisations were doing to address the severe shortage of Masters students with research skills in Africa. The Chair of the session said TDR had addressed this in the past by promoting four different courses across the continent. Now their focus was on improving training capacity rather than awarding scholarships. They would also provide re-entry grants to help people finishing a training programme establish themselves as researchers in their home institutions. Decisions to provide support have to examine various contextual factors to assess whether an individual's potential is strategically relevant too.

### 2. Capacity building

#### a. Sustainability

The Chair of the session was then asked if, as a result of its monitoring effort, TDR had retention figures on the projects it had supported. He answered that retention tended to be high, because TDR would fund people already based within institutions. Retention is above 80% for PhD students, for example. However, individuals may go on to other governmental, administrative or industrial positions, although very few stayed in the West. Those who TDR has once funded continue to be nurtured in their future activities, as part of a big family. A participant urged a focus on ways to keep former research students in scientific careers after completion of their training.

#### b. Application of learning

A participant from TB Alliance believed that capacity building must include an element of capability building, which was about the holistic application of knowledge and training in real-life settings. He hoped that the two concepts could be interlinked as one. The Chair of the session thought the two terms were often used synonymously, but also recommended careful monitoring of results to ensure they reflected reality, were traceable and reproducible.

#### c. Salaries

One participant stated that one of the major issues with capacity building in Africa was the fact that people were so poorly paid. WHO is one of the main funders of researchers, but does not give any direct compensation to those working on grants. This was based on the understanding that all are

engaging in a public health mission, and it should be the responsibility of each institution to ensure an individual's subsistence. Research projects' funding is perhaps not the best way to correct any imbalance of people's salary, although some disagreed with this point.

### **3. EDCTP improvements**

#### **a. Focus**

EDCTP's Capacity Building Manager updated the group on EDCTP's approach to capacity building. The organisation encourages training at Masters and PhD level, as well as sandwich programmes and involvement in developing projects. Three-year post-doctoral training is also incorporated in the calls for proposals and the senior fellowship programme, encouraging people to build research teams around themselves. All this is integrated in the career development programme of the institutions to which individuals are attached. EDCTP also encourages distance learning as a means to retain human resources in African sites.

#### **b. Site-based training**

An EDCTP-EEIG Assembly member from Spain informed the group there was a programme on applied epidemiology, where people are trained while they work on posts, and they receive condensed theoretical training programmes two or three times a year. This model works well to ensure researchers remain in their communities.

#### **c. Mentorship**

In continuing to draw out ideas, supervisors from strong institutions could act as mentors to guide the continuing development of students over the long term, up to the point that the student is able to create their own research group. There was concern, however, that even if research PhDs were created in Africa, people would leave for Western countries where they could gain better training and higher pay. A participant from MRC echoed these concerns, supporting the use of distance-learning programmes. PhD students should be linked to supervisors who visit the host countries, rather than the other way round, in order to encourage retention. One critical factor in the continuing success of capacity development was equal balance in the North-South relationship, where the North must not be excluded too much.



# Networks of Excellence: Difficulties, Solutions and Challenges

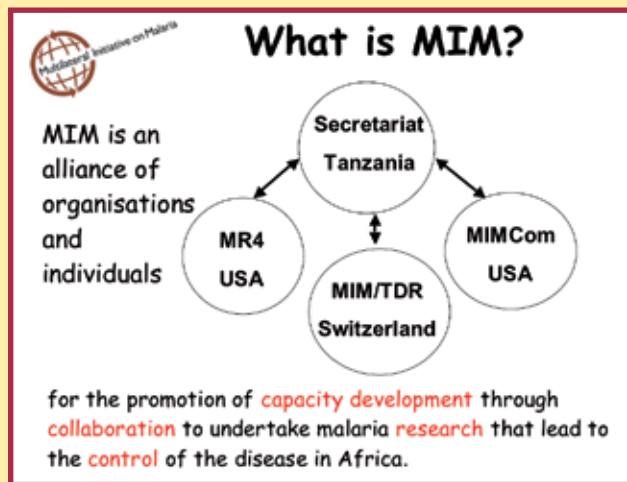
**Facilitator: Andrew Kitua (EDCTP DCCC)**  
**Rapporteur: Rosemary Musonda (EDCTP PB)**

## I. Challenges of the Multilateral Initiative on Malaria

**Dr Francine Ntoumi, Multilateral Initiative on Malaria (MIM), Tanzania**

### I. What is MIM?

The Multilateral Initiative on Malaria (MIM) is an alliance of organisation and individuals for the promotion of capacity development through collaboration to undertake malaria research that leads to the control of the disease in Africa. Its secretariat is in Dar es Salaam in Tanzania with other partners in MIM-TDR, MR4-USA and MIM-Com in USA.



### 2. Vision

The vision of MIM is to enhance public and international malaria awareness and response to level matching the disease burden and facilitating African participation in the development of effective control tools.

### 3. Mission

The mission of MIM is maximising scientific research impact on malaria through coordinated global collaboration and strengthening African research capacity to participate in the development of treatment and control tools.

### 4. MIM strategic objectives

- Promote African involvement
- Strengthen research capacity
- Advocate on global/African malaria burden
- Enhance communication/coordination with MIM constituents and malaria control alliances
- Facilitate translation of research findings into malaria control programs.

### 5. MIM-TDR projects

- 56 PI awarded, Post-docs, PhDs, MSc trainees, more than 100 publications, Many networks (ADRN, MIMPAC, AVRN)
- MIM has contributed to the emergence of a growing body of reference research institutions staffed by well-trained national scientists.

### 6. MIMCom

- Unique organisational and technical strategy to strengthening communication between malaria research sites and scientific community
- Access to electronic information.

### 7. Malaria pan-African conferences

- First MIM Conference, 06-09 January 1997 Dakar, Senegal
- Second MIM Conference, 15-19 March 1999 in Durban, South Africa
- Third MIM Conference, 18-22 November 2002 in Arusha, Tanzania
- Fourth MIM Conference, 13-18 November 2005 in Yaounde, Cameroon
- Fifth MIM Conference, 2-5 November 2009 Nairobi, Kenya.

### 8. What next?

- Have the goals determined in Dakar 1997 have been achieved?
- Changes in funding landscape and partnerships
- How to give a better support to African researchers?
- Strong MIM Secretariat in Africa

## 9. New MIM secretariat strategy

- Research capacity
  - Development of networking activities to bridge the gap between universities and research institutions
  - Coordination of specific Educational programmes (special attention paid to language issue)
- Translation of research findings into applied tools
  - Drive research and gaps analysis surveys
  - Promoting interface control people-researchers
- Increasing communication, sharing information, networking
  - Website, newsletters, meetings and conference.

## 10. Challenges

- To contribute to break some lines of isolation
- Increase the ownership of Africans to MIM
- Increase the impact of malaria research in the control of the disease
- MIM as a platform of communication and information.

MIM continues to strengthen African research leadership and management, and to facilitate the “incubation and emergence” of the next generation of African scientists, thereby ensuring sustainability.

## II. TB Vaccine Phase III Trial Site Networking

**Dr Hassan Mahomed,**  
**University of Cape Town, South Africa**  
**TBVACSIN: Tuberculosis Vaccine Site Network**

TBVACSIN comprises the following sites:

- Siaya District/Kisumu, Kenya
- Worcester/ Cape Town, South Africa
- Iganga/Mayuge/ Kampala Uganda
- Manhica / Mozambique (new).

Objectives are:

- To share experiences with respect to TB vaccine trial site development
- To assist each other with respect with building capacity to conduct TB vaccine clinical trials
- To work towards developing feasible diagnostic and quality

- standards for TB vaccine trials in developing countries
- To strengthen African TB vaccine trial capacity.

Kenyan site is hosted by KEMRI while the site in Worcester is a University of Cape Town (SATVI) research site. Manhica is a newly co-opted site from Mozambique. The host university of the Uganda site is Makerere University. In the same way as the Kenyan site, it is funded by a phase III capacity-developing grant for TB vaccine trials, with significant additional support from the Aeras Global TB Vaccine Foundation. There are high rates of TB, HIV and malaria. TB incidence in the area is estimated to be 368 per 100,000. The site is centred on the Iganga/Mayuge area. The study population is currently 65,000, with a plan to expand it to 130,000.

A partner in the network has had an established research centre, linked to the University of Barcelona, since 1996. It is an established malaria vaccine trial site that wants to develop the capacity to run TB vaccine trials. The study area has a population of 82,000. The sick population is 140,000. They also have high rates of TB, HIV and malaria.

Other partners include:

- The Aeras Global TB Vaccine Foundation
- The KNCV Tuberculosis Foundation in The Hague
- Karolinska Institutet in Sweden
- The Institute of Tropical Medicine in Antwerp
- NACCAP, an important partner in terms of co-funding for EDCTP grants
- The Vienna School of Clinical Research
- The San Raffaele Scientific Institute in Milan
- The Swedish Institute for Infectious Disease Control
- The Institute for Medical Immunology in Brussels.

### I. Network origins

There was a response to EDCTP's 2005 call for proposals for capacity-development for phase III TB vaccine trials. Initially, the Kenyan and Ugandan proposals were developed separately. The South African Tuberculosis Vaccine Initiative (SATVI) and KNCV had links with both groups, which ultimately led to joint discussions among all the parties involved. The SATVI was used as a model to develop proposals for the Kenyan and Ugandan sites, since it had had experience of running TB vaccine trials. Both neonatal and adolescent cohort studies were used in the Kenyan and Ugandan proposals for EDCTP for capacity-development purposes.

## 2. Planned cohort studies

Planned cohort studies would focus on measuring disease incidence in neonates and adolescents, both of which are considered targets for TB vaccine trials. There are differences in the way in which these studies are going to be conducted.

## 3. Network activities

In terms of network activities, there have been joint telephone conferences and communications. We held our first joint meeting in April 2007, which included a visit to the SATVI research site. Another meeting was held in September 2007. Experiences have been shared on ethics, quality management, GCP, standard operating procedures, etc. There has been lots of collaboration on the harmonisation of protocols, looking at diagnostic methods and the main outcomes. Although there are similarities between the sites, there are also differences that need to be taken account of.

## 4. Future plans

A small meeting is planned at the International Union against Tuberculosis and Lung Disease (IUATLD) conference in Cape Town. A training process will start in October/November 2007, with people from Kenya and Uganda coming to Cape Town. The Vienna School is running training in February 2008, in which participants will be participating. The implementation of studies in Kenya and Uganda is planned for next year.

## 5. Summary

- Our insights are based on our experiences so far
- The southern part of this network is very important to us
- The northern contribution has also been key to making this network successful
- We felt the sharing of experience was vital
- We also felt that diversity is important to recognise in Africa and that there should be room for trying out different methods, at least in this preparatory phase, for vaccine trials
- Ultimately, multi-centre trials of TB vaccines will be needed, and we are sure that this network will provide one means by which we can prepare for such multi-centre trials.

## III. Progress on EDCTP Regional Networks of Excellence

**Dr Thomas Nyirenda,  
EDCTP Secretariat**

### 1. Preamble

The idea of forming networks of excellence has been in the EDCTP joint programme documents since 2004. Progress in the past three years has been made in constituency meetings and the empowering of the DCCC (Developing Countries Coordinating Committee) to draw up the first conceptual framework on which funding can be based.

### 2. Rationale behind Networks of Excellence

The rationale behind the establishment of networks of excellence was based on a number of challenges faced by the African continent:

- A high burden of disease
- Poor clinical services
- High morbidity and mortality of preventable and avoidable conditions
- Inadequate human resources
- Other emerging, non-communicable diseases
- A weak infrastructure for research
- Support.

Without addressing the challenges that we have in accelerating the development of clinical interventions, health for all is unachievable.

### 3. Purpose

The purpose of the networks of excellence is to create and maintain sufficient capacity within Africa to formulate and conduct clinical research, with a focus on product research development (PRD) to create new drugs for treatment and to raise the quality of practice.

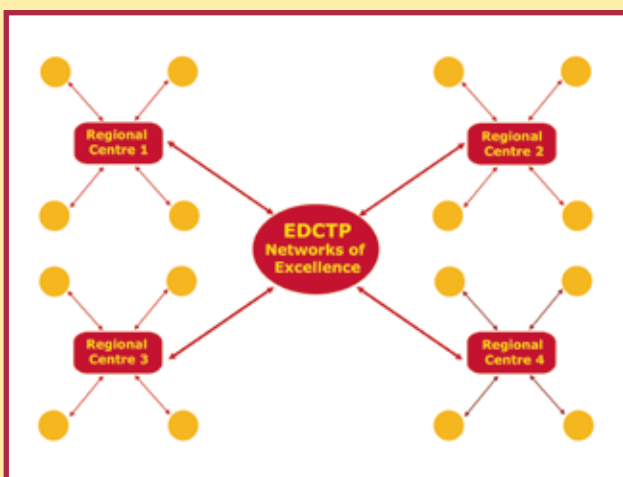
### 4. Objectives

- To create and strengthen African institutions to become specialised research and training centres in clinical research
- To strengthen their capacity in basic skills required for the conduct of research
- To strengthen their capacity to hold quality training across a spectrum of sciences required

- To enhance research collaboration and networks between African institutions, coordinated by the centres that would be identified as nodes.

## 5. Centre network

Centres would have the resources and mandate to support what we call satellite centres or sister centres around them, to uplift them and to bring them to a level where they can participate in multi-centre clinical trials.



## 6. Expected outcomes

- Enhanced production of doctorates and MSc graduates
- Establishment of strong regional networks in clinical research fields, linked and coordinated by EDCTP, and generated under EDCTP principles
- Enhanced capacity to access global funds for research
- Accelerated participation of numerous research centres in multi-centre sites and contribution towards EDCTP goals of accelerating the development of improved tools.

## 7. Methodology

- To consider a call for proposals or letters of interest from institutions
- To assess the capacity of these institutions
- To accredit them for full application as EDCTP networks of excellence
- Centres with insufficient capacity could apply to increase their capacity in one of the areas required to bring themselves to a level at which they can provide support to others.

## 8. Achievements so far

A stakeholder meeting was convened on 8 May 2007 in Douala to discuss the call for proposals. It was decided that it should be an open call and it was launched on 1 August 2007, with a deadline of 3 December 2007. At the same meeting, there was a concern that institutions might not be clear on how to apply to this call. There was a need for seed money provided by EDCTP to convene a network meeting at which several institutions could meet and start discussing how to collaborate, taking into account the short duration between the call and the deadline. Several institutions were encouraged to attend the meeting although it was made clear that those that did were not automatically grantees.

## 9. Next steps

We are awaiting proposals from the different regional networks. We are aware that some of the networks are going to use this Forum as an opportunity to finalise their proposals. We plan to have the call peer-reviewed by February 2008, so that funding can start thereafter.

## 10. Challenges

The two immediate challenges reported are the short duration between the call and the deadline, and the issue of cross-regional collaboration. Members in certain networks feel that they would be better placed if they linked with institutions outside their region. To my knowledge, there is no restriction around doing that. The ultimate aim is to have a pan-African network.

## IV. General Discussion

One delegate asked how the networks related to malaria research fit together and how they avoid duplication of effort. In response, the MIM presenter explained the clear distinction between the three networks that she presented and their objectives. The same key words appear in the objectives but there are different categories of research and there is room for other networks. There does, however, need to be coordination of these initiatives. Asked further what lessons might be learned or pitfalls avoided, she encouraged dialogue and an awareness of what already exists, rather than wasting time and money on duplicating efforts.

A question from the floor asked presenter of TBVACSIN about the aim of his network and whether others already

exist, and about how he sees his network linking with the work of EDCTP. He explained how his network grew up spontaneously and organically following an EDCTP call. Unlike TB-VAC, which is predominantly European, TBVACSIN's network is wholly African. There are unique issues in African countries and a need to share experiences that are relevant in African sites. A participant from South Africa knew of no other TB vaccine networks in Africa or other developing countries. The questioner underlined the importance of finding out about existing networks and possibilities before creating new ones with exactly the same aim.

In response to a question from the floor, TBVACSIN presenter felt it would be difficult for his cross-regional network to fit in with the EDCTP regional initiative. The Chair of the DCCC asked the south-south Networking Manager of EDCTP to clarify an issue around the location of coordinating and satellite centres, to explain whether institutions can make multiple applications, and to suggest ways in which two countries that border each other but which fall into separate regions might collaborate. In response, the presenter's understanding was that the only restriction is that there should be at least three different institutions from three different countries. There are no restrictions around the location of satellite centres. His colleague set out the aim of having regional networks network with each other. He added that institutions involved are centres of excellence that complement each other and decide which one coordinates. The number of satellite centres depends on what the network wants.

A question asked what could be done to address the problem of salaries for MIM principal investigators. The MIM presenter said that, in 1997, funding levels were higher, since when they have reduced, due to the number of players and the need for them to rethink their strategies. A decision needs to be taken around whether to fund a big project with high levels of funding or several small projects with lower funding. She agreed that PI salary levels needed to be reviewed.

One delegate expressed how impressed he was with the progress being made with the networks, but wondered whether the sites already identified through calls could also become satellite centres in the networks of excellence initiative. The EDCTP presenter feared that such a move

might lead to some duplication, although there are no restrictions on centres already receiving EDCTP funding applying for network of excellence status.

A comment from the floor raised concerns about the December 2007 deadline and asked whether it might be extended for a further month. Another delegate asked whether there were plans to finance a single network covering TB, HIV and malaria or, if not, whether it would be feasible to do so. The EDCTP presenter stated that the call was not by disease, but by expertise, which may lead to the formation of networks acting in multiple disease fields. One recommendation from the floor was around the need to clarify what the desired outcomes of the networks are in terms of EDCTP support. Some centres have greater expertise in one disease, but not the others. Some are already members of capacity-building networks, so the question is whether they are going to re-group with other networks in this process. The MIM representative rejected the idea of overlapping between the EDCTP networks of excellence concept and other networks. The EDCTP networks will be organised around the three diseases, with specific needs in terms of conducting clinical trials. They will decide what expertise they need from other networks.

A delegate felt that, although there would be enormous overlap, it would not be a problem, since what has to be done is to utilise and integrate the expertise that exists in other networks, rather than to compete with it. His recommendation in terms of judging the applications was not to use rigid rules, other than those included in the call, but to decide whether what is submitted can achieve the capacity-building and institutional development aims that EDCTP has set itself. Good ideas need to be treated with flexibility. Another participant preferred the word 'collaboration' to 'excellence', and added that the aim of the networks is to improve the entire region in the conduct of clinical trials, and not necessarily in a single disease. The EDCTP presenter remarked that numerous participants in the southern region refused to cooperate with others that did not have a plan. EDCTP expects to see more than three proposals from this region. The challenge will come at review level in terms of what advice the scientific review committee will have to provide if there are three or more proposals all proposing to do the same thing.



# Regulatory and Ethics Environment: Difficulties, Solutions and Challenges

**Facilitator: Sodiomon Sirima (EDCTP PB)**  
**Rapporteur: Aissatou Toure (EDCTP DCCC)**

## I. Update on Research Ethics in Africa: Achievements and Challenges

**Dr Marie-Charlotte Bouësseau,**  
**WHO Switzerland**

This year, we collaborated with EDCTP in two projects: one in Nigeria to strengthen capacity in research ethics committees and one in Gabon. We also held training workshops in North Africa and in Ouagadougou. The Three For Africa project aims to provide distance-learning tools in English and French, focusing on national and international regulations. Basic materials should be available at the end of next year.

There is a need for international debate. EDCTP is now taking greater responsibility in the steering committee of the Global Forum on Bioethics in Research (GFBR) initiative, which provides an opportunity for researchers and members of ethics committees from the north and the developing world to discuss specific issues. We have to discuss the different stakeholders involved in the field of ethics and



how to help countries have national and regional strategies based on the three pillars of strong institutions, harmonised regulations, and network initiatives. We have to be realistic and to think about the long term rather than simply setting up committees to approve current protocols. We have to be transparent and inclusive.

### I. Discussion

One delegate referred to the problems around harmonisation of different activities in Africa in terms of ethics capacity building. Many cultural and socioeconomic factors play an important role. He asked whether the WHO, which is probably the most impartial body to do so, had contemplated facilitating such harmonisation activity. A WHO representative recalled how, at the last GFBR, there had been pleas for no more guidelines. The WHO tries to collaborate with various players such as EDCTP and UNESCO. The WHO could also work with regional initiatives to collect information on existing ethics committees, regulations and training, rather than simply creating another new initiative. Asked how her unit links with the WHO's Tropical Disease Research (TDR) group, the WHO representative outlined how her unit tries to collaborate in concrete ways.

## II. Update on National Regulatory Development in Africa - Vaccines Perspective

**Richard Mihigo,**  
**WHO Office, Burkina Faso (on behalf of the WHO group: Modibo Dicko, Adiele Onyeze, Pierre Kandolo, Lahouari Belgharbi and Liliana Chocarro)**

### I. Key messages

There are two key messages concerning the development of regulatory functions in Africa. Firstly vaccine development pipeline is buoyant. Complex products are under development and specialist regulatory oversight is needed.

### 2. Objective of WHO

The World Health Organization (WHO) objective is that 100% of vaccines used in all national immunisation programs are of assured quality and that National Regulatory

Authority (NRA) strengthening is one strategy to attain this goal. The definition of “assured quality” is that NRAs are independent from manufacturers and NRAs are functional (a system with 6 regulatory functions). This process is guided by Expert Committee on Standardisation of Biologicals (ECSB) recommendations on safety, efficacy and quality issued in WHO Technical Report Series (TRS).

### 3. New challenges:

Responsibility for regulation of new vaccines is a big challenge since:

- Now more on Developing Countries using vaccines
- Less on Industrialized Countries producing vaccines
- Countries have insufficient expertise and experience to assess data and dossiers

Therefore NRAs must acquire new skills. Clinical trials for new vaccines are being run in any country, regardless of the levels of required expertise/strength of their NRA. Therefore quality of the trials must be guaranteed.

### 4. Process to strengthen NRAs

Strengthening of NRAs involves a five-step capacity building program that includes benchmarking, NRA assessment, planning to address gaps (IDP), implementation of plan, including technical inputs (Global Training Network), and monitoring and evaluation. Between 2003 and 2005 WHO led to a process where 7 NRAs were assessed and 26 self-assessed their functions in Africa. It was concluded that countries that have functional NRAs are South Africa, Algeria, Nigeria, Zimbabwe and Senegal. Uganda and Cote d'Ivoire had non-functional NRAs. The status in 18 countries is unknown. In many African countries the problems are of inadequate legislation and regulation due to:

- Outdated, not comprehensive or absent policies
- Inadequate staff by number, training, professional diversity, etc
- Inadequate and unsustainable funding
- Lack of access to independent and objective information.

There have been regional high-level decisions to address the weaknesses. Firstly, the twelfth and thirteenth meetings of the Task Force on Immunization in Africa (TFI) were held in 2004 and 2006. The meetings recommended strengthening DRAs through networking and implementation of IDPs. The status was presented at the 56th meeting of the Regional Committee (all Ministers of Health) held in Addis Ababa,

Ethiopia, from 28 August to 1 September 2006 where a resolution was adopted to strengthen DRA. Secondly, there has been promotion of the “Regional Approach” in:

- Planning workshops to strengthen NRAs
- Development of (harmonised) procedures for regulation of vaccines
- Joint review of clinical trial applications/discussion of regulatory challenges
- Joint monitoring of clinical trials
- Identification of regional needs for training on regulation of vaccines
- Exchange of expertise and networking.

### 5. African Vaccine Regulators Forum (AVAREF)

AVAREF was initiated in 2006 to support NRAs and National Ethics Committees (NECs) in the evaluation of vaccines. It consists of plenary meetings (Accra 2006 and Ouagadougou 2007) plus support activities between meetings. Nineteen countries are involved with NRA and NEC representatives. The objectives of AVAREF are:

- To provide information to regulators of countries that are targets for clinical trials
- To promote communication/collaboration between NRAs and Ethics Committees, among regulators of the region and others
- To provide a resource of expert advice to regulators
- To identify needs for expert support to NRAs

In general about 200 persons have been trained from all over Africa.

### 6 Joint Inspections of clinical trials

A historical moment took place in Bamako, Mali in January, 2007 when for the first time in the African Region, regulators and ethics committee members from Burkina Faso, The Gambia, Ghana, Ethiopia and Mali conducted a joint good clinical practice (GCP) inspection of a phase II observer-blind, randomised, active controlled clinical trial of meningococcal conjugate vaccine at the Centre for Vaccine Development (CVD).

Template Regulatory Procedures were produced for submission of clinical trial applications, clinical trial application review, importation and release of investigational materials, storage and export of human samples from clinical trial sites. Templates were translated in French and shared with all countries for adaptation and adoption. These are already used by a few countries like Ethiopia, Cameroon and Malawi.

## 7 Technical Support to Countries

WHO provides support to countries. These have included:

- Bi-annual monitoring visits to Senegal ANR in GMP, laboratory access, lot release and post-marketing surveillance of adverse events following immunization (AEFIs) – that is part of pre-qualification process of yellow fever vaccine done by WHO staff and consultants that seeks to promote consultants from the African Region
- National stakeholder sensitization workshop in Uganda (2006) to support IDP implementation. Requests for similar workshops have been received from Democratic Republic of Congo (DRC) and Cameroon and one is expected from Burkina Faso.

A journey of 1,000 miles starts with a first step. Previously in most countries in Africa IRBs were the only ones reviewing protocols and no clinical trials application was sent to the NRA until recently. The exception was South Africa where no GCP inspections were conducted. DRAs were not involved in vaccine regulation. As a result regulators were feeling isolated and powerless. Since 2006 NRAs and NECs of Gambia, Mali, Ethiopia, Ghana, Burkina Faso and Senegal have jointly reviewed clinical trial applications and participated in joint GCP inspections. DRAs accept vaccine regulation as part of their responsibilities and are building capacity through the “regional approach” that makes regulators feel empowered as they are no longer alone and know where to seek advice and support. For the future there is need for the following:

- Promotion of confidentiality agreements and memoranda of understanding among countries
- Harmonisation of regulatory procedures. Seven countries have agreed to accept one clinical trial application format (Ghana, Burkina, Mozambique, Gabon, Tanzania, Kenya, and Malawi). This is to be extended to other areas of vaccine regulation
- Training for NRAs in pharmacovigilance for PMS and oversight of clinical trials. This was limited to surveillance of AEFIs and left to EPI
- Advocacy with National Governments for more support (staff and funds) for NRAs
- Advocacy with Regional Political Organisations like South African Development Community (SADC), Economic Community for West African States (ECOWAS) and African Union (AU) to support harmonization

- Advocacy with NRAs of developed countries for increased technical support.

## III. Regulatory and Ethics Environment – Difficulties, Solutions and Challenges

### Dr Ramadhani Noor, AMANET (African Malaria Network Trust)

Only South Africa has a fully functional national regulatory agency (NRA); other countries have NRAs that need strengthening.

Despite the substantial improvements seen in ethical frameworks, they are not as easy to map as the regulatory frameworks. In 2000, 36% of WHO member states did not have ethics committees. Results from a recent survey by AMANET are undergoing analysis. This survey looked at 28 committees and focused on the availability of resources, training needs, the availability of standard operating procedures, and data management and archiving systems. AMANET has also addressed the needs of 21 of these committees by providing up to \$50,000 grants for capacity strengthening.

#### I. Common issues

##### a. Regulatory frameworks

- Few NRAs formally exist; only 10% of medicines authorities have even moderate capacity
- Registration processes are outdated and unapproved or unregulated products are commonplace. For example, in 2005, the WHO estimated that up to 30% of products on the Kenyan market were unapproved or unregulated
- Inadequately monitored or approved clinical trials are becoming common, as is inadequate pharmacovigilance.

##### b. Ethics frameworks

Ethical frameworks have undergone significant improvements but most generally operate below international standards, with:

- Inadequate training of ethics committee members
- Limited professional or educational diversity within committees

- Limited experience, particularly in terms of complex trials being introduced on the continent
- Most committees facing challenges with data management and archiving systems.

## 2. Initiatives

### a. Regulatory

- We have a very good example of a phase II vaccine trial – the meningococcal type A – which was to be conducted in Mali and Gambia. The NRAs in these two countries agreed to hold a joint review and invited three more African countries to assist with the process
- We also have the African Vaccine Regulatory Forum (AVAREF) and the Global Training Network, supported by EDCTP
- There is ongoing harmonisation of guidelines
- The Developing Countries' Vaccine Regulatory Network (DCVRN) is a network of NRA members from developing countries whose aim is to share information, develop a mutual understanding of policies, identify the gaps and assist countries that have no capacity.

### b. Ethics

- EDCTP is a major supporter of training programmes in ethics, as well as providing grants to ethics committees
- AMANET has its ongoing survey
- Other initiatives include the integrated capacity building project, the Pan-African Bioethics Initiative (PABIN) and the South African Research Ethics Training Initiative (SARETI).

## 3. Ongoing efforts

The WHO has 350 regulatory specialists around the world to assist countries develop regulatory capacity. In Africa, there is not much available expertise, which occasionally necessitates Africa to solicit input from outside the continent.

The WHO estimates that, by the end of 2010, 37 of 46 countries will have developed the appropriate critical regulatory functions.

## 4. Challenges

- Despite such wonderful ongoing efforts by various partners, we also have various challenges, the main one being a lack of legal framework in which most NRAs can exercise their authority

- The process of articulating applicable laws in most African countries is slow, which is not helped by the slowness with which the regional harmonisation of regulations is proceeding
- With the changing regulations and a shift in burden to African NRAs, there is a need for the development of pharmacovigilance systems. Even in developed countries, it sometimes takes several years for this to happen and for the system to identify unsafe products
- The issue of regulatory pathways is becoming complicated, particularly in the context of emerging regulations such as Article 58, which is designed specifically for diseases of poverty most commonly found in Africa and less so in developed countries. The pathway along which these products go for authorisation is changing. For example, the leading malaria vaccine, which is expected to be ready for regulatory submission in 2010-11, will require approval by the European Medicines Agency (EMA). EMA will issue a certificate of a pharmaceutical product – a process which is estimated will take at least 13 months. Thereafter, the product will have to be approved by African NRAs, adding another 12 months at least. Finally, WHO pre-qualification procedures for the UN procurement system add a further 18 months. In total, therefore, products submitted for regulation will take at least 30 months to be authorised for market circulation
- There are inadequate numbers of staff with the proper skills. In 42% of cases, Africa solicitation of expertise from outside the continent
- Most structures are relatively poor since they are financed from state budgets. Even if fees are introduced, any revenues generated are paid back to the public treasury, which does not solve the problem
- Often, sponsors and manufacturers try to influence these structures by pushing their products forward for authorisation.

## 5. Recommendations

- We need to continue supporting the networks and initiatives already in place
- We need to invest more in the development and harmonisation of standard operating procedures guidelines for ethics committees and NRAs in Africa
- It is critical to have an accelerated regulatory pathway
- It is in our best interests to look at ways of developing better synergies or reducing duplication in terms of

Article 58 and pre-qualification procedures. There are ethical questions around holding back some of these life-saving products for a long time due to the bureaucratic procedures in place.

## 6. Discussion

A comment from the floor suggested that Africa should take advantage of being late and avoid the deficiencies and failures of Europe. Given the high level of cross-border clinical trials in Africa, it would be illogical to develop completely regulations in each country, as has happened in Europe, which hinders multi-centre research. A suggestion was made to put in place an electronic submission system for ethics committees in Africa and for the WHO to design guidelines around training requirements in different fields. Another delegate agreed that guidelines should be harmonised at a level where one single project in does not have to meet multiple requirements in different countries. Ethics committees look at things from a moral point of view and are not entitled to start judicial proceedings in the case of medical errors. NRAs are mandated to clear projects, and any mistake would result in legal proceedings. They too need ethics committees, so there would be two national ethics committees.

A third comment was that much work has been done on ethics committees and NRAs, but that they have to be based on legal frameworks. In many African countries, there are not even laws regulating research. The participant asked what proposals are being made to put in place such laws. Moving to the issue of funding, another delegate referred to some trial activities being funded by those who have a stake in their outcome.

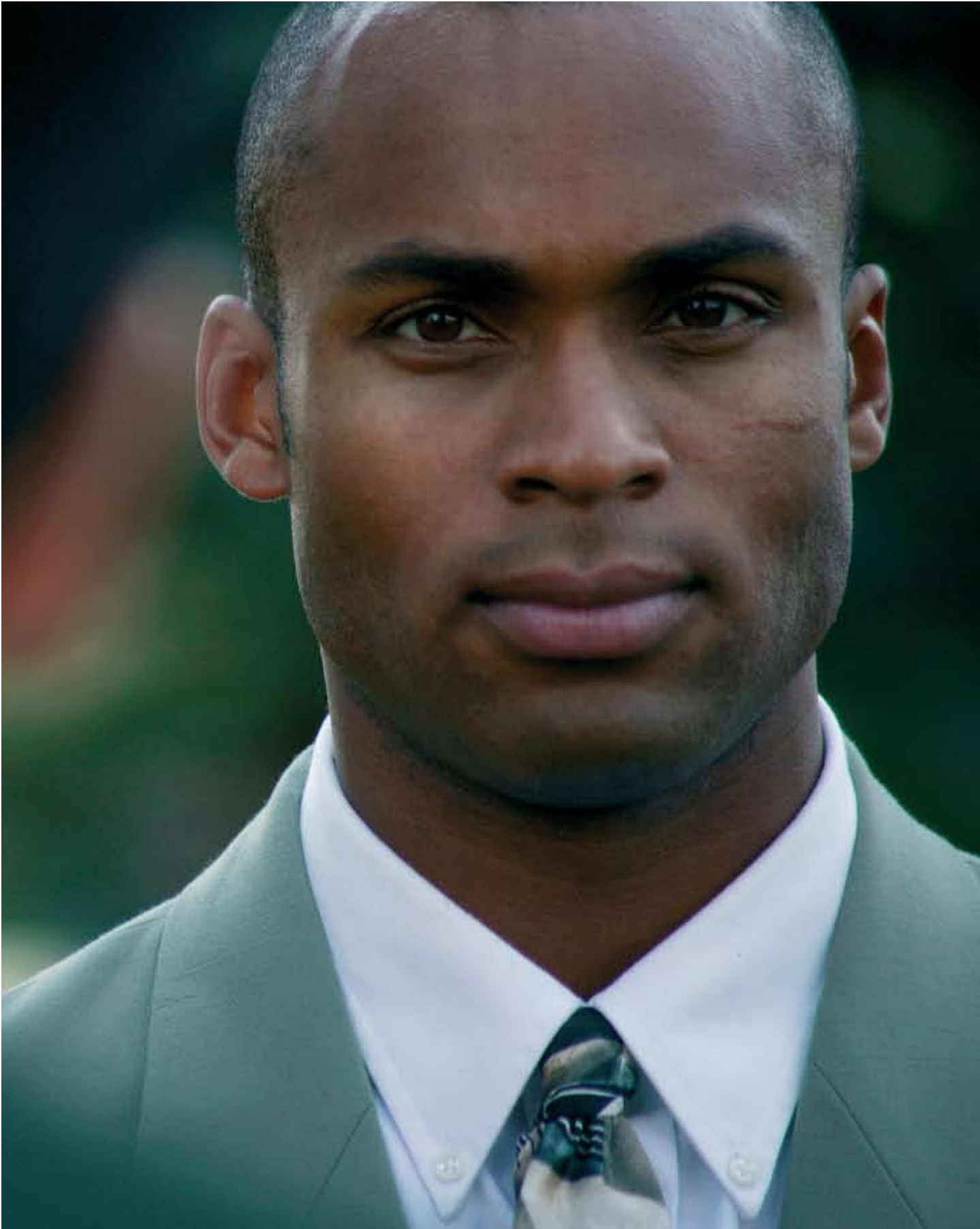
The first presenter of the session suggested that any lawyer asked to look at regulations in African countries would probably find some elements that would have an impact on the way in which to implement an informed consent process. Efforts need to be made to avoid implementing new regulations and laws which take too much time and are not always consistent with existing frameworks. In terms of sharing responsibilities between research ethics committees and regulatory authorities, the function of ethics committees is to evaluate the proposal against different criteria. However, in order to start any clinical trial, formal authorisation is usually required from the body which is able to stop the trial if there is a problem. In terms of harmonisation, she warned against dictating to countries what good models are. It is vital to recognise what exists while trying to facilitate collaboration. The Chair of the session summarised the outcomes of the session:

- The group agreed that good research requires ethical committees
- Ethical committees in Africa need to be strengthened.
- One concern is the risk of duplication between various initiatives
- A question was raised around whether the scope of ethical committees should cover scientific review as well as ethical aspects
- The registration of new vaccines will require functioning NRAs, of which there are very few in Africa
- Work needs to be done to avoid multiple ethics committees in different countries reviewing the same protocol
- Efforts are required to avoid any interference in the outcome of any review decision by the amount of financial contribution made by an applicant.

**[Electronic Poster Sessions followed]**









# Feedback and Final Summaries

## Feedback on: Clinical Trials Updates and Networks of Excellence

**Chairs: Richard Adegbola (EDCTP PB)  
Peter Ndumbe (EDCTP DCCC)**

**Dr Thomas Nyirenda, EDCTP Secretariat**

### I. Malaria

#### 1. Clinical Trials Update

Investigators need to identify credible and experienced sponsors. There is a need for normal laboratory values supported by studies that have generated baseline data on appropriate populations for clinical trials. On quality assurance, sensitive tests must be carried out in certified, centralised laboratories. Electronic data transfer was also discussed, where resources were an issue. It was also highlighted as investigators' responsibility to plan and budget for clinical trials adequately.

#### 2. Networks of Excellence

##### a. Issues

There were ethical issues related to the direct feeding of mosquitoes on persons. This group also discussed ownership responsibilities when government funding was used and how they interacted with African stewardship. It is important to have a critical mass of trained, young scientists for the future, where the matter of salaries should not be neglected.

##### b. Recommendations

- EDCTP must continue to support malaria research
- There is a need for attractive conditions for African scientists in terms of salary increases
- The follow-up period for monitoring ACTs' efficacy must be extended
- The assessment of chloroquine resistance should continue
- Continue researching methotrexate as an antimalarial drug.

### II. Tuberculosis

#### 1. Clinical trials update

An observation made in this group was that, quite often, even EDCTP-funded projects addressing similar questions do not know about one another. There were considerations about whether moxifloxacin-containing regimens should be rolled out to children when there was a realisation that this drug was unsafe. Better understanding of therapeutic vaccines and immunomodulators going into phase II was needed, as was clarity on the difference between paying and reimbursing study volunteers.

#### 2. Networks of Excellence

Epidemiological studies were supported to generate normal range values and to determine the burden of pulmonary, extra-pulmonary and bovine TB. Studies were also sought on diagnostics, correlates of immunity, the economics of intervention and the baseline genetic profile of African populations. There is a need for continued assessment of clinical trial sites alongside quality management of trials. An increased governance contribution towards research in Africa should ensure greater sustainability.

### III. HIV/AIDS

#### 1. Clinical trials update

##### a. Issues

Concerns centred on the duplication of failed studies. It was also felt that there was a lack of understanding of basic HIV immunology. In trials, the function of vaccines was not being clearly explained to participants, nor were microbicides clearly defined. This group identified a lack of monitoring tools for the safety of microbicides. Concerns were also expressed over the development of resistance to ART, the use of single-dose NVP instead of full-dose ART, and that there were fewer combinations available for children.

##### b. Recommendations

There is a need for better science to understand the basic immunology behind the design of vaccines and help explain to trial participants what they can do. Biomarkers for efficacy must be developed to improve the safety of microbicides. Genetic studies could be carried out to better understand

MTCT, and more studies need to show how children respond to ART, including immunologic and virologic responses. This group also proposed the standardisation of assays for protective immunity, perhaps achievable through regional nodes of excellence.

## Workshop Feedback

### I. Enhancing Capacity – Difficulties, Solutions and Challenges

**Dr Michael Makanga,**  
**EDCTP Secretariat**

Discussions were based on innovative ways of enhancing capacity, drawing lessons from TDR's research and capacity-development strategy, distance learning and research ethics in Malawi. Some recommendations include:

- Build on country networks where these exist
- Capacity development requires increased collaboration to minimise complexity
- Host African countries must be more involved in resource mobilisation and prioritisation
- Pay attention to regional variations in capacity and encourage mentorship schemes
- Encourage focused well-designed lines of research with monitoring and evaluation
- Promote best practices and encourage quality control.
- Innovate collaborative work between Franco-, Anglo- and Lutherphone institutions
- Improve institutional infrastructure including IT support to assist distance learning
- Retain more staff longer by creating a critical mass of researchers
- Continue mentorship between North and South scientists
- Disseminate research findings to local communities and sensitise them to findings.

### II. Networks of Excellence – Difficulties, Solutions and Challenges

**Dr Rosemary Musonda,**  
**Botswana Harvard School of Public Health**

#### 1. Issues raised

There are a lot of issues around malaria, HIV/AIDS and TB, but how do they fit together? How does the new TB network link to the existing one? There was also discussion around the proposed regional structure of EDCTP's network of excellence.

#### 2. Conclusions

Networks should aim to reduce overlapping activities in their mandates. To do this, there is a need for more information so that the individuals managing them have a better idea of what others are doing. That requires complementarity and a recognition of the different strengths each can bring.

#### 3. Recommendations

To minimise overlaps, networks need to be clear on their roles, but they should also have some flexibility so they are able to support emerging networks when their proposals are viable. EDCTP can collaborate with other organisations involved in networking like the Wellcome Trust. Indeed, there is a strong need for coordination across all networks.

### III. Feedback on Regulatory and Ethics Environment – Difficulties, Solutions and Challenges

**Dr Aissatou Toure, EDTCP DCCC**  
**Dr Sodiodom Sirima, EDCTP PB**

#### 1. Context

We discussed the need for new drugs and high-quality research taking place in an adequate environment. Different initiatives are ongoing in terms of those aims, across



many different bodies. Although there have been some achievements in terms of capacity building and networking, all speakers believed challenges remained.

## 2. Issues

There was again concern about duplication of activities due to lack of information sharing. Another issue raised was the scope of activity of the ethical review committee, which might conflict with national regulatory authorities. Perhaps this is due to inadequate funding or a lack of the expertise needed to evaluate and monitor clinical trials.

## 3. Recommendations

- Improve coordination between stakeholders and joint activities
- Collect and disseminate information on ongoing activities.
- Harmonise standards of practice and regulations, but avoid too much uniformity
- Continue to support networking
- Clarify the different functions of ethics review committees and national authorities
- Provide tools and guidelines in different languages
- Advocate that ethics committees are funded sustainably
- Strengthen the capacity of ethical and regulatory bodies.

## IV. General Discussion

### I. Additional recommendations

Members were asked if there were any amendments or additions they wanted to add to these recommendations.

One DCCC member emphasised the need to study correlates of immunity in malaria, just as there is for other diseases.

One ex-PB member felt there were common problems to all three diseases, so maybe EDCTP should work towards more global recommendations.

### 2. Capacity building and Networks of Excellence

#### a. Retention

One respondent warned that, although there was consensus on the need to develop African scientists, it was essential they did not neglect their retention.

#### b. Facilities

In setting up clinical trials, notions of versatility of sites should be emphasised, so that centres do not have to be rebuilt. Researchers in different fields can learn from one another, rather than disassociating, allowing scientists to network and share resources.

#### c. Funding

Another participant thought funding strategies needed to project further ahead to ensure sustainability and retention.

## Closing Remarks

### **Prof. Charles Mgone**

On behalf of all invited, I would like to thank the organisers for their hard work and dedication. I acknowledge the hard work of our travel bureau and secretariat in putting this conference together. Special thanks to the local organising committee for their tireless effort to making this event as successful as it was.

Going forward, this Forum will take place biennially. There are plans for each meeting to be held in Africa, since Africa is our focus, but that decision is still pending.

### **Dr Sodiomon Sirima**

I am sure many of you did not know where Burkina Faso was until you looked it up on the map. If nothing else, at least you now know where we are located. Thank you for your belief in us and for making the trip here. Thank you to my colleagues for their trust in our achievements.



## Annex I: List of Participants

<p><b>Abdoulaye Djimde</b> University of Bamako MEDRU/MRTC/DEAP/ FMPOS <i>Mali</i></p>	<p><b>Aline Uwimana</b> NMCP Rwanda <i>Rwanda</i></p>	<p><b>Brian Abel</b> University of Cape Town <i>South Africa</i></p>	<p><b>Christian Burri</b> Swiss Tropical Institute <i>Switzerland</i></p>
<p><b>Abdoulaye Kone</b> University of Bamako Malaria Research and Training Centre <i>Mali</i></p>	<p><b>Ambrose Talisuna</b> East African Network for Monitoring Anti-Malarial Treatment <i>Uganda</i></p>	<p><b>Bocar Kouyate</b> Centre de Recherche en Sante de Nouna (CRSN) <i>Burkina Faso</i></p>	<p><b>Christian Lienhardt</b> UR 36 - SIDA et Maladies Associées Programme Tuberculose, Dakar, Senegal <i>France</i></p>
<p><b>Abraham Alabi</b> Viral Diseases Programme (HIV) <i>The Gambia</i></p>	<p><b>Andrew Yona Kitua</b> National Institute for Medical Research <i>Tanzania</i></p>	<p><b>Bornwell Sikateyo</b> Ministry of Health <i>Zambia</i></p>	<p><b>Christiane Druml</b> Ethics Committee of the Medical University of Vienna <i>Austria</i></p>
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## Annex II: Glossary of abbreviations

<b>AAVP</b>	African AIDS Vaccine Programme	<b>EDCTP</b>	European & Developing Countries Clinical Trials Partnership
<b>AAV</b>	Adeno-Associated Virus	<b>EDCTP-EEIG</b>	EDCTP European Economic Interest Group
<b>ACT</b>	Artemisin-based Combination Therapies	<b>eCRF</b>	Electronic Case Report Form
<b>ADRN</b>	MIM's Antimalarial Drug Resistance Network	<b>ECSA-HC</b>	East, Central and Southern African Health Community
<b>AFB</b>	Acid-Fast Bacilli	<b>EFV</b>	Efavirenz
<b>AIA</b>	The Afro Immunoassay Network	<b>EIR</b>	Entomological Inoculation Rate
<b>AL</b>	Artemisin	<b>ELISA</b>	Enzyme-Linked Immunosorbent Assay
<b>AMANET</b>	African Malaria Network Trust	<b>ENNP</b>	European Network of National Programmes
<b>AQ-AS</b>	Amodiaquine-Artesunate	<b>ERA-NET</b>	The EC's European Research Area Networks
<b>ART</b>	Anti-Retroviral Therapy	<b>EU</b>	European Union
<b>ARV</b>	Anti-Retrovirals	<b>FDC</b>	Fixed-Dose Combination
<b>AS-AQ</b>	Amodiaquine-Artesunate	<b>FTC</b>	Emtricitabine
<b>AS-SP</b>	Artesunate Sulphadoxime Pyrimethamine	<b>GA</b>	EDCTP's General Assembly
<b>AST</b>	Aspartate Aminotransferase	<b>GCP</b>	Good Clinical Practice
<b>AUC</b>	Area under the Curve	<b>GDP</b>	Gross Domestic Product
<b>AVRN</b>	MIM's African Network on Vector Resistance Network	<b>GFBR</b>	Global Forum on Bioethics in Research
<b>AZT</b>	Azidothymidine	<b>GLP</b>	Good Laboratory Practice
<b>BCG</b>	Bacillus Calmette-Guérin	<b>GMP</b>	Good Manufacturing Practice
<b>BMFG</b>	Bill & Melinda Gates Foundation	<b>HAART</b>	Highly Active Anti-Retroviral Therapy
<b>BMI</b>	Body Mass Index	<b>Hb</b>	Haemoglobin
<b>CDA</b>	Chlorproguanil-Dapsone-Artesunate	<b>HIV/AIDS</b>	Human Immunodeficiency Virus/ Auto-Immune Deficiency Syndrome
<b>CHU</b>	University Hospital Centre (Dakar, Senegal)	<b>HMC</b>	The Health Ministers' Conference
<b>CIDA</b>	Canadian International Development Agency	<b>HLA</b>	Human Leukocyte Antigens
<b>Cmax</b>	Maximum concentration	<b>HTLV</b>	Human T-Lymphotropic Virus
<b>CNRFP</b>	Centre National de Recherche et de Formation sur le Paludisme (Ouagadougou, Burkina Faso)	<b>ICRH</b>	International Centre for Reproductive Health
<b>CRO</b>	Contract Research Organisation	<b>IFN(-γ)</b>	Interferon (-gamma)
<b>CQ</b>	Chloroquine	<b>INDEPTH Network</b>	International Network of field sites with continuous Demographic Evaluation of Populations and their health in developing countries
<b>CTL</b>	Cytotoxic T-Lymphocyte	<b>INH IPT</b>	Isoniazid (INH) Preventive Therapy (IPT)
<b>DAIDS</b>	Division of AIDS	<b>IRS</b>	Indoor Residual Spraying
<b>DfID</b>	NIAID's Department for International Development	<b>ITIM</b>	Immunoreceptor Tyrosine - based Inhibition Motifs
<b>DHA</b>	Dihydro Artemisinin	<b>ITN</b>	Insecticide-Treated bed Nets
<b>DIH</b>	Drug-Induced Hepatotoxicity	<b>KEMRI</b>	Kenya Medical Research Institute
<b>DOTS</b>	Directly Observed Treatment, short course	<b>KIR</b>	Killer Immunoglobulin-like Receptors
<b>DSMB</b>	Data Safety and Monitoring Board		
<b>EC</b>	European Commission		

<b>KNCV</b>	Royal Netherlands Tuberculosis Association	<b>RCT</b>	Randomised Controlled Trial
<b>LC-MS</b>	Liquid Chromatography-Mass Spectrometry	<b>R&amp;D</b>	Research & Development
<b>L-J</b>	Lowenstein-Jensen	<b>RT(-PCR)</b>	Reverse Transcription (Polymerase Chain Reaction)
<b>LM</b>	Lumefantrine	<b>RTV</b>	Ritonavir
<b>LPV</b>	Lopinavir	<b>SATVI</b>	The South African Tuberculosis Vaccine Initiative
<b>LSTM</b>	Liverpool School of Tropical Medicine	<b>SIDCER</b>	Strategic Initiative for Developing Capacity for Ethical Review
<b>MCTA</b>	Malaria Clinical Trials Alliance	<b>SIV</b>	Simian Immunodeficiency Virus
<b>MDP UK</b>	Microbicides Development Programme (United Kingdom)	<b>SOP</b>	Standard Operating Procedure
<b>MHC</b>	Major Histocompatibility Complex	<b>STI</b>	Sexually Transmitted Infections
<b>MIM</b>	Multilateral Initiative on Malaria	<b>TB</b>	Tuberculosis
<b>MIMPAC</b>	MIM's network of scientists with interest in immunology and pathogenesis of malaria in Africa	<b>TBVACSIN</b>	Tuberculosis Vaccine Site Network
<b>MRC</b>	Medical Research Council	<b>TDF</b>	Tenofovir Disoproxil Fumarate
<b>MSP3 vaccine</b>	Merozoite Surface Protein-3 vaccine	<b>TDR</b>	WHO's Tropical Disease Research group
<b>MTCT</b>	Mother-to-child transmission	<b>THIBELA</b>	'Prevent' in Sotho, the predominant language of the gold miners of South Africa
<b>NACCAP</b>	Netherlands-African Partnership for Capacity Development and Clinical Trials Interventions against Poverty-Related Diseases	<b>TDM</b>	Therapeutic Drug Monitoring
<b>NCA</b>	Non-Compartmental Analysis	<b>TMG</b>	Trial Management Group
<b>NGO</b>	Non-Governmental Organisation	<b>UCL</b>	University College London
<b>NIBSC</b>	National Biological Standards Board	<b>UK</b>	United Kingdom
<b>NK cells</b>	Natural Killer cells	<b>UN</b>	United Nations
<b>NLME</b>	Nonlinear Mixed-Effects	<b>US</b>	United States
<b>NNRTI</b>	Non Nucleoside Reverse Transcriptase Inhibitors	<b>VCT</b>	Voluntary Counselling and Testing
<b>NRA</b>	National Regulatory Agency	<b>VL assays</b>	Viral Load assays
<b>NVP</b>	Nevirapine	<b>VSCR</b>	The Vienna School of Clinical Research
<b>PABIN</b>	Pan African Bioethics Network	<b>VRC</b>	Vaccine Research Centre
<b>PB</b>	Partnership Board	<b>WB</b>	World Bank
<b>PCR</b>	Polymerase Chain Reaction	<b>WHO</b>	World Health Organization
<b>PDP</b>	Product Development Partnership	<b>XDR-TB</b>	Extensively Drug-Resistant Tuberculosis
<b>PI</b>	Principal Investigator	<b>ZDV</b>	Zidovudine
<b>PIHCT</b>	Provider Initiated HIV Counseling and Testing	<b>ZEHRP</b>	Zambia Emory HIV Research Project
<b>PK(-PD)</b>	Pharmacokinetic (Pharmacodynamic)		
<b>PMTCT</b>	Prevention of Mother-To-Child Transmission		
<b>PPD</b>	Partners in Population and Development		
<b>PQ</b>	Piperaquine		
<b>PTB</b>	Pulmonary Tuberculosis		





## Colophon

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