



EDCTP



THE FIRST
EDCTP INVESTIGATORS' MEETING REPORT

24 — 25 July 2006



REPORT ON THE FIRST EDCTP INVESTIGATORS' MEETING

*Medical Research Council Conference Centre, Cape Town, South Africa
24 to 25 July 2006*

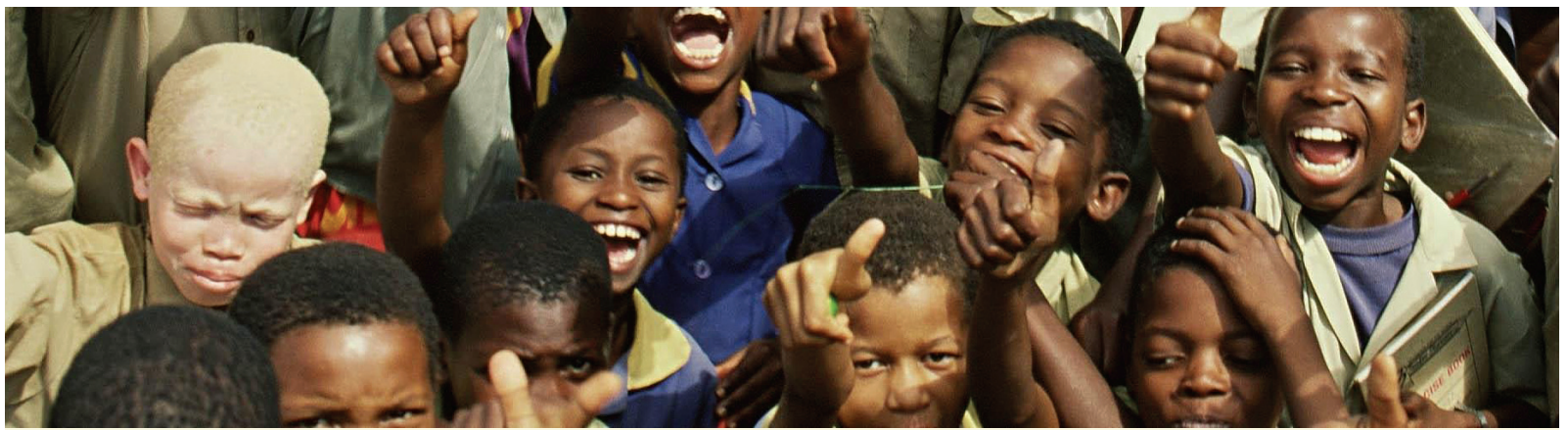


THE POWER OF SHARING SCIENCE



CONTENTS

| | |
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| TABLE OF CONTENTS | 1 |
| LIST OF ABBREVIATIONS | 2 |
| 1.0 EXECUTIVE SUMMARY | 4 |
| 2.0 OPENING AND KEYNOTE ADDRESSES | 5 |
| 2.1. Welcoming remarks - Professor Anthony MBewu, MRC President (South Africa) | 7 |
| 2.2. Opening address - Dr Odile Leroy, Executive Director, EDCTP (Netherlands) | 8 |
| 2.3. Regulatory issues in Africa - Dr Lahouari Belgharbi, WHO-Geneva (Switzerland) | 9 |
| 2.4. The role of African institutions in clinical trial sponsorship - Professor Charles Mgone, Head of Africa Office-EDCTP (South Africa) | 19 |
| 2.5. The AMANET experience in trial sponsorship - Dr Roma Chilengi, AMANET (Tanzania) | 21 |
| 3.0 PRESENTATIONS BY EDCTP GRANTEES – DAY 1 | 24 |
| 3.1. Development and evaluation of high throughput, cheap and reliable assays for monitoring HIV-1 and HIV-2 viral loads in ARV programmes and clinical trials in developing countries - Dr Abraham Alabi (Gambia) | 24 |
| 3.2. CHAPAS Trials: children with HIV in Africa: pharmacokinetics and adherence of simple antiretroviral regimens - Professor Chifumbe Chintu (Zambia) | 29 |
| 3.3. Evaluation of 4 artemisinin-based combinations for treating uncomplicated malaria in African children - Professor Umberto d'Alessandro (Belgium) | 32 |
| 3.4. Assessment of the public health benefit of artemisinin-based combination therapies for uncomplicated malaria treatment in Mali - Dr Bakary Fofana and Dr Abdoulaye Djimde (Mali) | 36 |
| 3.5. 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, (Cote d'Ivoire) | 42 |
| 3.6. Rapid evaluation of moxifloxacin in the treatment of sputum smear positive tuberculosis: REMoxTB - Professor Andrew Nunn (United Kingdom) | 48 |
| 3.7. BCG-induced immune correlates of protection against tuberculosis - Dr Willem Hanekom (South Africa) | 52 |
| 4.0 PRESENTATIONS BY EDCTP GRANTEES – DAY 2 | 57 |
| 4.1. EDCTP funded clinical trials registry - Professor Jimmy Volmink (South Africa) | 61 |
| 4.2. A controlled clinical trial to evaluate high dose rifapentine and moxifloxacin in the treatment of pulmonary tuberculosis - Dr Amina Jindani (United Kingdom) | 61 |
| 4.3. 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 Helen McIlleron (South Africa) | 68 |
| 4.4. The burden of tuberculosis in eastern Sudan: epidemiology and drug resistance patterns of <i>Mycobacterium tuberculosis</i> isolates - Professor Maowia Mukhtar (Sudan) | 77 |
| 4.5. Understanding the mechanism of piperaquine resistance - Dr Alexis Nzila (Kenya) | 82 |
| 4.6. Surrogate markers to predict the outcome of anti-tuberculosis therapy - Professor Paul van Helden (South Africa) | 82 |
| 5.0 SUMMARY OF RECOMMENDATIONS | 85 |
| 6.0 CLOSING REMARKS - DR PASCOAL MOCUMBI, HR - EDCTP (Netherlands) | 86 |
| LIST OF PARTICIPANTS | 87 |



LIST OF ABBREVIATIONS

| | | | |
|------------------|--|----------|--|
| 3-TC | Lamuvudine | EANMAT | East African Network for Monitoring Anti-malarial Treatment |
| AAVP | African AIDS Vaccine Programme | EC | European Commission |
| ACT | Artemesine Combination Therapy | EC-AIDCO | EuropeAid Coopertaion Office of the European Commission |
| ADRN | Antimalarial Drug Resistance Network | ECBS | Experts Committee on Standardization of Biologicals |
| AE | Adverse events | EC-DG | European Commission-Directorate General |
| AEFI | Adverse events following immunisation | EDCTP | European and Developing Countries Clinical Trials Partnership |
| AIDS | Acquired Immune Deficiency Syndrome | ELISA | Enzyme linked immunosorbent assay |
| AL | Artemisinin | EMVI | European Malaria Vaccine Initiative |
| AMANET | Africa Malaria Network Trust | EPI | Expanded Programme on Immunisation |
| ANRS | Agence Nationale de Recherches sur le Sida et les Hépatites Virales | EudraCT | European Clinical Trials Database |
| AQ | Amodiaquine | FMPOS | Faculté de médecine, de pharmacie et d'odontostomatologie |
| ART | Anti-retroviral Therapy or Artemesine | FTC | Entricitabine |
| ARV | Anti-retroviral | GCP | Good Clinical Practice |
| AS | Artesunate | GLP | Good Laboratory Practice |
| ATK | Artekin (PQ + DHA) | GMP | Good Manufacturing Practice |
| AUC | Area under the curve | GPC | Gel Permeation Chromatography |
| AVAREF | African Vaccine Regulators' Forum | GSK | GlaxoSmithKline |
| BL ₃ | Biological Safety Level 3 | GTN | Global Training Network |
| CEO | Chief Executive Officer | GUM | Genito-urinary medicine |
| CHAPAS | Children with HIV in Africa Pharmacokinetics and Adherence of Simple Anti Retroviral Regimes | HAART | Highly Active Anti-retroviral Treatment |
| CIHR | Canadian Institutes of Health Research | HAS | Albert Schweitzer Hospital |
| C _{max} | Maximum Plasma Concentration | Hb | Haemoglobin |
| CQ | Chloroquine | HIV | Human Immunodeficiency Virus |
| CQR | Chloroquine resistance | IAMP | Inter Academic Medical Panel |
| CRO | Clinical Research Organisation | ICH | International Committee of Harmonisation |
| CTU | Clinical Trials Unit | ICMJE | International Committee of Medical Journal Editors |
| D4T | Stavudine | IDP | Institutional Development Plans |
| DANIDA | Danish International Development Agency | IMPACT | International Maternal Pediatric Adolescent AIDS Clinical Trials |
| DCVRN | Developing Countries Vaccines Regulatory Network | IMPD | Investigational Medicinal Product |
| DEAP | Département d'Epidémiologie des Affections Parasitaires | INH | Institute for National Health |
| DHA | Dihydro artemisinin | INSERM | Institut National de la Santé et de la Recherche Médicale |
| DHFR | Dihydrofolate reductase | INTERTB | International Consortium for trials of chemotherapeutic agents in tuberculosis |
| DNA | Deoxyribonucleic acid | | |
| DOTS | Directly Observed Treatment – Short Course | | |
| DRC | Democratic Republic of Congo | | |
| E | Ethambutol | | |



| | | | |
|-------|--|-------|--|
| IPR | Intellectual Property Rights | PCV | Packed corpuscular volume |
| IRB | Institutional Review Board | PK | Pharmacokinetic |
| IRIS | Immune Reactivation Inflammatory Syndrome | PQ | Piperaquine |
| IRSS | Institut de Recherche en Science de la Sante | R | Rifampicin |
| ISPED | Institut de Santé Publique, d'Epidémiologie et de Développement | RNA | Ribonucleic Acid |
| JHU | Johns Hopkins University | Rpe | Rifapentine |
| KCMC | Kilimanjaro Christian Medical Centre | SACC | South African Cochrane Centre |
| KEMRI | Kenya Medical Research Institute | sdNVP | Single dose Niverapine |
| LM | Lumefantrine | SAMRC | South African Medical Research Council |
| LSHTM | London School of Hygiene and Tropical Medicine | SIV | Simian Immunodeficiency Virus |
| LTR | Long term repeat | SOP | Standard Operating Procedure |
| MDR | Multi-Drug Resistance | SP | Sulphadoxime pyrimethamine |
| MEDRU | Molecular Epidemiology and Drug Resistance Unit | SPSS | Statistical Package for Social Sciences |
| MEMS | Medication Events Monitoring System | SU | Stellenbosch University |
| MIAM | Malaria Institute at Macha | TEmAA | Tenofovir Emtricitabine in Africa and Asia |
| MIC | Medicine Information Centre | TB | Tuberculosis |
| MIM | Multilateral Initiative for Malaria | TBTC | Tuberculosis Trials Consortium |
| MOTT | Mycobacteria other than TB | TDF | Tenofovir disoproxil fumarate |
| MRC | Medical Research Council | TDRC | Tropical Diseases Research Centre |
| MRTC | Malaria Research and Training Centre | TDRI | Tropical Diseases Research Institute |
| NCL | National Control Laboratory | TF | Treatment Failure |
| NIH | National Institutes for Health | Tmax | Time to maximum plasma concentration |
| NRA | National Regulatory Agency | TSR | WHO Technical Report Series |
| NTB | non-tuberculous | UCL | University College of London |
| p-NPP | p-nitrophenyl phosphate | UK | United Kingdom |
| PMTCT | Prevention of Mother-to-Child Transmission | UN | United Nations |
| NIBSC | National Institute for Biological Standards and Control | USA | United States of America |
| NNRTI | Non-nucleotide Reverse Transcriptase Inhibitor | UTH | University Teaching Hospital |
| NRTI | Nucleotide Reverse Transcriptase Inhibitor | UTRN | Universal trial reference number |
| NVP | Niverapine | VL | Viral Load |
| OCEAC | Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale | WHO | World Health Organisation |
| OHRP | Office for Human Research Protections | ZDV | Zidovudine |
| PCR | Polymerase Chain Reaction | ZN | Ziel Nielsen |



Part of participants attending EDCTP Investigators' meeting. Front row (from left to right) Prof. A MBewu, President of MRC South Africa; Prof. Charles Mgone, Head of Africa Office of EDCTP; Dr Pascoal Mocumbi, High Representative for EDCTP, Dr Michel Klein, Partnership Board Member of EDCTP and Dr Louahari Belgharbi of WHO.

1.0 EXECUTIVE SUMMARY

The EDCTP Investigators' Meeting took place at the Medical Research Council (MRC) in Cape Town from 24 to 25 July 2006. The goal of the meeting was to establish a south-south network of researchers and institutions for coordinating and synergizing activities related to clinical trials on the three major poverty-related diseases of HIV/AIDS, malaria and tuberculosis in Africa through the EDCTP platform.

This meeting brought together 88 participants: 43 African scientists from research sites in Burkina Faso, Cote d'Ivoire, Gabon, Gambia, Kenya, Mali, Mozambique, Nigeria, Rwanda, South Africa, Sudan, Tanzania, Uganda, Zambia and Zimbabwe; 9 collaborators from research institutions in United Kingdom, Belgium, Ireland and USA; 13 invited guests from bodies like Department of Science and Technology (South Africa), MRC (South Africa), Africa Malaria Network Trust (AMANET), World Health Organisation (WHO), European Commission (EC) and a National Regulatory Officials from Zambia; 11 members of EDCTP Developing Countries Coordination Committee; a member of the European Network of National Programmes; 3 members of the EDCTP Partnership Board and 8 members of the EDCTP secretariat.

At the meeting participants shared experiences and exchanged information on existing projects, facilitated the establishment of south-south links (e.g. mentorship programmes, nodes of excellence, and sharing of facilities and expertise), explored common grounds of interest such as possibilities of joint grant applications, proposed a direction of research agenda to EDCTP as determined by the experiences from the ongoing projects, discussed regulatory issues, discussed the use of the established EDCTP clinical trial registry, and role of African institutions in clinical trials sponsorship.

PARTICIPANTS RECOMMENDED THE FOLLOWING TO EDCTP:

- Extension of senior fellowships
- Enhancing capacity building in Africa by strengthening the regulatory framework, ethics review mechanisms, infrastructure and training of personnel
- Fostering closer collaboration between investigators and policy makers and other regional organizations in Africa
- Promoting and strengthening of south-south and north-south networking
- Devising strategy for accreditation of clinical trial sites
- Revisiting co-funding and budget cuts associated with EDCTP grant

All the recommendations made were discussed by DCCC on the following two days after the Investigators' Meeting. In addition, the DCCC will continuously discuss the recommendations with other organs of EDCTP.

2.0 OPENING AND KEYNOTE ADDRESSES

MONDAY, 24 JULY

Chair: *Mr Daan du Toit, Department of Science and Technology (South Africa)*

Rapporteur: *Dr Simon Agwale, DCCC chair (Nigeria)*

2.1. Welcoming remarks – *Professor Anthony MBewu, South Africa*

Prof Anthony MBewu is the President and Chief Executive Officer (CEO) of the South African Medical Research Council (MRC).

The MRC is the statutory health council of South Africa and funds around five hundred scientists throughout the country who engage in research producing six hundred and eighty publications a year, graduating fifty PhD students a year. Much of the research conducted by the MRC focuses on the problems of Africa in relation to communicative diseases. Approximately a quarter of MRC scientists are devoted to this area and a quarter of the MRC budget is spent on research in HIV and AIDS, and a large percentage on research in tuberculosis and also on malaria. EDCTP is therefore an important programme for the MRC's relations within the continent and internationally, in partnership with our European colleagues.

It is apt that we meet at a time when development in global health begins to provide a promise of change in both research commitments and agendas, and in global health itself – in particular the African continent. A few of the most recent activities in Africa that have fuelled this process include the World Health Organisation (WHO) resolutions on health research that were made in May, earlier this year, and the meeting of ministries of health from Africa and other developing countries in Accra. From the meeting in Accra, a communicator on health research for development was produced which will go to the heads of states of the African Union at a meeting in Addis Ababa. We have also seen the increasing commitments from funding foundations like the Gates Foundation with its funds doubled through the contributions from Warren Buffett and his family. Developments in the medical fraternity, and here I think particularly of a body that I have the privilege to coach, called the Inter Academy Medical Panel (IAMP), a group consisting of sixty two of the medical academies of the world that has engaged on several projects.

Other developments giving hope is the coming elections in the Democratic Republic of Congo (DRC). There are many developments in global health currently, possibly heralding a change in health research agendas and global health, and health in Africa. This year, the second year of EDCTP is a particularly promising year. Not just because of the agenda as set out for the two days at this investigators meeting, but because of the developments in global health and in peace and development in Africa.

Much of the credit for the progress of the European and Developing Countries Clinical Trials Partnership (EDCTP) must go to Dr Odile Leroy, the director of EDCTP, who has managed a very difficult task to ensure that this collaboration between European and African scientists should become established as a true partnership between equals and a true partnership in which both determines the research agenda. Conducting research and taking it beyond into the translation of the research into new drugs and vaccines and into a better health for people in Africa. A word of thanks should also go to Dr Pascoal Mocumbi, for all his efforts in ensuring that EDCTP, despite a slow start, became a vibrant and promising continental health research agenda. We should applaud the leaders of the EDCTP, the scientists involved and everybody who has ensured that this programme is well on track.

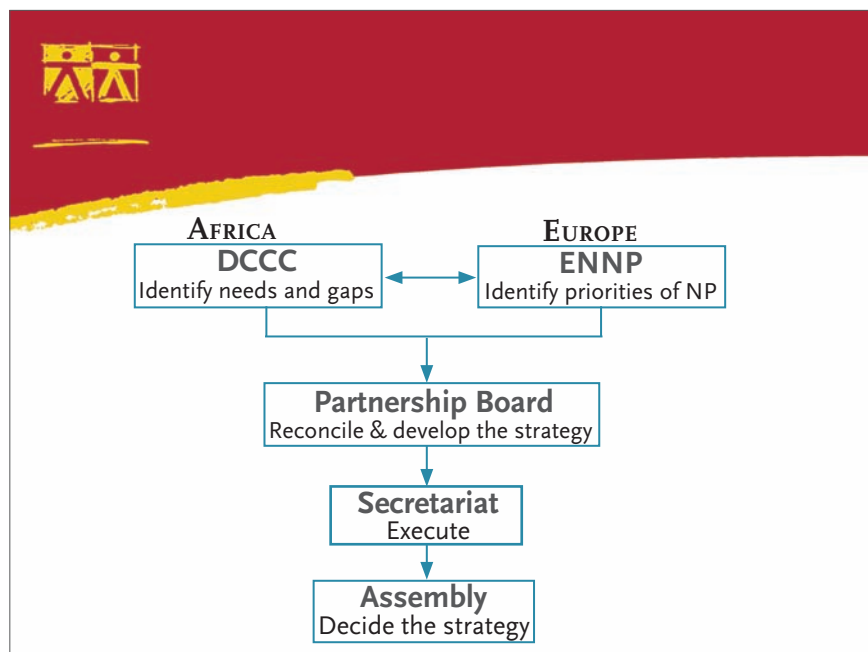


2.2. Opening Address – *Dr Odile Leroy, The Netherlands*

Dr Odile Leroy is the Executive Director of European and Developing Countries Clinical Trials Partnership (EDCTP)

EDCTP IS MOVING AND EDCTP IS CHANGING

- Switzerland has joined EDCTP in December 2006
- EDCTP has fine tuned its organisation at Secretariat level :
 - Implementation of Quality Assurance System and development of standard operating procedures (SOP)
 - Matrix organisation between African and European Office
- Three team leaders among four are Africans
- The Africa Office has a leading role in promoting the African leadership and in building on existing networks like African AIDS Vaccine Programme (AAVP), Africa Malaria Network Trust (AMANET), Multilateral Initiative on Malaria (MIM), and others
- The Africa Office has a leading role in communication
 - Quarterly e-newsletter
 - New corporate image (new website, new logo)
 - EDCTP is now a tri-language organisation (French, English and Portuguese)
 - Annual Report 2005
- EDCTP has fine-tuned its organisation
 - At constituencies level EDCTP Partnership Board and Developing Countries Coordinating Committee (DCCC) have renewed some of their members
 - Chair of the DCCC, Dr Simon Agwale
 - Chair of the Partnership Board, Dr Patrice Debré
- Interactions between the different constituencies has changed
 - More active role of the South-South Networking and of the North-North Networking





EDCTP HAS ADOPTED THE SWISS PRINCIPLES FOR RESEARCH IN PARTNERSHIP

- Decide on the objectives together
- Build up mutual trust
- Share information; develop networks
- Share responsibility
- Create transparency
- Monitor and evaluate the collaboration
- Disseminate the results
- Apply the results
- Share contributions and profits equitably
- Increase research capacity
- Build on achievements

EDCTP HAS ESTABLISHED ACTIVE COLLABORATION

- With New Partnership for African Development (NEPAD) there is a memorandum of understanding and plan of action
- With World Health Organisation (WHO) there is collaboration in training of regulatory agencies
- With Bill and Melinda Gates Foundation and HIV Vaccine Global Enterprise there is collaboration to support HIV vaccine capacity building
- With Pharmaceutical Industry there are plans for training of monitors in house

PLAN OF SITE VISITS HAVE BEEN IMPLEMENTED

- Objectives of these visits are:
 - Advocacy:
 - Enhance EDCTP visibility in the region and country
 - Reinforce the legitimacy of DCCC members
 - Data and information collection:
 - Research structures including financial data when possible
 - Health system (public and private when appropriate)
 - Regulatory structures
 - Ethics committee
 - Technical assessment:
 - Capacity building assessment in EDCTP sites (baseline data)
 - Networking: Preparation of workshops and investigators meetings
 - Financial audit

EDCTP WILL PROMOTE LARGER PROJECTS AFTER 2006

- Each project shall include work-packages on
 - Capacity building including Ethics Committee
 - Clinical trial
 - Networking
 - Training (fellowship, career development, PhD, MSc courses including training of monitors, data-managers, financial managers, project managers and many more)



EDCTP FUNDED PROJECTS INCLUDE:

- Clinical trial registry
- Joint effort of WHO and EDCTP in training of National Regulatory Agencies (NRA)
- Projects approved in 2006 and in negotiations phase:
 - Strengthening or support of 7 National Ethics Committees (NEC)
 - 5 Courses on ethics
 - 3 clinical trial and capacity building projects on microbicides
 - 3 capacity building projects on TB vaccine
 - 2 clinical trials on Anti-retroviral (ARV) treatment in TB patients
 - 1 MSc course in clinical trial methodology

ABOUT THE INVESTIGATOR MEETING OF 2006

- 89 delegates, including from 21 African countries attended this meeting
 - WHO/AFRO, WHO/Geneva
 - Organisation de Coordination pour la lutte contre les Endémies en Afrique Centrale (OCEAC)
 - AMANET
 - European Malaria Vaccine Initiative (EMVI)
 - Representative of National Regulatory Authorities
 - EDCTP constituencies are also present:
 - Haut Representant; Dr Mocumbi
 - Partnership Board representatives (Vice chair: Prof. Mboup, Prof. Sirima)
 - Large number of DCCC members (Chair: Simon Agwale, vice chair: Dr Manyando)
 - Chair of the European Network of National Programmes – ENNP (Prof. Laura Brum)
 - Secretariat
- We will learn about the experience of EDCTP grantees on:
 - 4 TB clinical trials
 - 2 malaria clinical trials and
 - 3 HIV clinical trials
 - But also on the general environment of clinical trials in:
 - Regulatory review
 - Ethics review
 - Registration of clinical trials
 - Sponsorship
- Visit to clinical trial centres in Cape Town had been arranged
- Objectives of the meeting were:
 - To reinforce networking
 - To use the unique position of EDCTP in having a cross-cutting approach and cross-fertilisation between:
 - Type of diseases: malaria; TB; HIV/AIDS
 - Type of intervention: treatment/prevention
 - To build on synergies in order to allow inter-disease approaches
 - To identify the challenges and prepare a plan of action to overcome them
 - To identify the gaps
 - To prepare for EDCTP Annual Forum in Stockholm, in October 2006

2.3. Regulatory issues in Africa – *Dr Lahouari Belgharbi, WHO-Geneva; Switzerland*

OUTLINE OF THE PRESENTATION

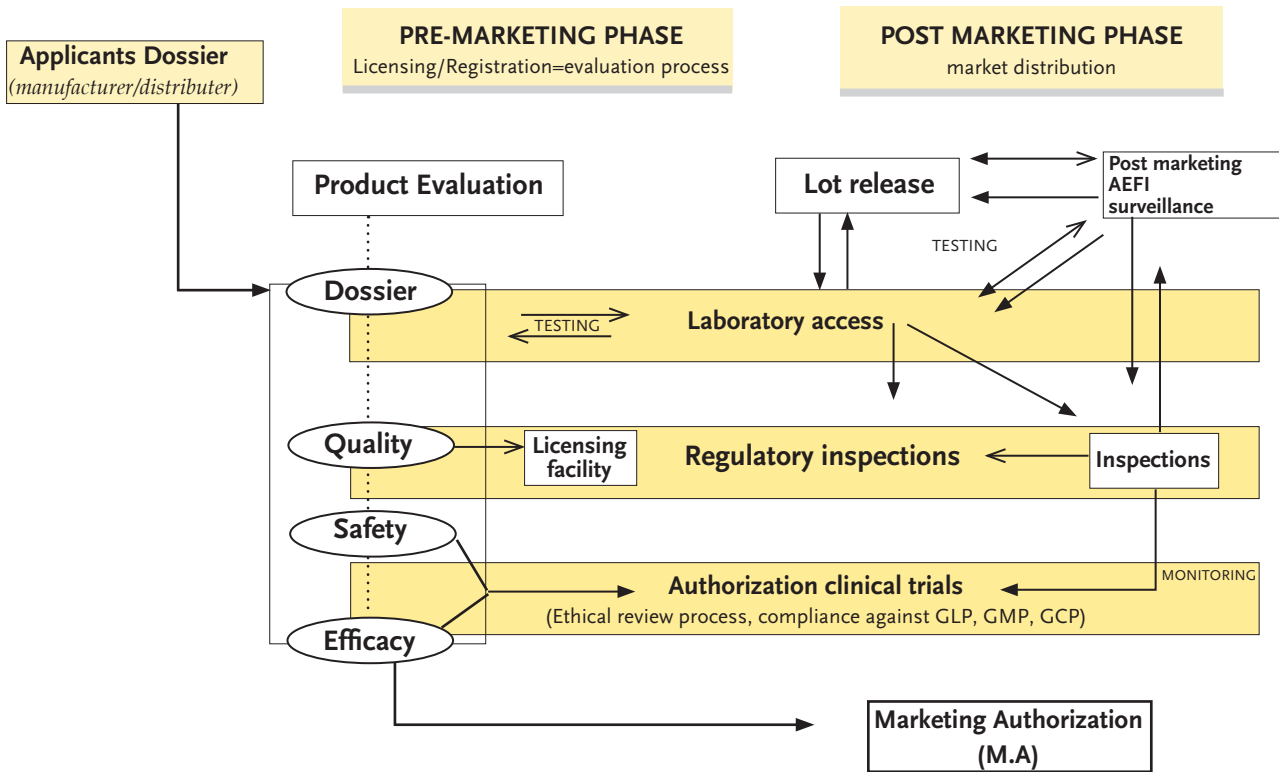
- Regulatory issues and challenges
- WHO policy to ensure quality, safety and efficacy of vaccines
- Activities planned and implemented
- Progress and impact on vaccine regulatory systems

REGULATORY ISSUES AND CHALLENGES

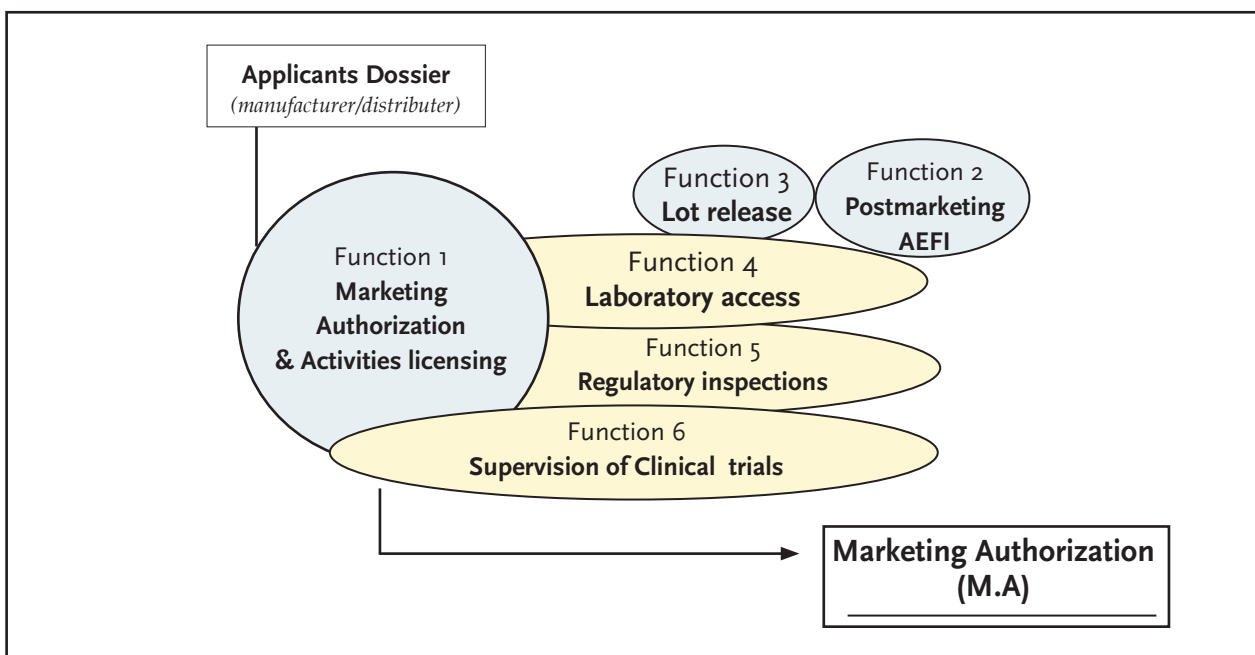
- Challenges and issues met by the vaccine regulatory systems in Africa
 - Public confidence about vaccine safety is key when dealing with adverse events following immunisation (AEFI)
 - Vaccine procurement and regulation must be managed by trained staff and relevant experts
 - Regulation of biological is confused with drug regulation or not addressed
 - When National Control Laboratory (NCL) exists, relevant expertise not always used for regulation of biologicals
 - Some regulatory functions do not exist for drugs or are managed in different manner or need specific expertise
 - Clinical trials are not always supervised or involving NRAs
 - Conflict of interest growing during registration, licensing, GMP inspections, evaluation of clinical trials, etc.
 - Independence questioned, limited mandate and authority not always clearly defined among stakeholders and within regulatory institutions (NRA; NCL, Ethics, Research Council, EPI, etc...)
 - Limited expertise in clinical evaluation of new vaccines
 - No formal procedures to conduct product evaluation, review of clinical trials applications and assess vaccine performances.
 - No regional/harmonized mechanisms to bring vaccine experts and African experts to share information on clinical evaluation of vaccines

WHO POLICY TO ENSURE QUALITY, SAFETY AND EFFICACY OF VACCINES

- World Health Organization's Goals: Ensure that "100%" of vaccines used in all national immunization programmes are of assured quality
- Guided by Experts Committee on Standardization of Biologicals (ECBS) recommendations on safety, efficacy and quality issued in WHO Technical Report Series (TSR)
 - Definition of "Assured quality vaccines" for a vaccine producing country
 - National Regulatory Authority (NRA) independent from vaccine manufacturer and or procurement system
 - NRA fully functional (*with a system and 6 regulatory functions implemented*)
 - No unresolved reported problem with vaccine
 - Definition of "Assured quality vaccines" for non-vaccine producing country
 - National Regulatory Authority (NRA) independent from vaccine procurement system
 - NRA fully functional according to source of vaccines (*with a system and 2 or 4 regulatory functions implemented*)
 - No unresolved reported problem with vaccine



VACCINE REGULATORY PROCESS 1: THE IDEAL VACCINE REGULATORY SYSTEM



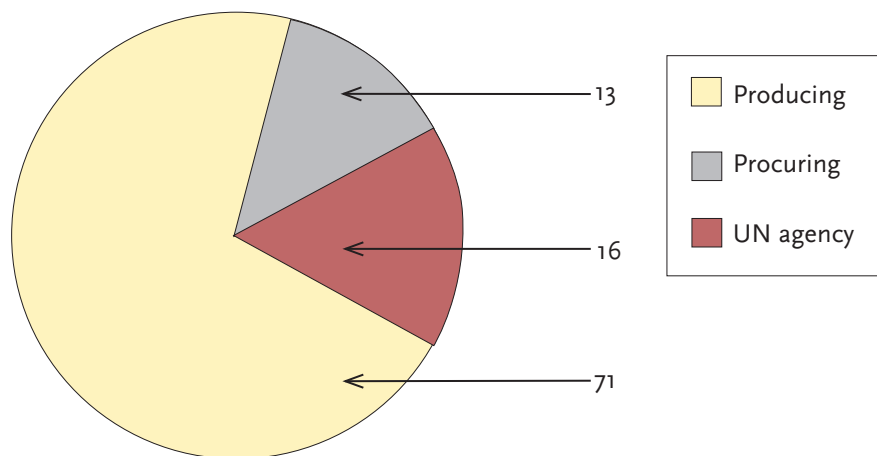
VACCINE REGULATORY PROCESS 2: THE IDEAL VACCINE REGULATORY SYSTEM



NATIONAL REGULATORY FUNCTIONS RECOMMENDED FOR VACCINE DEVELOPMENT

| Regulatory functions | SOURCE OF VACCINE | | |
|--|---|---------|---------|
| | UN Agency | Procure | Produce |
| Regulatory system | ✓ | ✓ | ✓ |
| Marketing Authorization & Licensing activities | ✓ | ✓ | ✓ |
| Postmarketing: AEFI | ✓ | ✓ | ✓ |
| Lot Release | Functions undertaken in producing countries that are functional | ✓ | ✓ |
| Laboratory access | | ✓ | ✓ |
| Regulatory inspections | | | ✓ |
| Authorization & monitoring of CTs | ✓ in countries that conduct clinical trials | ✓ | ✓ |

% TOTAL POPULATION ACCORDING SOURCE OF VACCINE

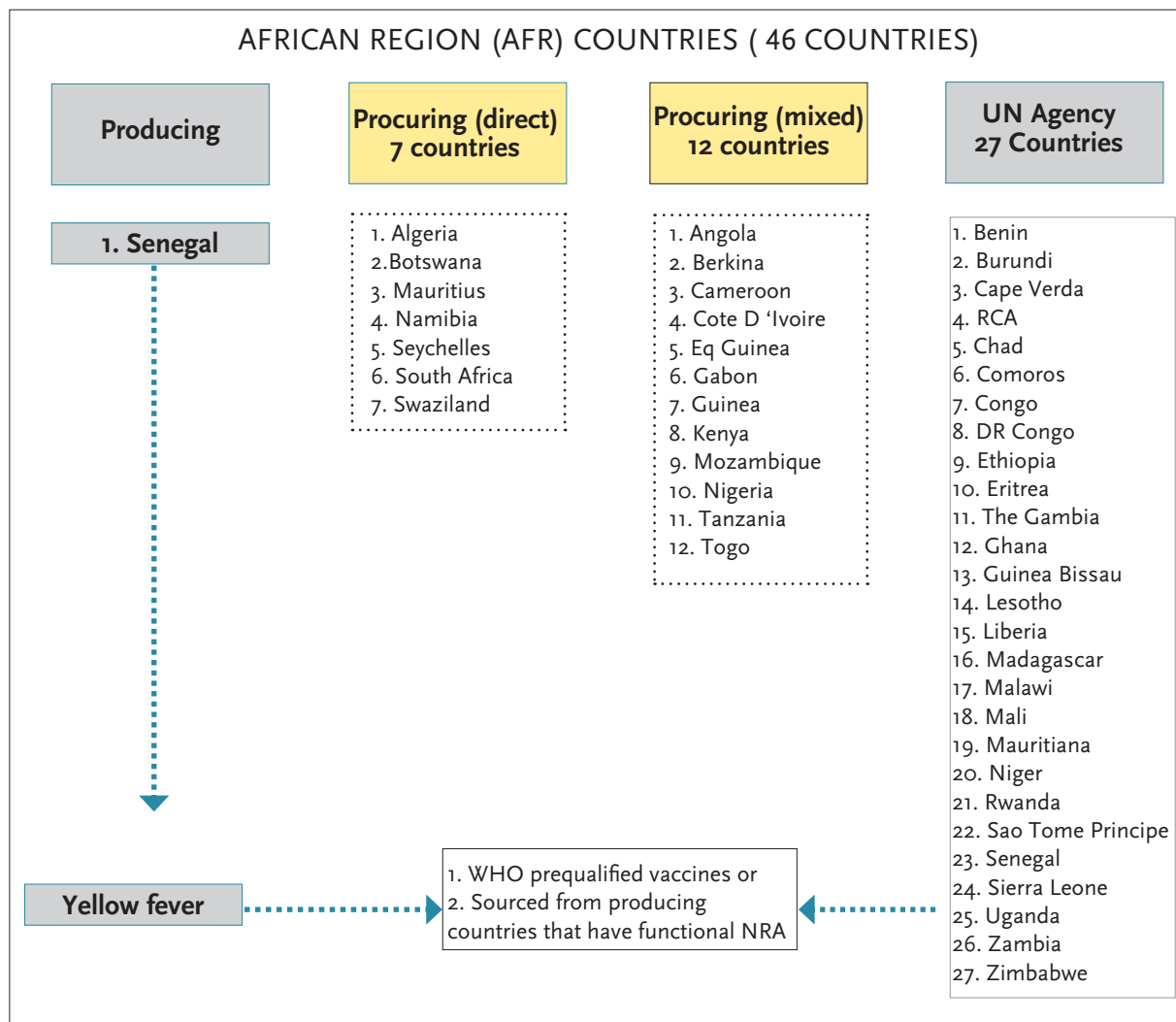
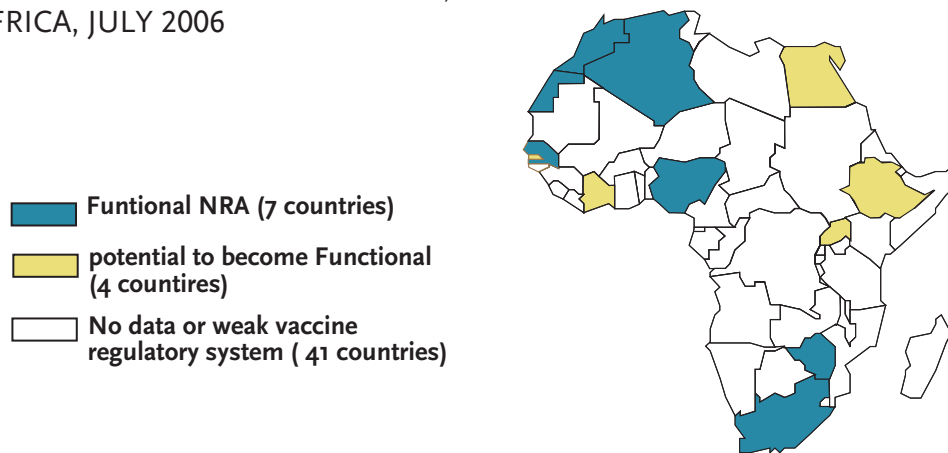


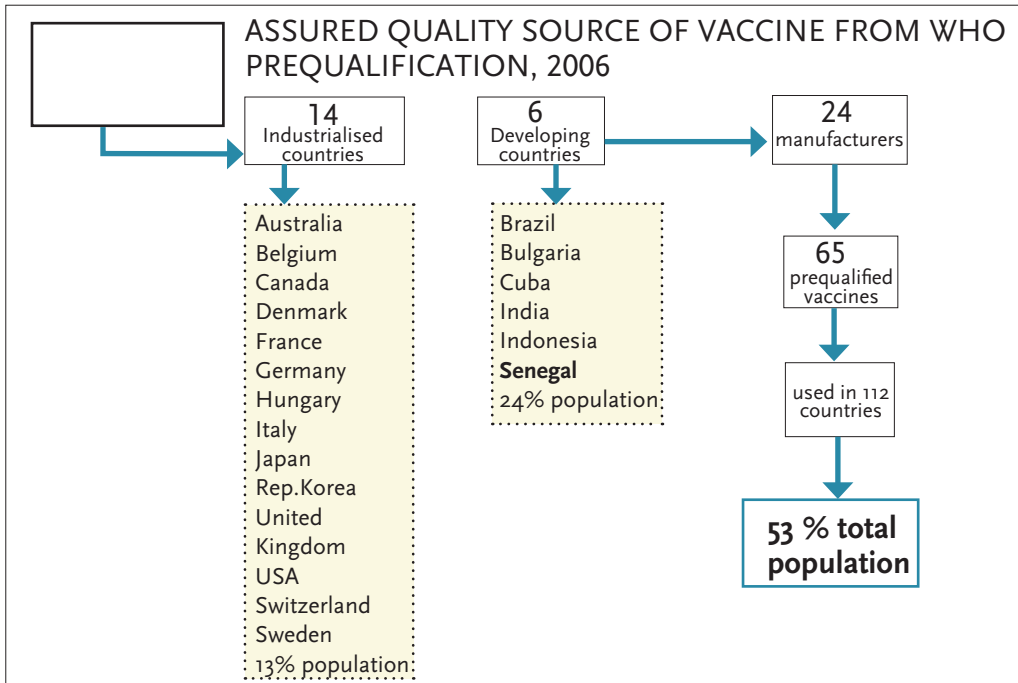
MAGNITUDE: TARGET POPULATION

| TOTAL POPULATION | PRODUCING COUNTRIES | UN AGENCIES | PROCURING COUNTRIES |
|------------------|---------------------|-------------|---------------------|
| 6 525 000 | 4 649 000 | 1 013 000 | 0 900 000 |
| 100% | 71% | 13% | 16% |
| 192 countries | 42 | 81 | 69 |



FUNCTIONAL NRA THAT HAVE CAPACITY TO REGULATE VACCINES AGAINST WHO NRA INDICATORS, AFRICA, JULY 2006





PLANNING TO ADDRESS GAPS

- Process to strengthen NRAs
 - The five step capacity building programme:
 - Benchmarking
 - NRA assessment
 - Planning to address gaps (Institutional Development Plans; IDP)
 - Implementation of plan, including technical inputs (Global Training Network; GTN)
 - Monitoring and evaluation

By end of 2007: 37 Countries with NRA Institutional Development Plan Developed or Updated in Eastern Mediterranean Region (EMR) and (AFR) of WHO

WHO/GTN TRAINING PLANNED (No. courses)

2005 — Clinical evaluation (1)
2006 — Clinical evaluation (1)
2007 — Clinical evaluation (2)

IN COUNTRY ACTIVITIES

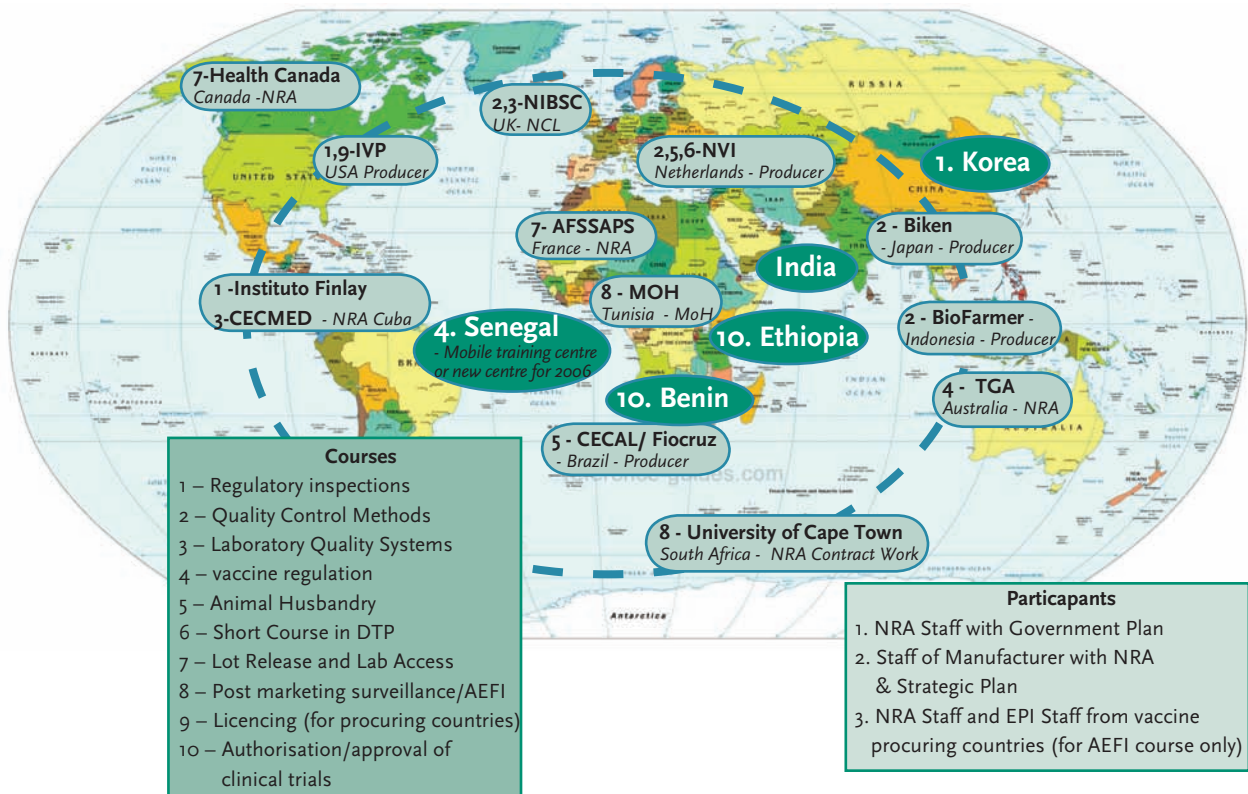
2005 — Follow up visits (3)
2006 — Follow up visits (5)
2007 — Follow up visits (5)

REGULATORY PATHWAY

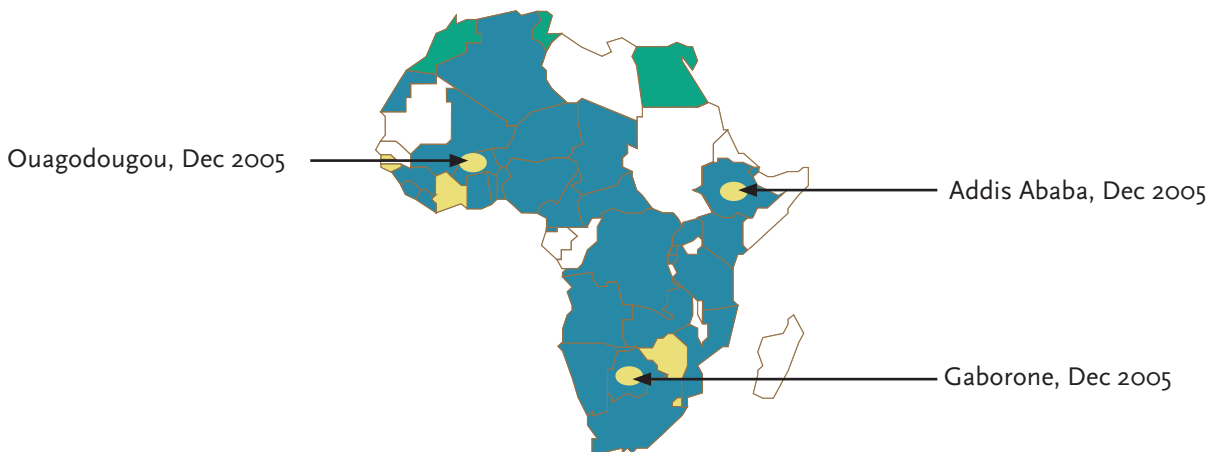
2005 — Meeting of experts (2)
2006 — Meeting of experts (3)
2007 — Meeting of CT's (3)
2008 — Meeting CT's (1)



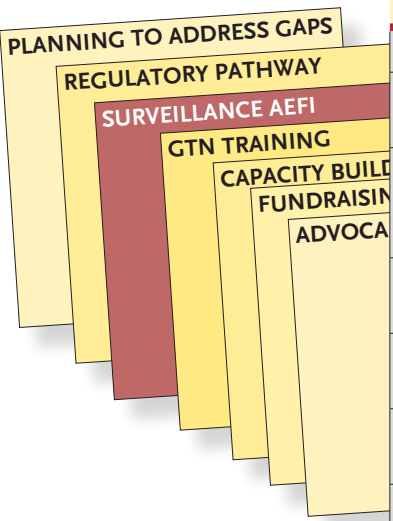
THE GLOBAL TRAINING NETWORK (GTN) TRAINED 1200 STAFF FROM 100 COUNTRIES SINCE 1996 AND WAS SUPPORTED BY WB, JICA, DFID, AUSAID, WHO, EU, IDB, UNICEF, WHO



ACTIVITIES PLANNED AND IMPLEMENTED: NRA PLANNING WORKSHOPS CONDUCTED TO DEVELOP INSTITUTIONAL DEVELOPMENT PLAN (IDP) FOR 28 COUNTRIES IN 2005



ACTIVITIES TO STRENGTHEN VACCINE REGULATORY SYSTEMS



| ACTIVITIES CONDUCTED | STATUS |
|--|---------------------------------|
| 1. Fund raising plan | Completed |
| 2. Three NRA planning workshops countries with IDP for 28 countries | Completed |
| 3. Meeting of Developing Countries Vaccines Regulatory Network (DCVRN) | Completed |
| 4. Joint review of CT's applications for Rotavirus & MeningioA | Completed |
| 5. Sensitization/advocacy workshop for all country stakeholders | 1 out of 3 completed |
| 7. GTN training provided to AFR countries on vaccine regulation | 9 out of 28 countries completed |
| 6. GTN Training provided to AFR countries on PMS/AEFI | 15 out of 28 completed |
| 7. GTN training provided to AFR countries on clinical evaluation | 6 out of 28 countries completed |

AFR: REGIONAL INITIATIVES 2004-2007

- Objectives and expected outcomes
 - Planning NRA activities through development of Institutional Development Plan: completed in 28 countries
 - Promote communication among NRAs and raise awareness on regulatory changes and challenges: Developing Countries Vaccine Regulatory Network (DCVRN), African Vaccine Regulators Forum (AVAREF), joint review, joint inspection of clinical trials, sensitization workshops (Uganda)
 - Promote communication between sponsors/regulators/ethics committees/ research centres to determine specific needs for different types of vaccines: same as point 2 above
 - Provide expert support to assess suitability of clinical data for registration : DCVRN, AVAREF, Joint review of clinical trials applications, training on clinical evaluation
 - Facilitate capacity building activities and availability of expertise for regulatory review of clinical trial applications and monitoring of clinical trials: NRA assessment, follow up visits, meeting of regulators and training on relevant regulatory functions.
 - Plan and organise training on relevant regulatory functions that are critical for African NRAs: Clinical evaluation, PMS/AEFI and regulation.



WHO/EDCTP ACTIVITIES PLANNED AND CONDUCTED TO SUPPORT THE DEVELOPMENT OF A HARMONIZED REGULATORY FRAMEWORK IN AFRICA, 2005-2007 – PLANNING PHASE: 2005

- January, May and December
 - 3 NRA planning workshops for 28 countries (Addis Ababa, Ouagadougou and Gaborone): 28 IDP to implement harmonized/common regulatory framework to ensure quality, safety, efficacy of vaccines and relevant clinical trials conducted in Africa.
 - Countries involved: Ghana, The Gambia, Ethiopia, Kenya, Uganda, Senegal, Mali, Central African Republic, Togo, Guinea, Chad, Benin, Cameroon, Niger, Rwanda, Angola, Botswana, DRC, Malawi, Namibia, Rwanda, South Africa, Tanzania Zambia and Zimbabwe, (EDCTP / WHO funding)
- March 2005: Training course on authorisation/approval of clinical trials (Pretoria, South Africa)
 - Main outcome: Providing knowledge to regulators and vaccine experts about principle of vaccine clinical evaluation relevant to authorisation and monitoring of clinical trials
 - Countries involved: Ghana, the Gambia, Uganda, Kenya, Nigeria and Ethiopia. WHO funding
- September 2005: Workshop on Regulatory Procedures for Clinical Evaluation of Vaccines (Addis Ababa, Ethiopia)
 - Main outcome: Templates procedures for submission/review clinical trials applications and integration of activities and importation/release of clinical batches
 - Countries involved: Botswana, Ghana, Cameroon, Ethiopia, The Gambia, Uganda, Kenya, Mali, Nigeria, Senegal, Tanzania, Zambia, and South Africa (WHO funding)
- December 2005: Regulatory forum on clinical evaluation of rotavirus vaccines (Botswana, December 05)
 - Main outcome: a) Presentation and discussions of scientific information on issues that may affect the efficacy and safety of rotavirus vaccines b) allow countries to make a final decision with regards to registration of rotavirus vaccines
 - Countries involved: Botswana, Ghana, Gambia, Zimbabwe, Malawi, Cote d'Ivoire, South Africa, Zambia, and Cameroon (WHO funding)

WHO/EDCTP ACTIVITIES PLANNED AND CONDUCTED TO SUPPORT THE DEVELOPMENT OF AN HARMONIZED REGULATORY FRAMEWORK IN AFRICA, 2005-2007 - IMPLEMENTATION PHASE: 2006

- January to May: EDCTP/WHO agreement developed and signed
 - Main outcome: 360.000 Euros for 18 months. (June 2006-December2007)
 - Countries involved: Ghana, Uganda, Tanzania, Nigeria, Malawi, The Gambia, Mozambique, Rwanda, Gabon, Mali, Burkina Faso, Kenya, Ethiopia, Zambia, and Cote d'Ivoire (EDCTP funding)
- June: Joint review of CTA of Conjugate Meningitis A vaccine (Banjul, The Gambia)
 - Main outcome: Review of clinical trials application for phase II Conj: Meningitis A vaccine by Mali and the Gambia national regulatory and vaccine experts on relevant gaps/missing information concerning Meningitis A vaccine clinical trials.
 - Country involved: The Gambia, Mali, Ghana, Senegal (WHO funding).
- April and July: Country visits and Country workshop for follow up implementation of IDP recommendations
 - Main outcome: Updated IDP and coordination plan to involved all stakeholders in



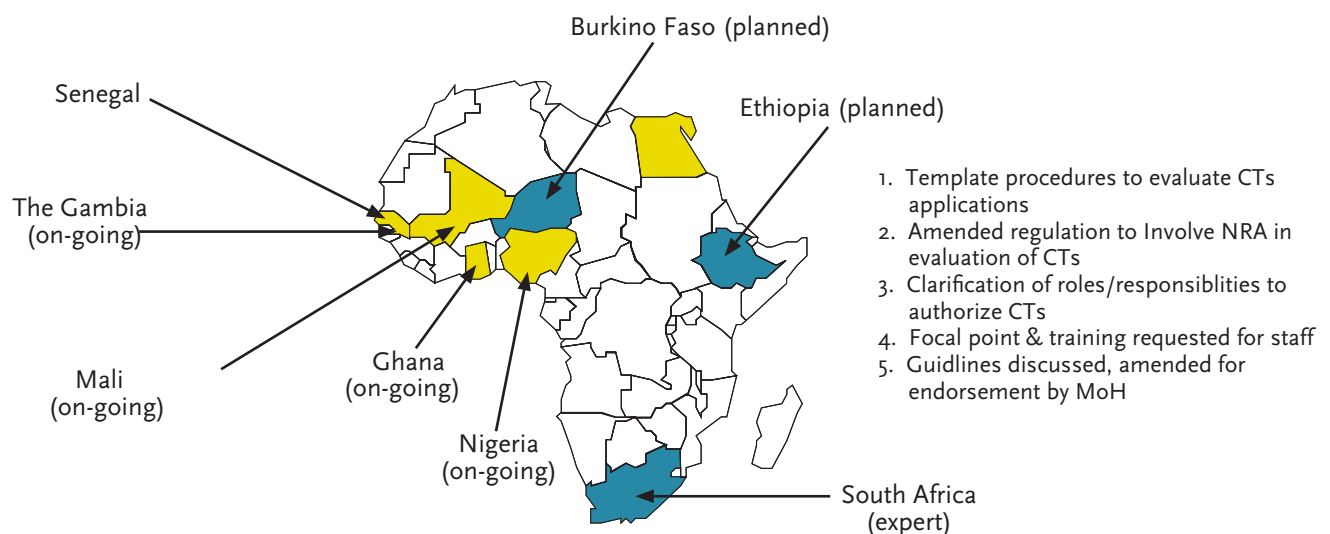
- follow up implementation of recommendations
- Country involved: Senegal and Uganda (WHO funding).

WHO/EDCTP ACTIVITIES PLANNED AND CONDUCTED TO SUPPORT THE DEVELOPMENT OF A HARMONIZED REGULATORY FRAMEWORK IN AFRICA, 2005-2007 - IMPLEMENTATION PHASE: 2006-2007

- 2006
 - September – AVAREF (Accra, Ghana, 19-22 Sept) –Partial EDCTP funding
- 2007
 - January – Joint inspection of CT of Conjugate meningococcal A vaccine – Partial EDCTP funding
 - March – Workshop on regulatory inspections of clinical trials (tentative) – Partial EDCTP funding
 - September – Training for 10 countries (French speaking) on authorisation and monitoring of clinical trials – Partial EDCTP funding
 - February and June – Training for 20 countries (English speaking) on authorisation and monitoring of clinical trials (Addis Ababa, Ethiopia) – Partial EDCTP funding
 - January to December: Follow up IDP and monitoring activities in 5 countries

PROGRESS AND IMPACT ON VACCINE REGULATORY SYSTEMS

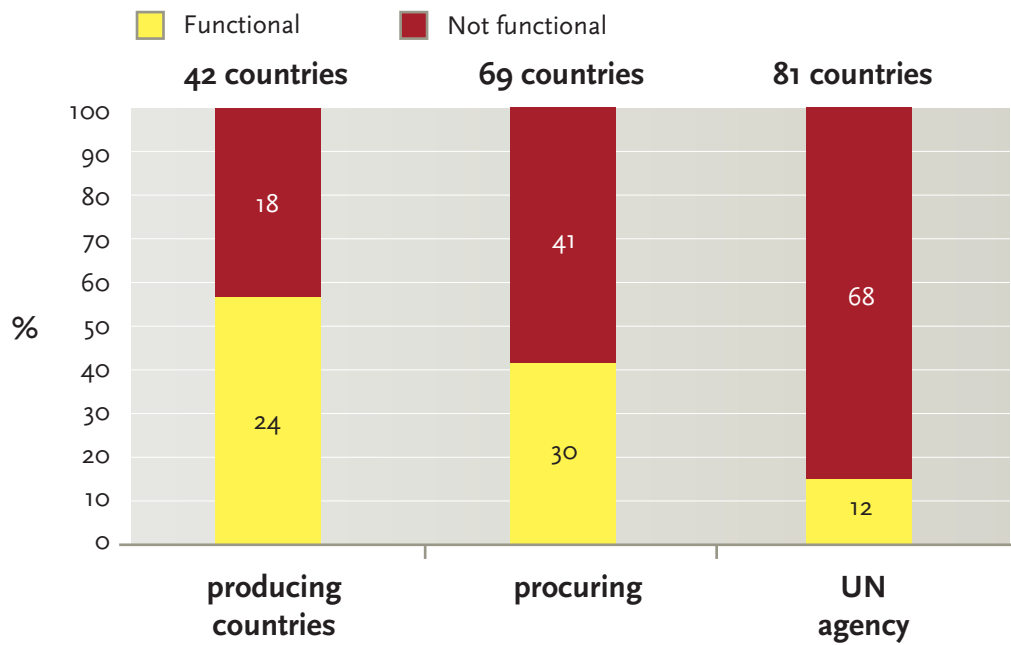
- 68 NRA assessments conducted (Oct 1998 to Dec 2005)
- 220 experts recruited (Oct 1998 to April 2006)
- By 2006 Only Yellow fever is produced in Africa, all other vaccines are procured through UNICEF. 92% of countries used WHO prequalification system
- Changes documented to improve evaluation of vaccines:



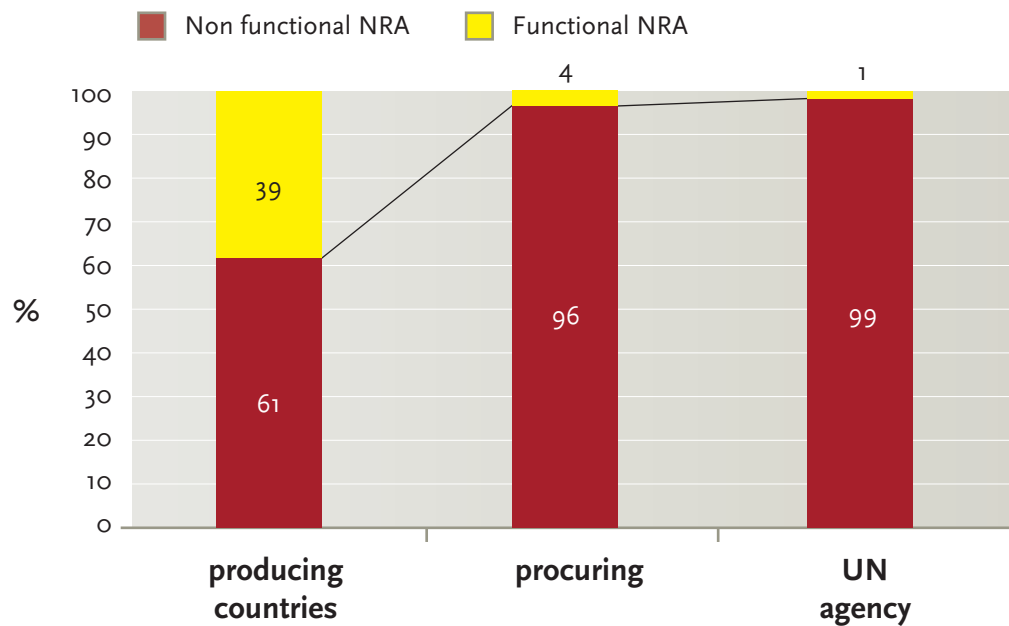


■ NRA functions status, 2006

Number of countries that have a functional vaccine regulatory system
(denominator = 192 member states)



■ % Total population monitored by a functional NRA according to source of vaccine



Functional NRA: meeting 2, 4 or 6 regulatory functions

Information sources: www.who.int
www.sharepoint.who.int/ATT



2.4. The Role of African Institutions in clinical trial sponsorship – *Professor Charles Mgone, South Africa*

Professor Mgone is the Head of Africa Office of EDCTP

THE ROLE OF A SPONSOR HAS THE FOLLOWING CATEGORIES:

- Quality Assurance and Quality Control
 - Trial design
 - Trial management
 - Data handling
 - Record keeping
- Safety management
 - Pre-clinical and previous clinical data
 - Safety monitoring during and after completion of the trial
- Selection of the investigators and assignment of responsibilities
 - Competence
 - Experience
 - Qualification
- Notification and submission to regulatory authorities
- Compilation of investigator's brochure and handling of the investigation product
 - Properties
 - Safety data
 - Transportation and storage
 - Stability assays
 - Labelling
 - Supply
 - Use
 - Disposal
- Compensation, Insurance and Indemnity (Financial and legal)
 - Research participants
 - Investigators
- Financial management
- Audit

EDCTP CHECK-LIST ON SPONSORSHIP

- 1) Set up quality assurance and quality control system
- 2) Assess medical expertise of investigator and monitors
- 3) Assess clinical trial design
- 4) Take care of trial management, data handling and record keeping
- 5) Ensure clear allocation of tasks and function between partners
- 6) Take care of compensation to subject and investigators (insurance)
- 7) Support extra costs that are not covered by EDCTP
- 8) Take responsibility of the notification of the mission of the clinical trial to regulatory authorities
- 9) Check that the PI has submitted the protocol to an independent ethics commission and ensure approval this review



- 10) Provide information on the investigatory product (investigatory product brochure and investigational medicinal product; IMPD)
- 11) Take responsibility for manufacturing, packing, labelling and coding the investigational product
- 12) Responsibility for supply handling of the investigational product
- 13) Record access to regulatory authorities
- 14) Collect and report safety information
- 15) Report adverse drug reactions to regulatory authorities and/ or ethics commission
- 16) Monitoring of the clinical trial
- 17) Auditing of the clinical trial
- 18) Solving the problem of non compliance
- 19) Design a specific procedure for preliminary suspension of the clinical trial
- 20) Responsibility for the clinical trial reports





2.5. The AMANET Experience in Trial Sponsorship

— Dr Roma Chilengi, AMANET, Tanzania

AMANET is not for profit NGO, registered under Tanzanian Law, and has been in existence since 2002 based in Dares Salaam. AMANET is also host for MIM Secretariat.

THE MISSION OF AMANET

- Global awareness of malaria disaster
- Promote cooperation and collaboration
- Develop potential trial sites in infrastructure and human capacity development
- Sponsorship of clinical trials
- Promote good governance
- Ultimately AMANET seeks to shorten the period of developing Malaria interventions with the African participation in the process

RATIONALE

- Malaria is largely an African problem
- Lack of an African product (malaria) development platform
- Despite developments in antimalarial drugs, the numbers are getting worse
- With the current profile of candidate vaccines in development, a lot of work is yet to be done to improve knowledge
- Investment and preparation of trial sites across the continent is inevitable especially if vaccines are to be developed

MALARIA R&D CAN BE ACCELERATED: AMANET IS SET TO CREATE A “PULL” MECHANISM.

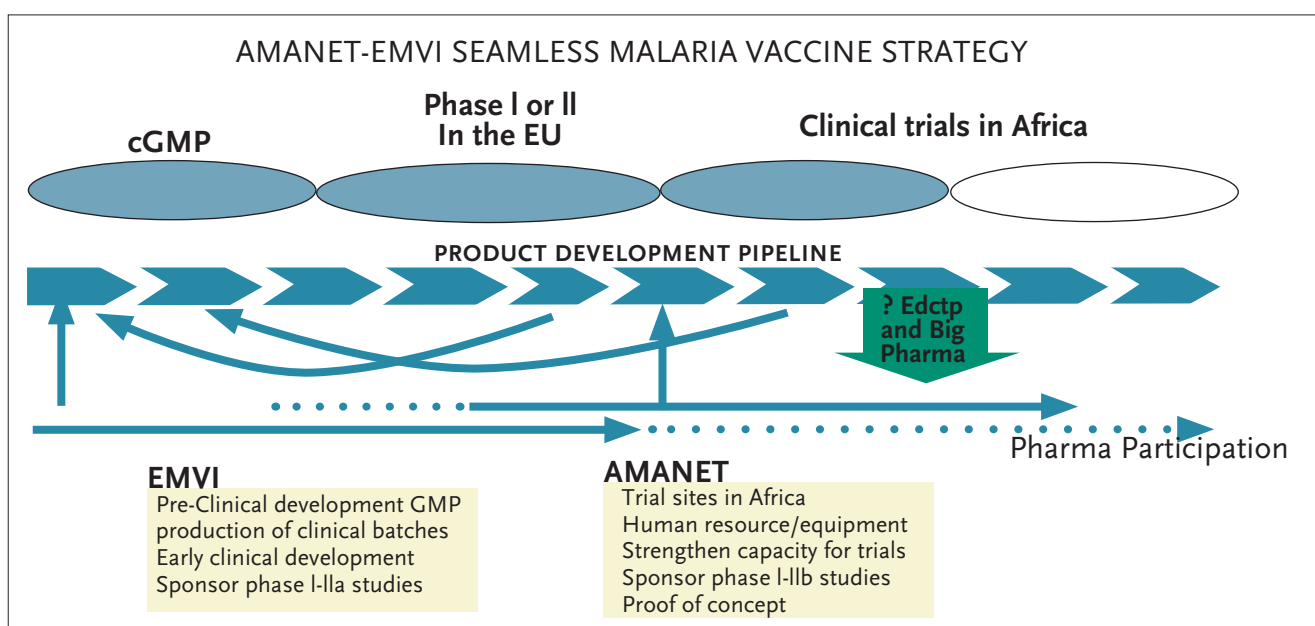
OUR EXPERIENCES AT AMANET

- Funding sources
 - EuropeAid Cooperation Office of the European Commission (EC-AIDCO)
 - Danish Agency for International Development (DANIDA)
 - European Commission Directorate General, Research (EC-DG Research)
 - Netherlands Foreign Affairs
 - Others i.e. National Institutes of Health (NIH), Office for Human Research Protections (OHRP), World Health Organisation (WHO), European and Developing Countries Clinical Trials Partnership (EDCTP)
- Fund raising
 - Trans-Atlantic “polarisation”
 - Who sets the research agenda
 - Time lag from grant application to award
 - Sustainability of funding
 - Difficult to remain focussed
- Trial sites
 - Inadequate for huge phase III trials

- Same centres for the major diseases
- Poor local support
- Skilled human resource inadequate
- No systematic training/staff retention programmes
- “Territorialism” by northern collaborators and their institutions
- Regulatory framework
 - Few regulatory agencies formally exist, mostly medical advisory offices
 - Outside formal International Committee on Harmonisation (ICH) coverage
 - Registration mainly through colonial lines or WHO
 - Inadequate capacity to review product dossiers by ICH standards
- Ethical review framework
 - Generally improving, though many still below international standards
- Role of sponsor
 - Scarcity of relevant human resources
 - Pessimistic attitudes
 - Time for development of a system and SOP's
 - Trial insurance cover in Africa
 - Intra continent travel time
 - Unresolved IPR position
 - Sources of products

Our current focus: Malaria vaccine development

- Vaccines to be evaluated
 - Contacts with strategic partners who will deliver vaccines ready for endemic country evaluation





- Trial sites preparedness
 - Institutional set up
 - Human resources-Professional training in key fields
 - Characterisation of field testing sites
 - Infrastructure and equipment
 - Short term training- GCP; GLP; vaccinology; molecular biology; immunology; data management; design and methodology; ethics; management/leadership; accounting etc

- Challenges
 - Lack of experience
 - Lean Secretariat
 - Delayed vaccine availability versus grant deliverables
 - Dependence on part time “experts” causes delays
 - Inadequate funding for research capacity strengthening programmes

- Way forwards
 - Work on “Attitude”
 - Clear understanding with partners/collaborators
 - Learn best practices from pharmaceutical companies, especially
 - Timeliness
 - Progression criteria and pre-set targets
 - Appropriate resources to where it works
 - Strategy to deal with conflicts of interest
 - Ownership of programmes

- Our current portfolio

| CANDIDATE VACCINE | STATUS |
|--|---|
| MSP 3 LSP (Merozoite surface protein 3, Long synthetics peptide) | Completed phase Ib adults; planned phase Ib in children Q4 2006 Burkina Faso |
| AMA 1 (Apical Membrane Protein 1) | Ongoing phase Ia in Netherlands; planned phase Ib adults in Mali Q4 2006 |
| GMZ 2 (MSP 3 + GLURP: Recombinant) | Starting phase Ia in Germany; planned phase Ib adults in Gabon Q1 2007 |
| GMZ 1 Glutamate Rich Protein (GLURP) | Planned phase Ia in Germany; Planned phase Ib in Africa (site to be allocated) Q3 2007 |
| ? PEV 302 AMA 1 + CSP (Circumsporozoite Surface Protein) Virosomal expression system | Ongoing document review; vaccine completed phase Ia and IIa. Agreement with company not yet reached |



3.0 PRESENTATIONS BY EDCTP GRANTEES – DAY 1

MONDAY, 24 JULY

Chair: Mr Daan du Toit, Department of Science and Technology (South Africa)

Rapporteur: Dr Simon Agwale, DCCC member (Nigeria)

3.1. Development and evaluation of high throughput, cheap and reliable assays for monitoring HIV-1 and HIV-2 viral loads in ARV programmes and clinical trials in developing countries – *Dr Abraham Alabi, Gambia*

Background

- There is high cost of commercial HIV-1 viral load (VL) assays including inadequate infrastructure and expertise
- Both HIV-1 and HIV-2 are prevalent in West Africa
- No commercial assays for HIV-2 VL are available
- Robust and cheap VL assays is needed to monitor viral control in clinical trials/intervention programmes

Objectives

- To develop a robust and affordable in-house viral load assay for quantifying HIV-1 and HIV-2 ribonucleic acid (RNA)
- To evaluate assay for sensitivity, specificity, and reproducibility
- To conduct a sub-regional training workshop on the assay
- To coordinate a multi-site evaluation and possible use of assay

Basic description of assay

- Extraction of HIV RNA from 200 µl patients plasma
- Reverse transcription of RNA to copy deoxyribonucleic acid (DNA)
- Polymerase chain reaction (PCR) using specific HIV long term repeat (LTR) primers
- Colorimetric detection of PCR product by a pharmaceutical company called Elona
- Internal calibrator to make assay competitive
- Dynamic Range : 10^2 - 10^6 RNA copies/ml

Validation for assay

- Assay of National Institute for Biological Standards and Control (NIBSC) international standards (with working reagents coded PWS1-3, 97/656)
- Comparison with Roche Amplicor v. 1.5
- Limiting Dilution for HIV-2
- Reproducibility Testing:
 - Intra-assay variation
 - Inter-assay variation
- Specificity Testing

TABLE1. DIFFERENCES IN RNA COPIES/ML AS DETERMINED BY IN-HOUSE ASSAY VERSUS NIBSC EXPECTED VALUES

| SAMPLE | IN-HOUSE | NIBSC | LOG ₁₀ DIFFERENCE |
|--------|----------|-------|------------------------------|
| PWS-1 | 1055 | 1270 | -0.08 |
| PWS-2 | 18467 | 12700 | -0.16 |
| 97/656 | 32676 | 35000 | 0.03 |
| PWS-3 | <100* | 175 | - |

* Less than the detection limit of in-house assay

TABLE2. DIFFERENCES IN RNA COPIES/ML AS DETERMINED BY IN-HOUSE ASSAY VERSUS ROCHE AMPLICOR 1.5

| SAMPLE | IN-HOUSE | ROCHE | LOG ₁₀ DIFFERENCE |
|---------|----------|-------|------------------------------|
| P873 | 12828 | 26600 | -0.32 |
| N23576 | 2650 | 5000 | -0.28 |
| N70032 | 42496 | 15000 | 0.45 |
| W1216 | 9991 | 4000 | 0.40 |
| N172248 | 5830 | 9600 | -0.22 |

TABLE 3. COMPARISON OF IN-HOUSE ASSAY VERSUS LIMITING DILUTION (HIV-2)

| ID | RNAVL (X 10 ³) | | LOG DIFF |
|--------|----------------------------|------------|----------|
| | in-house | Limit dil. | |
| N76433 | 20 | 23 | -0.06 |
| N17567 | 17 | 14 | 0.08 |
| N19397 | 13 | 15 | -0.06 |
| N16345 | 54 | 45 | 0.08 |
| N77288 | 80 | 64 | 0.10 |
| N76073 | 18 | 20 | -0.05 |

Mean Log difference = 0.09



TABLE 4. REPRODUCIBILITY RESULTS

| SAMPLE | RNA copies/ml | | |
|--------------|---------------|---------|---------|
| | DAY 1 | DAY 2 | DAY 3 |
| No27140 | 455006 | 892806 | 401574 |
| No27140 | 450127 | 410250 | 542787 |
| No27140 | 480784 | 569695 | 865829 |
| No27181 | 1341509 | 673780 | 1090521 |
| No27181 | 791436 | 1110525 | 1093882 |
| No27181 | 1038602 | 903523 | 1304591 |
| No27085 | 5443 | 5157 | 9294 |
| No27085 | 5108 | 27680 | 9872 |
| No27085 | 8340 | 9836 | 5753 |
| No27184 | 126911 | 246819 | 605581 |
| No27184 | 455144 | 494012 | 516497 |
| No27184 | 515089 | 363862 | 641109 |
| No27183/10 | 2010 | 3531 | 2319 |
| No27183/10 | 3503 | 3571 | 4629 |
| No27183/10 | 2092 | 6661 | 4026 |
| No27185/2000 | 643 | <100 | <100 |
| No27185/2000 | 519 | <100 | <100 |
| No27185/2000 | 1580 | 446 | <100 |

CoV = 3.2% - 6.9% intra-assay; 0.77% - 1.6% inter-assay

TABLE 5. SPECIFY RESULTS

| Sample | Sample ID | samples type | copies/ml |
|--------|-----------|-----------------|-----------|
| 1 | Neg. ctrl | | <100 |
| 2 | Pos.ctrl | | 5310 |
| 3 | No04007 | HTLV+ve,HIV-ve | <100 |
| 4 | No04008 | HTLV+ve,HIV-ve | <100 |
| 5 | No04072 | HTLV+ve,HIV-ve | <100 |
| 6 | No27158 | HIV2=ve,HIV-ve | <100 |
| 7 | No27160 | HIV2+ve,HIV-ve | <100 |
| 8 | No27180 | HIV2+ve,HIV-ve | <100 |
| 9 | No27238 | HIV2+ve,HIV-ve | <100 |
| 10 | MVA-190 | Hep.B+ve,HIV-ve | <100 |
| 11 | MVA-197 | Hep.B+ve,HIV-ve | <100 |
| 12 | MVA-373 | Hep.B+ve,HIV-ve | <100 |

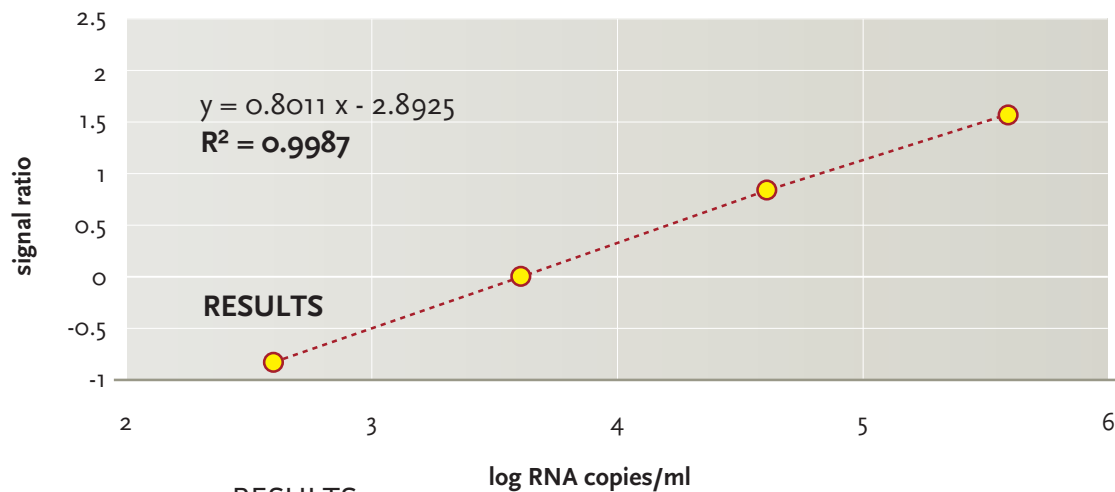
Quality control / quality assurance

- Positive and negative controls included in each assay run
- Use of HIV-1 international standards (PWS-1 to PWS-3)
- Evaluation of new batch of reagents

Raw data

| | 1 | 2 | 3 | 4 |
|---|-------|-------|-------|-------|
| A | 5643 | 38547 | | |
| B | 5403 | 38099 | | |
| C | 19498 | 19119 | | |
| D | 21014 | 19518 | | |
| E | 30318 | 4397 | 12567 | 21136 |
| F | 29937 | 4549 | 13015 | 20496 |
| G | 33587 | 894.1 | 24.6 | 43999 |
| H | 37554 | 1067 | 34.7 | 17928 |

Standard curve



RESULTS

| SAMPLE | SAMPLE ID | SAMPLE DATE | SAMPLES TYPE | COPIES/ML |
|--------|-----------|-------------|--------------|-----------|
| 1 | | | | <100 |
| 2 | | | | 2223 |

Institutional and infrastructural facilities

- Strong international scientists and clinicians on site
- Proven ability to undertake large clinical trials
- Rigorous scientific and ethical review process
- Extensive laboratory facility for biomedical research
- Good data management capability
- Up-to-date information technology (IT) and library services
- Established training capacity for West Africa sub-region
- Enjoys full cooperation of Gambian government and its people
- Strong collaborations with scientists and institutions in the North and the South

Existing and proposed networks to which the project is part

- North-south
 - A Collaboration on HIV-2 infection in Europe (ACHIEV2E) - a multi-site project to evaluate various HIV-2 assays in Europe (coordinated by Bernard Antoine, Bordeaux, France)
- South-south
 - Collaboration with Gambia's National AIDS Programme
 - Scientists and institutions participating in proposed sub-regional viral load training workshop

Problems and how resolved

- Recruitment and training of staff
- Delays in equipment & reagents deliveries
- Limited funding
 - Pending application with African AIDS Vaccine Programme (AAVP)
 - EDCTP
 - Other sources

Where are we?

- A colorimetric assay has been developed using p-Nitrophenyl Phosphate (p-NPP) as substrate
- Assay evaluated & satisfactory for sensitivity, specificity, and reproducibility
- Assay being used routinely to monitor patients on HAART in our genito-urinary medicine (GUM) clinic
- Sub-regional training/workshop scheduled for September 18-22, 2006 in Banjul

Future outlook

- Data analysis and publication of results
- Source additional funds for
 - African wide training
 - Multi-site evaluation
 - Wider use of assay
- Possibly develop an isothermal format of assay

ACKNOWLEDGMENT

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GUM Clinic
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Viral Data Office

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GLOBAL FUND

NIBSC, UK

Neil Berry
Harry Holmes

EDCTP



3.2. CHAPAS Trials: Children with HIV in Africa: Pharmacokinetics and Adherence of Simple Antiretroviral Regimens – *Professor Chifumbe Chintu, Zambia*

BACKGROUND

- Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is a major health problem in Zambia not only in adults but in children as well.
- The Zambian government is providing free antiretroviral therapy (ART)
- Pharmacokinetic (PK) of most antiretroviral (ARV) is done in adults and extrapolated for children
- Most ARV formulations are in capsule or tablet form and few in liquid form for children
- Liquids are bulky, generally have short shelf life and are more expensive than tablets. Not ideal for poor resource setting.

CHAPAS TRIAL-TWO OPEN LABEL TRIALS

The overall aim of the CHAPAS 1 study is to study the appropriate dosing of and adherence to a fixed –dose combination of stavudine, lamivudine and nevirapine in a formulation specifically developed for children (Pedimune)

Trials conducted in children who took part in the Children with HIV Antibiotic Prophylaxis (CHAP Study) which ended in 2003

PRIMARY OBJECTIVES

- To describe toxicity (rash, hepatic toxicity) probably or possibly related to niverapine (NVP), when NVP is initiated at full dose versus half dose, to determine the necessity for dose escalation.
- To determine the PK of NVP in twice daily paediatric formulated fixed dose crushable tablet combination of NVP, lamuvidine (3TC) and stavudine (D4T; Pedimune Cipla), in children of different age groups and varying degrees of malnutrition.

SPECIFIC OBJECTIVES

- To determine the possible PK interactions between NVP and common concomitant medications such as rifampicin and fluconazole
- Visual analogue developed by Dr David Bangsberg will be evaluated alongside other methods
- To describe mortality, disease progression, hospital admission rates and laboratory markers (CD4 %, Haemoglobin, viral load) after starting effective ART.
- To estimate the budget impact , cost effectiveness of effective highly active antiretroviral treatment (HAART) in HIV infected children in Zambia
- Effect of ART on growth nutrition and development of opportunistic infection

STUDY DESIGN

- An open, randomised , controlled phase I/II trial randomising 200 children in a 1:1 ratio to start with Pedimune either at full dose in twice daily schedule or in a dose escalation schedule of once daily administration for 14 days which is then increase to full dose
- 64 children (16 per age group, i.e. less than 3, 3-6, 7-10, 11-14 yrs) will be enrolled in a 12 hour



PK sub-study at least 4 weeks after starting ART.

- Adherence questionnaires and a visual analogue scale will be used to evaluate adherence in all participants in CHAPAS 1 trial at the time of clinic visits. In addition, 96 children will be enrolled in an adherence sub-study using the same age bands as in PK sub-study (but 24 per age group).
- In all children in CHAPAS Trial single plasma samples for PK at 12, 24, 48, 72, 96 weeks. In these PK will be done without observing intake of ARV

STUDY SITE

- University Teaching Hospital (UTH) Lusaka Zambia, Department of Paediatrics

SELECTION OF PARTICIPANTS

- Invited from children with HIV antibiotics prophylaxis trial follow up CHAP2 cohort and siblings who are HIV positive and ART naive
- CHAP2 provide a well followed up cohort with pre ART longitudinal clinical and laboratory data. Some are on ART now
- Eligibility criteria
 - WHO criteria for ART in children
 - WHO stage IV and severe stage III regardless of CD4 %
 - CD4 count <15% in children >18 months
 - CD4 count <20% in children < 18 months

PEDIMUNE FORMULATION

- Baby Pedimune
 - 6mg d4T
 - 30mg 3TC
 - 50mg NVP
- Junior twice the amount in baby Pedimune

DOSING OF PEDIMUNE TABLE

| WEIGHT RANGE | RECOMMENDED DAILY DOSE (MIN-MAX) | | | TOTAL DAILY TABLET | SCHEDULE | D4T | 3TC | NVP |
|--------------|----------------------------------|---------|---------|--------------------|----------|-----|-----|-----|
| | D4T | 3TC | NVP | | | | | |
| 3-5kg | 6-10 | 24-40 | 42-70 | 1 | 1/2BD | 6 | 30 | 50 |
| 5-7kg | 10-14 | 64-56 | 70-98 | 2 | 1BD | 12 | 60 | 100 |
| 8-9kg | 16-18 | 64-72 | 160-174 | 3 | 1 1/2BD* | 18 | 90 | 150 |
| 10-14kg | 20-28 | 80-112 | 180-25 | 2 | 1BD | 24 | 120 | 200 |
| 15-19kg | 30-36 | 120-152 | 240-320 | 5 | 2 1/2BD* | 30 | 150 | 250 |
| 20-24kg | 40-48 | 160-192 | 304-376 | 3 | 1 1/2BD* | 36 | 180 | 300 |
| 25-29kg | 50-58 | 200-232 | 400 | 4 | 2BD | 48 | 240 | 400 |
| 30-39kg | 60 | 300 | 400 | 2 | 1BD | 60 | 300 | 400 |
| 40-49kg | 60 | 300 | 400 | 2 | 1BD | 60 | 300 | 400 |
| 50-59kg | 60 | 300 | 400 | 2 | 1BD | 60 | 300 | 400 |

*Can split in unequal doses and take whole tablets; 2 morning, 3 evening for 2 1/2BD

FOLLOW UP PK SAMPLING

- Quality control of Pedimune will be done at UTH pharmacy on each batch of Pedimune

MONITORING ADHERENCE

- Pill counts , medication events monitoring system (MEMS) caps, 3-day structured self report questionnaire (to carers only) and 28-day visual analogue self report

CURRENTLY

- Recruitment started in Feb 2006, to date 53 children have been recruited to CHAPAS 1 study, 35 to PK sub-study, and 25 to adherence sub-study.
- Recruitment has been slow- eligibility criteria and competing for children with the government ART program.

ADMINISTRATION AND DATA MANAGEMENT

- Budget has been distorted due to the appreciation of the Zambian Kwacha.
- One of the best IT centres in the country, improved markedly on data management.
- Finance management is also being improved.

CAPACITY BUILDING

- Investigators workshop in January 2006
- Training workshops- data management, PK sampling and handling, adherence monitoring.

COLLABORATION

- MRC- London
- Nijmegen-Netherlands
- San Francisco- USA
- Uganda
- Ireland

CONCLUSION

- Important study
- Good start despite teething problems
- Teams good cooperation
- Regular telephone conferences

3.3. Evaluation of 4 artemisinin-based combinations for treating uncomplicated malaria in African children

— Professor Umberto d'Alessandro, Belgium

RATIONALE

- Crucial period: several African countries have already chosen artemisinin-based combination therapy (ACT) and others will follow
- Insufficient (fragmentary) data for informed choice on the most appropriate ACT
- Need information going beyond what is required for the drug registration

WHAT ARE THE QUESTIONS?

- What is the relative value of the different and available ACTs (safety and efficacy)?
- What is the impact of treatment on the child's health on the short and medium term?
- What is the frequency of treatment? (depends on transmission intensity and on the drug)
- Is there selection of resistant genotypes?

OBJECTIVES

- **Main objective:**
 - To compare the safety and efficacy of 4 ACT, i.e. amodiaquine and artesunate (AQ+AS), artemisinin (AL), dihydro-artemisinin piperazine (DHAPQ) and chlorproguanil/dapsone/artesunate (CDA) for single and repeat treatments of uncomplicated malaria
- **Specific objectives:**
 - To evaluate the efficacy of the 4 ACTs for the treatment of children with uncomplicated *P. falciparum* malaria (first active follow-up)
 - To determine after the first active follow-up the incidence rate of a second clinical episode of uncomplicated *P. falciparum* malaria
 - To evaluate the efficacy of treating the second clinical episode of uncomplicated *P. falciparum* malaria with the same ACT used for the first one (second active follow-up)
 - To evaluate during the active and passive follow up the safety of the 4 ACTs for the treatment of children with uncomplicated *P. falciparum* malaria
 - To establish the impact of using CDA on the selection of *P. falciparum* genotypes linked to SP resistance.

STUDY DESIGN

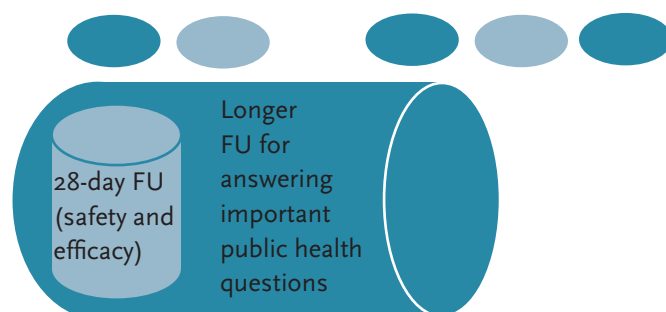
- Three-arm, multi-centre, randomised, open label trial
- First follow up of 28 days
- Beyond 28 days, passive follow up for detection of a second clinical episode within 6 months;-> re-treatment
- Second follow up of 28 days
- 510 patients per site and 170 per arm.

STUDY TREATMENT TO BE STUDIED BY COUNTRY

| COUNTRY | NUMBER OF SITES | AFFILIATION | STUDY TREATMENTS | | |
|--------------|-----------------|---|------------------|-------|-------|
| Burkina Faso | 1 | Centre Muraz/ Institut de Recherche en Science de la Sante (IRSS) | AQ+AS | DHAPQ | AL |
| Nigeria | 1 | Tropical Disease Research Institute (TDRI) | AQ+AS | DHAPQ | AL |
| Zambia | 1 | Tropical Disease Research Centre (TDRC) | AQ+AS | DHAPQ | AL |
| Gabon | 1 | HAS (Albert Schweitzer Hospital)/ Tübingen | AQ+AS | DHAPQ | AL |
| Uganda | 1 | East African Network for Monitoring anti-malaria treatment (EANMAT) | DHAPQ | CDA | AL |
| Uganda | 2 | EANMAT/EPICENTRE | AQ+AS | CDA | DHAPQ |
| Rwanda | 2 | EANMAT | DHAPQ | CDA | AL |
| Mozambique | 1 | Manhiça | AQ+AS | CDA | DHAPQ |

END POINTS

- **Primary**
 - PCR unadjusted treatment failure (TF_{28U})
 - PCR adjusted treatment failure up to day 28 (TF_{28A})
- **Secondary**
 - PCR unadjusted treatment failure up to day 63 (TF_{63U})
 - PCR adjusted treatment failure for the whole period of passive surveillance
 - Fever clearance time
 - Asexual parasite clearance time
 - Gametocytaemia at day 7, 14, 21 and 28
 - Hb changes day 3, 7, 14 and 28
 - Clinical malaria after first active follow-up
 - Clinical malaria after second active follow-up
 - TF second clinical episode (day 28 and day 63)
 - Changes in the frequency of mutations in the dihydrofolate reductase (DHFR) (for patients treated with CDA)
 - Safety profiles including significant changes in relevant laboratory values.



FIRST AND SECOND FOLLOW UP

| DAY | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|------------------------|---|---|---|---|---|---|---|---|
| History | X | | | | | | | X |
| Examination (clinical) | X | X | X | X | | | | X |
| Temperature | X | X | X | X | | | | X |
| Blood film | X | | X | X | | | | X |
| Filter paper PCR | X | | | | | | | X |
| Treatment | X | X | X | | | | | |
| Adverse drug reactions | | X | X | X | | | | X |
| Haematology | X | X | X | X | | | | X |
| Biochemistry | X | | | | | | | X |

| 14 | 21 | 28 | ANY OTHER DAY ¹ |
|----------------|----|----|----------------------------|
| X | X | X | X |
| X | X | X | X |
| X | X | X | X |
| X | X | X | X |
| | | | |
| X | X | X | X |
| X | | X | X |
| X ² | | X | |

¹ Spontaneous attendance to health facility, ² If abnormal at day 7.

INCLUSION CRITERIA

- Age 6 months and 59 months inclusive
- Bodyweight from 5 kg above
- Mono-infection of *Plasmodium falciparum* (parasitaemia $\geq 1,000/\mu\text{L}$ to $200,000/\mu\text{L}$).
- Fever/history of fever
- Haemoglobin value ≥ 7.0 g/dl
- Signed informed consent

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 inter-current illness
- Severe malnutrition
- Ongoing prophylaxis with drugs having anti-malarial activity

PASSIVE FOLLOW UP

- Parents/guardians asked to attend for any illness
- Monthly visits at home to keep contact without collecting blood samples unless sick
- When attending health centre; blood slides, body temperature and Hb/PCV collected systematically
- If inclusion criteria included in the second follow up
- If malaria not fulfilling criteria, treated with 1 line treatment.



PROBLEMS ENCOUNTERED (MANY)

- Non-flexibility during the contract negotiation
- GCP/GLP standards more costly than previously anticipated
- Slow procedures and
- Slow disbursement of funds
- Difficult requests, e.g. presentation of all SOP for record and report before approving the clinical protocol
- Existing gaps in human resources and infrastructure
 - More resources needed than previously anticipated (project conceived/written beginning 2004)
- Type of equipment in the institution
 - More than half of the sites able to do all lab tests
- Data management capacity
 - GCP compliant software (to be bought, not in the budget)
 - CTU in Antwerp and Liverpool University for statistics
- Ethics and regulatory issues

QC/QA, ACCREDITATION

- Molecular biology lab in Antwerp, accreditation for genotyping
- QC/QA system in Antwerp
- Monitoring of the study by independent clinical monitor(s) or Clinical Research Organisation

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 Anti-malarial 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 Manhica Health Research Center, Mozambique

3.4. Assessment of the public health benefit of artemisinin-based combination therapies for uncomplicated malaria treatment in Mali

— Dr Bakary Fofana and Dr Abdoulaye Djimde, Mali

Molecular Epidemiology and Drug Resistance Unit (MEDRU), Malaria Research and Training Centre- Département d'Epidémiologie des Affections Parasitaires-Faculté de médecine, de pharmacie et d'odontostomatologie (MRTC-DEAP-FMPOS), University of Bamako-Mali

DESCRIPTION OF THE PROJECT

- Drug resistance is hampering the control of malaria
- Sub-Saharan African countries are adopting artemisinin combination therapies (ACT) as first line therapy.
- The efficacy measured at Day 14 or 28 may not adequately reflect the true public health impact of a treatment regimen
- It is important to assess the safety and overall public health impact of the repetitive administration of these new combinations in the African context
- We proposed to assess the public health benefit of the use of ACTs in sub-Saharan Africa.

OBJECTIVE OF THE PROJECTS

- Test the hypothesis that repeated administration of artesunate/amodiaquine (AS/AQ), artesunate/sulphadoxime pyrimethamine (AS/SP) and Coartem (AR-L) for the treatment of consecutive episodes of uncomplicated malaria reduces the incidence of uncomplicated falciparum malaria and malaria attributable anaemia
- Measure the impact of the repeated administration of AS/AQ, AS/SP and AR-L on anti-malarial immunity and malaria transmission.

METHODS

- Started July 2005
- Randomized controlled trial in Bougoula-Hameau
 - malaria is hyper – endemic with
 - seasonal transmission in Southern Mali
- Patients with uncomplicated malaria are randomized to receive AS/AQ (Arsucam® from Sanofi Synthelabo), AS/SP or AR-L (Coartem®, Novartis)
- Once subjects have been assigned to a given group, subsequent malaria episodes are re-treated with that same treatment regimen
- Patients are closely followed both clinically and biologically to record any adverse event.

RESULTS

- Baseline characteristics of subjects

| TREATMENT ARM | < 5 YEARS % | SEX (MALE) % | GAMETOCYTES CARRIAGE (%) | ANEMIA (%) |
|---------------|-------------|---------------|--------------------------|------------|
| AR-L | 58.3 | 50.8 | 11.1 | 49.0 |
| AS/ AQ | 59.0 | 45.9 | 6.5 | 51.6 |
| AS/ SP | 41.7 | 54.2 | 10.0 | 49.4 |
| P- values | NS | NS | NS | NS |

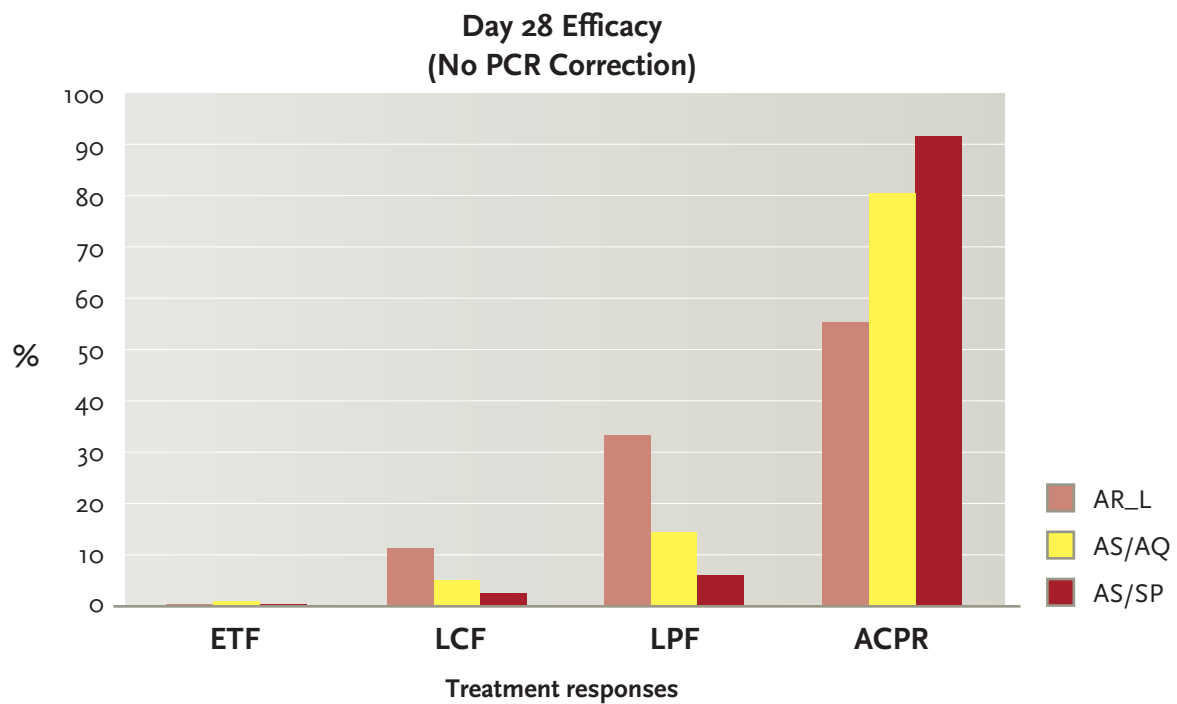
Three groups were comparable at inclusion according to these parameters



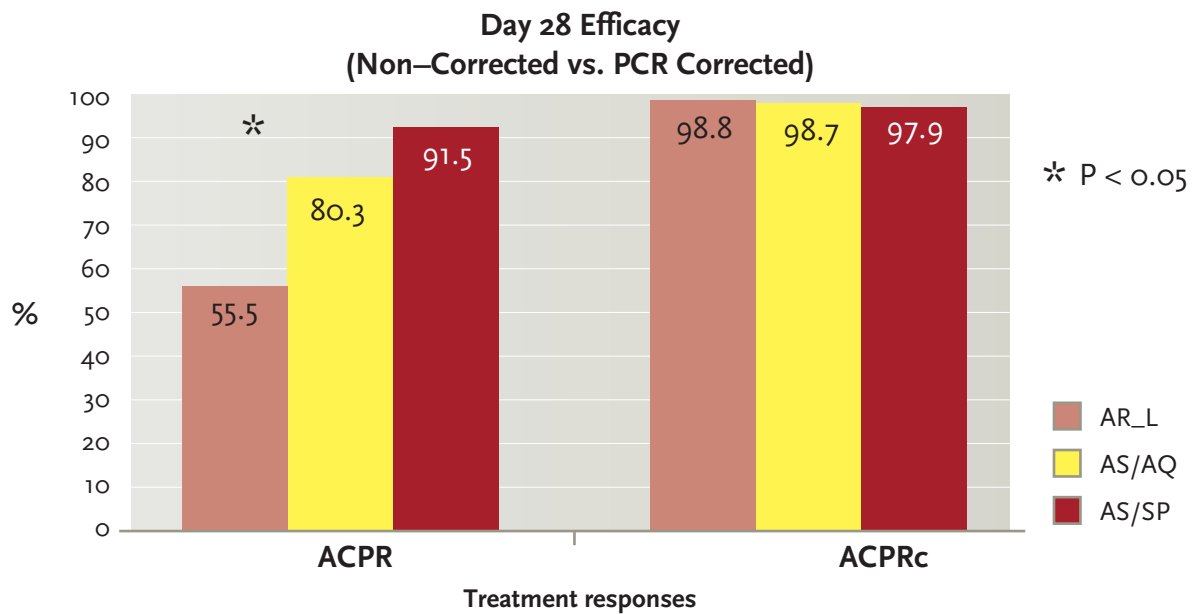
- Number of episodes by treatment arm on 18 July 2006

| EPISODES NUMBER | TREATMENT ARMS | | | TOTAL |
|-----------------|----------------|-------------|-------------|-------|
| | AR_L | AS/AQ | AS/SP | |
| 1 | 184 (55.9%) | 184 (59.6%) | 184 (56.7%) | 552 |
| 2 | 92 (28%) | 79 (25.6%) | 92 (27.5%) | 263 |
| 3 | 43 (13.1%) | 33 (10.7%) | 44 (13.1%) | 120 |
| 4 | 8 (2.4%) | 10 (3.2%) | 13 (3.9%) | 31 |
| 5 | 2 (0.6%) | 3 (0.9%) | 2 (0.6%) | 7 |
| Total | 329 | 309 | 335 | 973 |

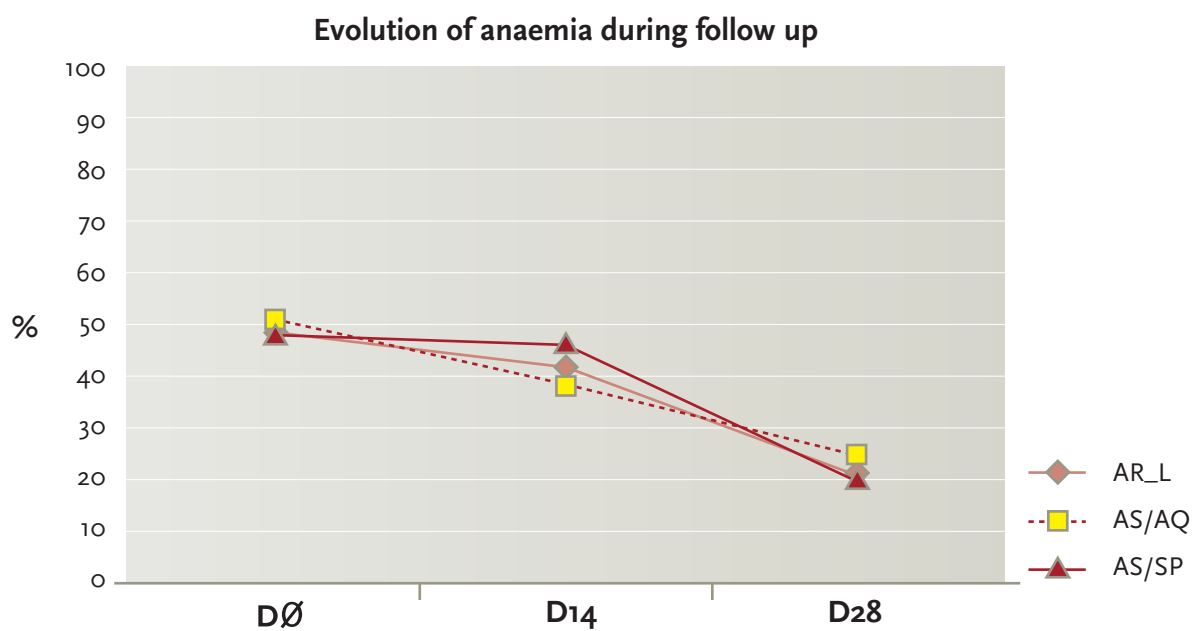
In one year some patients have already experienced their 5th episode of malaria. There was no significant difference in the frequency of clinical episodes.



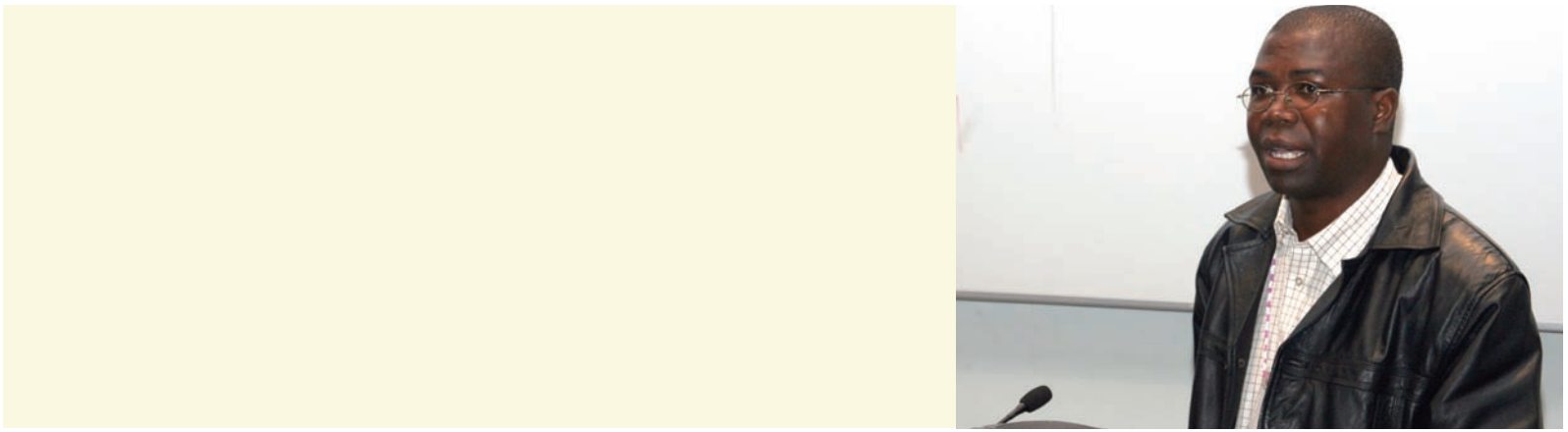
We observed that the AS/SP and AS/AQ groups were comparable but significantly better than the AR_L group ($p < 0.05$)



All the three treatment groups were comparable after PCR correction ($p > 0.05$) and furthermore, the efficacies levels are at all more than 95%



Significant decrease of anaemia after ACTs treatment, the three arms are comparable in the correction of anaemia



SERA COLLECTION

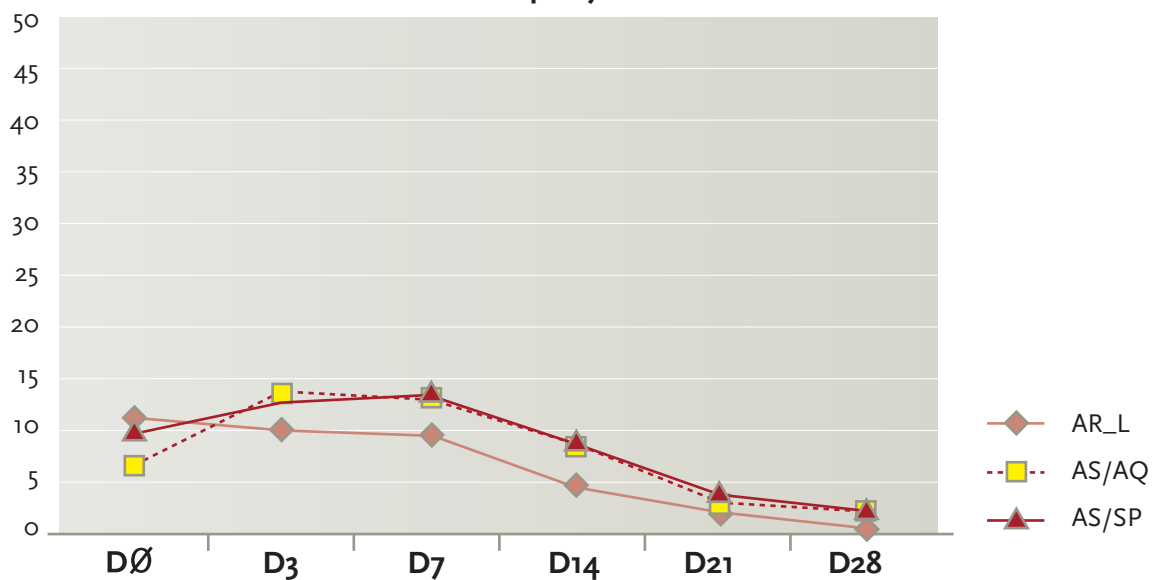
- Until 18 July 2006
 - 214 sera E1
 - 57 → E2
 - 50 → E3
 - 16 → E4
 - 4 → E5
- A total of 341 sera collected

IMPACT ON TRANSMISSION

- Methods
 - Drug efficacy study
 - Screening for gametocyte carriers
 - Include gametocyte carriers aged 6 – 18 years.
 - Direct feed starved F1 generation *Anopheles gambiae*
 - Maintain mosquitoes in field Insectaries for 8 days
 - Presence and number of oocysts measured by dissection
 - Compare the infectivity of pre-treatment vs. post-treatment gametocytes to *Anopheles gambiae*

EVOLUTION OF GAMETOCYTE CARRIAGE BY TREATMENT ARM ON FOLLOW UP DAYS

Evolution of gametocyte carriage by treatment arm on follow up days



Gametocyte carriage did not significantly increase following ACT treatment

INFECTIVITY OF MOSQUITOES BEFORE AND AFTER TREATMENT

| | OOCYST +/- MOSQUITOES FED | % |
|------------------|---------------------------|------|
| Before treatment | 3/173 | 1.7 |
| After AS/ SP | 7/123 | 5.7 |
| After AS/AQ | 12/85 | 14.1 |

ACT treatment do not decrease the infectivity of gametocytes to the vector

CAPACITY BUILDING

- Each member of the MEDRU has received various levels of training in Mali, Africa, Europe or America
- Office and laboratory space have doubled since the start of this EDCTP Fellowship
- New capacity acquired by the Unit include in vitro drug testing, HPLC analysis and antibody measurements by ELISA

ENCOUNTERED PROBLEMS

- No major hurdles were encountered

ETHICAL REVIEW AND APPROVAL

- Our study protocol was approved by the Ethics Committee of the Faculty of Medicine, Pharmacy and Odonto-Stomatology, University of Bamako, Mali.
- Any subsequent amendment was approved by the same Ethics committee prior to implementation
- Written informed consent was obtained from participants or parents prior to any protocol specific activity

QC/QA AND ACCREDITATION

- The microscope slides collected so far, the Case report forms, filter papers and other biological samples are moved to the main laboratory, logged into specific databases and stored.
- 10 % of microscopy slides were randomly selected and re-read by a reference microscopist at the main laboratory in Bamako.
- PCR gels and procedures were reviewed by several layers of senior investigators prior to data validation
- Monitoring by the sponsor
 - From November 8 – 10, 2005 and 15 to 18 February 2006 the monitor had several meetings with the staff at the main laboratory in Bamako and visited the facilities
 - The field site visited → team in activity
 - Reviewed Case Report Forms and all other source documents
 - Ms Brigitte Charron will be coming back for her third monitoring on July 31, 2006. We plan to work for a day in Bamako and travel to the field site for two days of monitoring



DATA MANAGEMENT CAPACITY

- Data are double entered and validated on Microsoft Access and analyzed with STATA or SPSS for Windows.
- Appropriate tests are used to compare categorical parameters.
- The control of quality of the data management
 - Collection, entry, treatment and analysis of data is monitored through internal controls and by supervisors
 - Data is entered in duplicate and reconciled to confirm the absence of conflict
 - The MRTC has a dedicated data management Unit capable of handling large sets of clinical trial data

NETWORKING ACTIVITIES

- We have initiated new collaborations with the University of Lyon I (Prof. Stephane Picot) and University of Glasgow, UK (Dr Lisa Ranford Cartwright).
- At the Regional level, as also stated above, students from neighbouring countries participated to some of the workshops that we organized during the past year.
- At the National level, we collaborate with our Entomology colleagues on all of the gametocyte and infectivity research described in this study.
- Our team is part of the Pal+, MIM-ADRN, BioMalPar and Malaria GEN Networks

SUMMARY AND CONCLUSION

- Senior fellowship contributed to improve the infrastructure and human capacity of the MEDRU
- Preliminary results suggest that
 - All three regimens are comparable in efficacy over 1 year of follow up
 - Although ACTs decrease gametocyte prevalence, they may not decrease infectivity to *Anopheles gambiae*
 - ACTs significantly decrease malaria attributable anaemia
- Additional analysis will include detailed analysis on incidence density of clinical malaria, impact on immunity, clinical and biological safety of the three regimens over time

FURTHER STUDIES

- Need to complete 24 months of follow up to have a better picture of the impact of repetitive treatment on malaria
- Need to check immune markers (antibodies) in sera collected at different episodes
- Need a third year of support to complete study

ACKNOWLEDGMENTS

- Molecular Epidemiology and Drug Resistance Unit (MEDRU) team
- MRTC-DEAP staff
- EDCTP
- IMPACT malaria (Sanofi-Aventis)
- Study populations



3.5. 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, Cote d'Ivoire

The combination of tenofovir-emtricitabine (Truvada®): a new antiretroviral (ARV) regimen for the prevention of mother-to-child transmission of HIV-1 (PMTCT) in resource-limited settings

The Phase II clinical trial of Tenofovir Emtricitabine in Africa and Asia; “TEMAA”

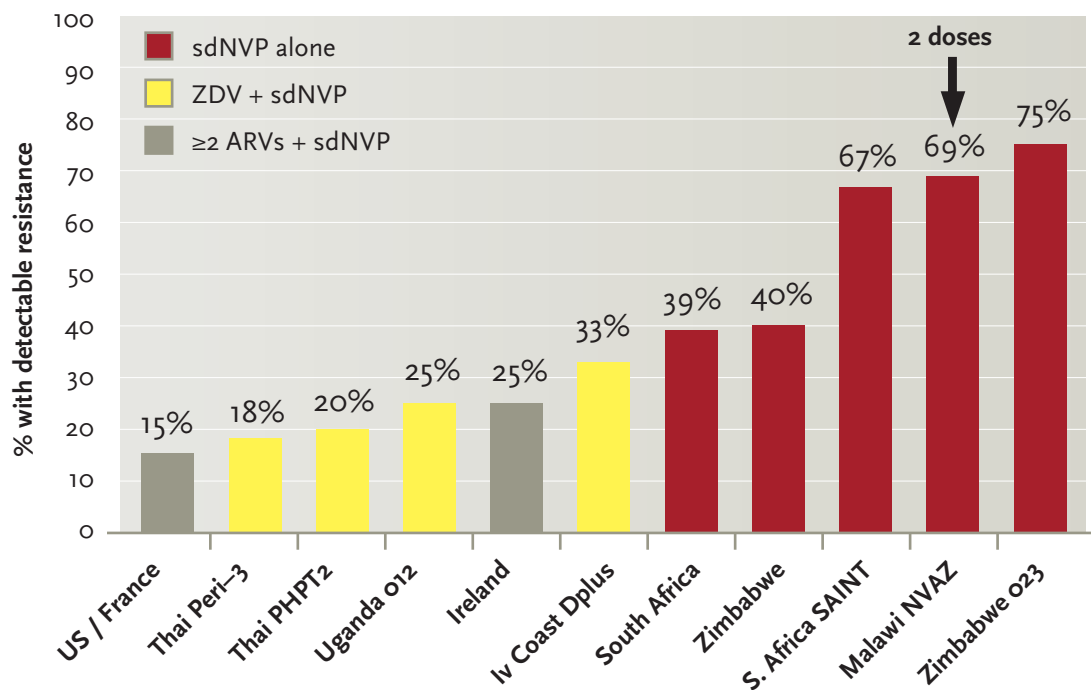
BACKGROUND

- A limited number of ARVs and drug regimens for PMTCT

| BIOAVAILABILITY | HALF-LIFE | PLACENTA | ELIMINATION | |
|-----------------|-----------|----------|-------------|--------|
| Zidovudine | 63% | 1 h | 85% | Kidney |
| Lamivudine | 86% | 2-6 h | 100% | Kidney |
| Nevirapine | 90% | 40 h | 90% | Kidney |

- Single-dose nevirapine (sdNVP) is the most common ARV regimen used for PMTCT: one 200 mg tablet at the onset of labour, together with one neonatal dose of syrup on Day 2
 - Reduction of 47% of the rate of transmission in comparison with a non efficacious regimen with a single-dose of zidovudine
 - Absolute rate of transmission at week 6 (breastfeeding) = 11.9%
- Viral resistance: the most worrisome problem with the single-dose nevirapine regimen
 - High rate of occurrence of NVP resistance mutations in the four weeks after exposure
 - In HIV-infected women (25-50%)
 - In HIV-infected children (20-87%) *Eshelman AIDS, 2001, Chaix CROI 2004, Arrive IAS, 2005*
- Resistance acquired to all non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Acquisition of NVP resistance in mothers following exposure SdNVP for PMTCT



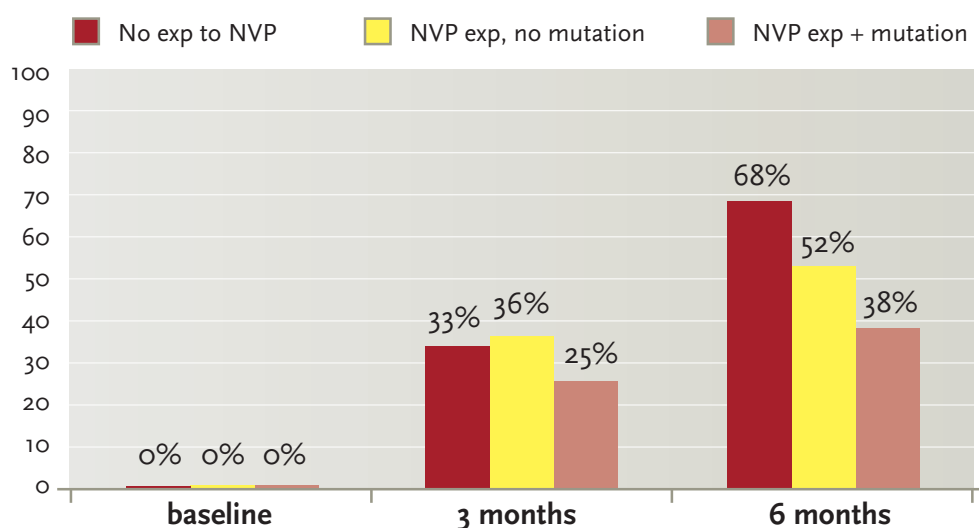
Adapted from L. Mofenson

HOW TO ADDRESS THE PROBLEM OF VIRAL RESISTANCE MUTATIONS WITH THE SINGLE-DOSE NEVIRAPINE PMTCT REGIMEN

- Since 2005, WHO recommends adding ZDV+3TC for one week postpartum to reduce the emergence of the NNRTI-associated mutations as demonstrated in ANRS 1201.1 Ditrane Plus in Abidjan (1%) and in TOPS trial in South Africa (10-12%): a complex solution
- Two questions:
 - Whether these levels of resistant virus have an impact or not on future maternal treatment options using NNRTIs?
 - Whether the repeated use of sd-NVP is appropriate in subsequent pregnancies?
 - The answer is that we still do not know

Response to d4T / 3TC / NVP in mothers by previous single - dose NVP exposure (PHPT 2, Thailand)

Response to treatment < 50 copies / ml



Jourdain et al. NEJM 2004; 351: 229-40

IS THERE AN ALTERNATIVE TO THE SINGLE-DOSE NEVIRAPINE PMTCT REGIMEN?

- Yes, and so follow the trials:
 - Tenofovir Emtricitabine in Africa and Asia
 - The ANRS 12109 - EDCTP TEmAA trial

TRUVADA®

- Truvada® is the combination of the two antiretroviral drugs:
 - Tenofovir disoproxil fumarate [TDF, 300 mg], nucleotide analogue
 - Emtricitabine [FTC 200 mg], similar to 3TC
 - Elimination half-life: 12-18 h for TDF and 10 h for FTC
- Dosage: 1 tablet of Truvada® per day in adults
- Animal studies with Tenofovir
 - TDF given in short-course is highly effective in protecting newborn macaques against simian immunodeficiency virus (SIV) infection (Van Rompay JAIDS 2006)
 - No major toxicity in animal with high doses of TDF

OBJECTIVES OF THE ANRS 12109 - EDCTP TEmAA TRIAL

- Primary objective:
 - To study the pharmacokinetic properties of TDF and FTC in pregnant women and their newborns
- Secondary objectives:
 - To determine the safety and toxicity of TDF and FTC in pregnant women and their newborns
 - To estimate the frequency of TDF and FTC resistance mutations at 4 weeks postpartum in women and at 4 weeks of life in infected children
 - To determine the frequency of peripartum mother-to-child transmission of HIV-1 after the use of this ARV drug regimen



STUDY DESIGN

- Phase II clinical trial: multi-centre sponsored by Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS) of France
 - Abidjan, Côte d'Ivoire (supported by EDCTP)
 - Soweto, South Africa
 - Phnom Penh, Cambodia
- Two steps
 - First step: Initiation of Truvada® only in HIV-infected mothers
 - Second step: Initiation of Truvada® in HIV-infected mothers and syrup of TDF + FTC in their neonates

INCLUSION CRITERIA

- Pregnant woman tested positive for HIV-1 or HIV-1 & 2
- Aged 18 years or older
- Informed consent given by the mother and the father of the child to be born (for Abidjan and Phnom Penh)
- Consents to at least a three day hospital stay after giving birth
- Haemoglobin ≥ 8 g/dl
- Creatinine clearance >49 ml/min
- Mother does not meet criteria for antiretroviral treatment for her own health during this pregnancy (CD4 ≥ 200 /mm³ and stage 1 or 2 or CD4 ≥ 350 /mm³ and stage 3)
- Must be antiretroviral-naïve

TRIAL ANTIRETROVIRAL REGIMEN

| Step 1 | Pre-partum | Intra-partum | Post-partum |
|---------|------------------------|-----------------|--|
| Mother | ZDV1 tablet X2 per day | Truvada® NVP | Truvada® 1 tablet/day (7days) |
| Newborn | | | NVP (D1) ZDV syrup (7days) |
| Step 2 | | | |
| Mother | ZDV1 tablet X2 per day | Truvada® NVP | Truvada® 1 tablet/day (7days) |
| Newborn | | | NVP+ FTC+TDF (D1) ZDV syrup (7days) |

2 tablets of Truvada® (600mg of TDF and 400mg of FTC) and one tablet of NVP (200mg)

SAMPLE SIZE

- Pharmacokinetics: no sample size estimation required
- NVP and TDF resistance study:
 - 60 mothers/infants for the three sites (20 per country)
 - In Abidjan, Côte d'Ivoire
 - Step 1: 10 mother/infant pairs
 - Step 2: 10 mother/infant pairs



OUTCOMES

- Safety: clinical and biological parameters
- Pharmacokinetics parameters of TDF, FTC
 - Peak plasma concentration (C_{Max})
 - Time of the peak concentration (T_{Max})
 - Elimination half-life
 - Area under the plasma concentration-time curve (AUC)
 - Ratio between the maternal and neonatal concentrations
- Viral resistance of TDF, FTC and NVP at week 4
- HIV infection in infant at week 4 and 6 (RNA PCR): simply indicative in the framework of this program

TEMAA TRIAL IN PRACTICE

- Enrolment of the HIV-infected pregnant women between 28 and 38 weeks of gestation (Avocatier and Niangon-Sud health facilities and in Yopougon University Hospital)
- Delivery and blood collection for the pharmacokinetics study in Gynaecology and Obstetrical Department in Yopougon University Hospital
- Pharmacokinetics analysis in pharmacology reference laboratory (St. Vincent de Paul Hospital, Paris)
- HIV diagnosis in children (RNA PCR) at CeDRoS laboratory in Treichville University Hospital, Abidjan
- Viral resistance analysis in ANRS reference laboratory (Necker Hospital, Paris)

TEMAA: WHAT HAS BEEN DONE SO FAR?

- Update of the protocol according to the new TDF data released in February 2006
- Agreement of the national Ethics Committee to conduct this trial has been obtained
- Ordering the study drugs and supplies
- Ethics training of the team that will conduct the trial (May 2006)
- Writing of the trial procedures: role and responsibility of each team member
- Registration of the trial by the sponsor: <http://clinicaltrials.gov/show/NCT00334256>

OVERALL DATA MANAGEMENT OF THE TEMAA TRIAL IN ABIDJAN

- Writing of the clinical forms:
 - Mother's clinical form
 - Infant's clinical form
 - Laboratory forms
- Creation of the database with Access® software
 - Data entry on each site
 - Controls: incoherence of data and missing data
 - Data reports will be sent to each site
 - Merger of the data in Abidjan
 - Gel permeation chromatography (GPC) software : to encrypt all the files sent par e-mail
- Writing of the data management manual is ongoing

REASONS OF THE DELAYS OF THE INITIATION OF THE TEMAA TRIAL

- Identify a sponsor for the trial: ANRS
- Signature of the contract between ANRS and Gilead for the provision of the study drug

- Amendments of the original protocol (3 versions)
- Organization of local ethics committee
 - 5 months to receive the written agreement
 - Conditional authorization for using the grant
- One year of delay, 30% of the budget was used so far

NEXT STEPS IN ABIDJAN

- Enrolment of the patients for step 1 (Sept-Oct 2006)
 - 3 sites (Abobo antenatal clinic, Avocatier antenatal clinic, Yopougon University Hospital)
 - 3 inclusions per month and per centre
- Delivery and blood collection
 - Nov 06 - Feb 07
 - Yopougon University Hospital
- Shipment and analysis of blood collection in France (March 07 – April 07)
- Results and first communication on the trial results in July 2007 (International AIDS Society Conference, Sidney)

TEMAA SCIENTIFIC ORGANIZATION

- Sponsor: ANRS (Trial 12109) since September 2005
- Primary investigators:
 - Prof François Dabis (l'Institut National de la Santé et de la Recherche Médicale ; INSERM U593, Institut de Santé Publique, d'Epidémiologie et de Développement ; ISPED, Bordeaux)
 - Dr Didier Ekouévi (Programme PAC-Cote d'Ivoire in Aconda, Abidjan)
- Co-investigators:
 - France: Profs Christine Rouzioux, Stéphane Blanche, Jean-Marc Treluyer
 - Côte d'Ivoire: Dr Didier Ekouévi, Prof N'dri-Yoman
 - Cambodia : Prof Sim, Dr Eric Nerrienet,
 - South Africa : Profs Glenda Gray and James McIntyre
- Trial coordinator: Dr Elise Arrivé
- Steering committee
- Independent Monitoring Committee
- Scientific Advisory Board

FUNDING OF TEMAA TRIAL

- European & Developing Countries Clinical Trial Partnership (EDCTP):
 - Didier Ekouevi fellowship (March 2005 – February 2007)
 - For the Abidjan site and the data management centre
 - 200 000 Euros
- Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS), Paris (France)
 - For Cambodia and South Africa sites
 - For Bordeaux coordination of the three sites
 - 500 000 Euros
- Gilead Sciences: provides the study drugs (Truvada tablets and syrups of tenofovir and emtricitabine)



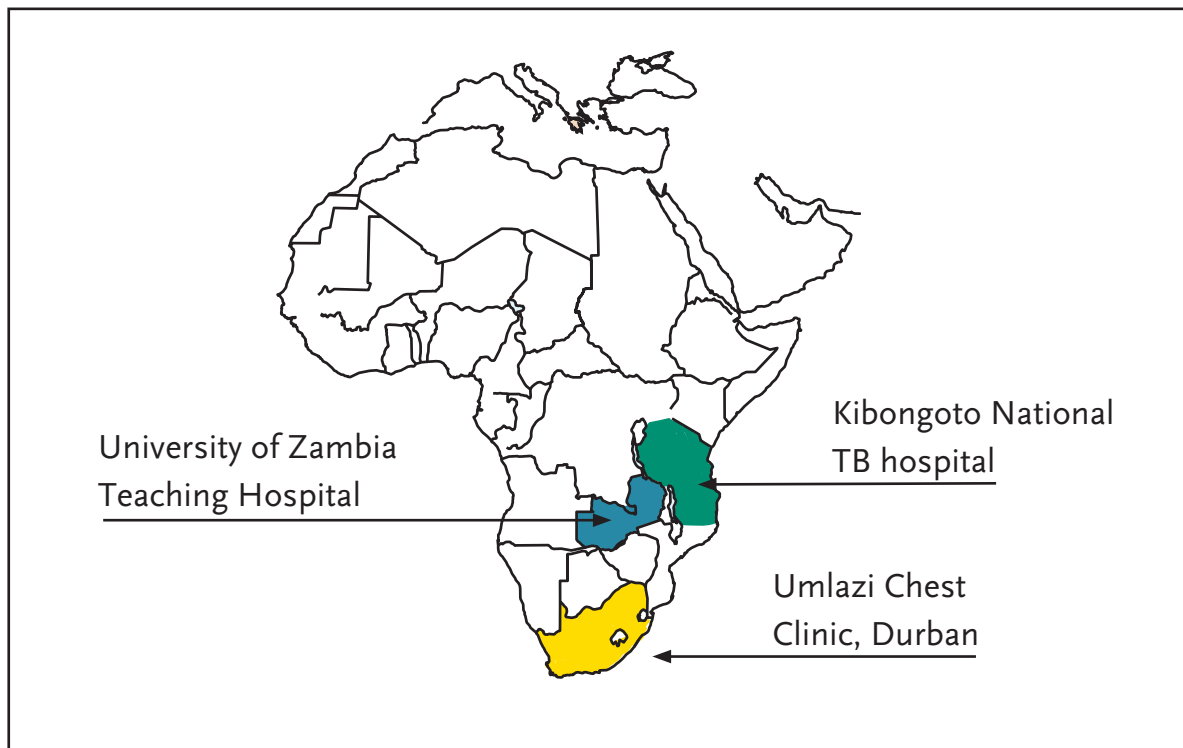
3.6. Rapid Evaluation of Moxifloxacin in the treatment of sputum smear positive tuberculosis: REMoxTB

– Professor Andrew Nunn, United Kingdom

REMoxTB

Investigators

- Chief Investigator - Stephen Gillespie
- UCL/MRC CTU Co-investigators:- Andrew Nunn, Tim McHugh, Ali Zumla
- Site Principal Investigators:
 - Lusaka - Dr Peter Mwaba
 - Moshi - Prof Noel Sam
 - Durban - Dr Roxana Rustomjee



HOME TEAM

- Dr Felicity Perrin (Clinical Co-ordinator)
- Paul Mee (Trial Manager)
- Anna Randall (Laboratory Co-ordinator)
- Marina Bogovac (Trial Administrator)
- Dr Sarah Meredith (Epidemiologist)
- Sue Tebbs (Senior Trial Manager)

THE REGIMENS

- 2EHRZ/4HR - control
- 2MHRZ/2MHR - substituting M for E and shortening to 4 months total duration
- 2EMRZ/4HR - substituting M for H in the initial intensive phase.
E = ethambutol, H = isoniazid, R = rifampicin, Z = pyrazinamide, M = moxifloxacin and the number preceding each combination shows duration of treatment in months.

OBJECTIVE 1

- If moxifloxacin is substituted for ethambutol and the total duration is reduced to 4 months will the failure/relapses rate be not inferior to that in the standard regimen?

2EHRZ/4HR v 2MHRZ/2HR

OBJECTIVE 2

- Does the substitution of moxifloxacin for isoniazid result in an increased proportion of patients who are culture negative at 2 months?

2EHRZ v 2EMRZ

PRIMARY ENDPOINTS

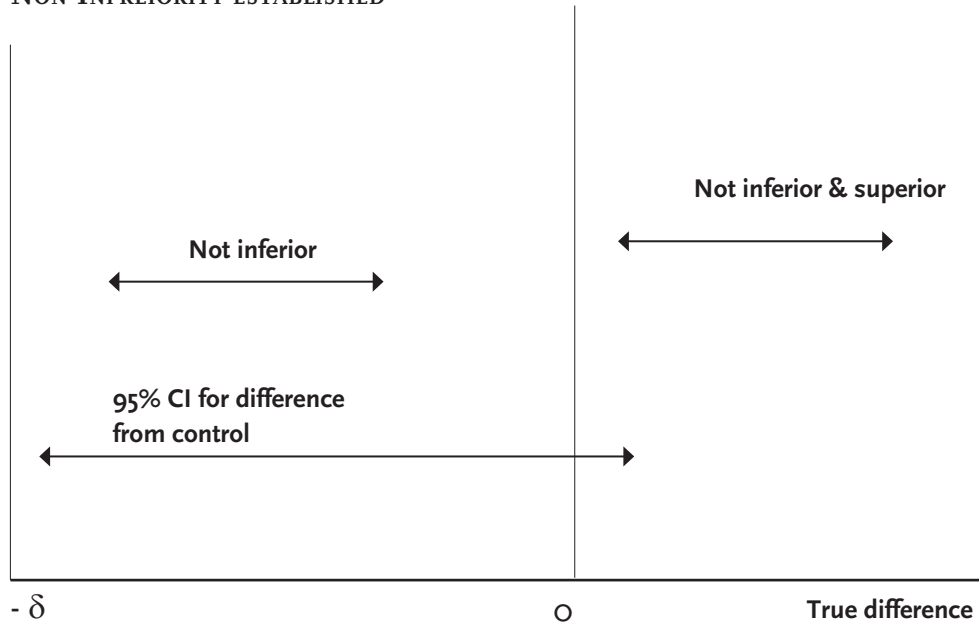
- Two comparisons
- Non-inferiority of 4-month regimen
 - Combined failure/relapse rate
- Superiority of culture conversion rate
 - 2 month culture negativity rate

NON-INFERIORITY

- Non inferiority means that the outcome in the 4 month regimen is no more than an agreed amount δ inferior to the control regimen.
- The lower 95% confidence interval for the difference in failure/relapse rates is greater than $-\delta$
- A failure/relapse rate of 4% is assumed in the standard regimen and δ has been set at 4%.



NON-INFERIORITY ESTABLISHED



BLINDING

- The trial will be conducted double blind to enable an objective assessment of side-effects and to reduce the possibility of differential management of patients receiving the shorter duration regimen.
- All patients will therefore have:
 - 5 drugs for 2 months
 - 3 drugs for 2 months
 - 2 drugs for 2 months
- Some drugs will be placebos.

BACTERIOLOGY

- Patients will be seen weekly and sputum collected for culture within the first 8 weeks to assess the rate at which cultures become negative.
- After treatment sputum specimens will be collected at 3-monthly intervals to assess possible relapse.
- Both liquid and solid medium cultures will be used.

CHALLENGES

- Double blind design
- Placebo match
- dispensing and accountability
- Recruitment and training of staff
- Laboratory upgrading
- Power supplies
- Funding

DATA MANAGEMENT

- Data entry at sites, central database at the MRC CTU
- Linking with CHAPAS in Lusaka (also funded by EDCTP)
- Strong existing facilities in Durban
- Developing new facilities in KCMC
- Project wide training programme
- Final independent audit of databases

QC AND QA

- Double data entry
- Onsite computer validation
- Laboratory QC and QA systems in place
- Monitoring of the study to registration level
- Audit of study for registration purposes

ETHICS AND REGULATORY

- University College of London (UCL) is the study sponsor
- Study approved by UCL ethics
- Study approved by local ethical review committee (ERC); approved Tanzania, Zambia, in process Kwa-Zulu Natal)
- Approved by National Ethics
- Approved by relevant drugs regulatory agency

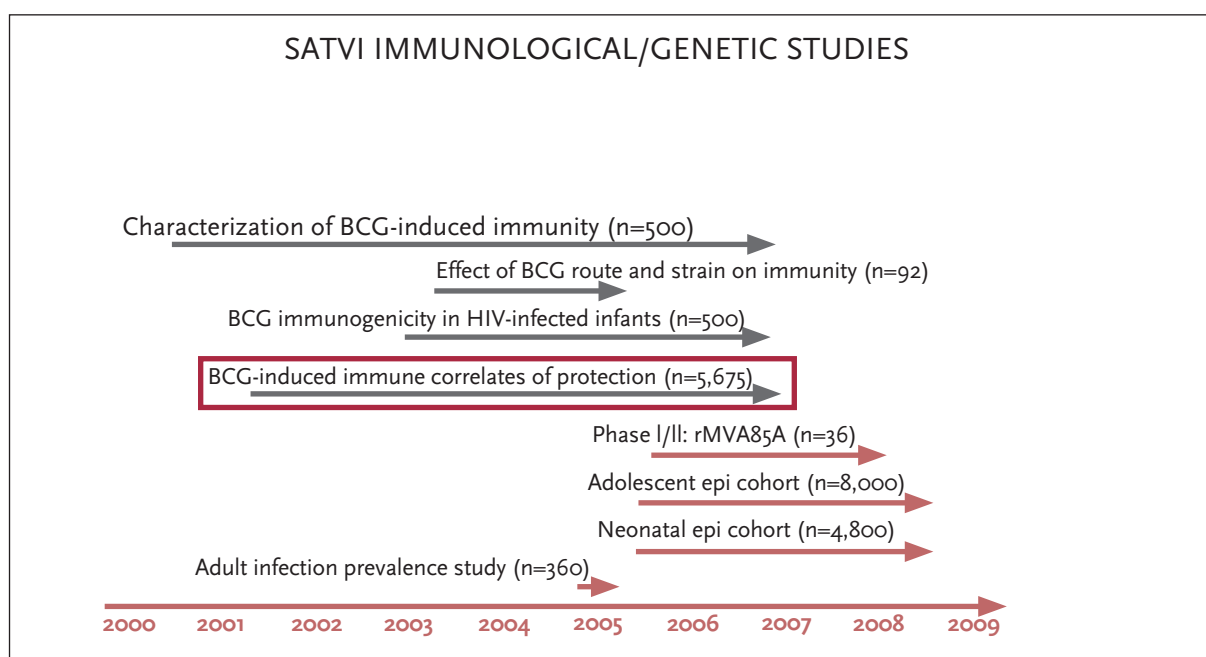
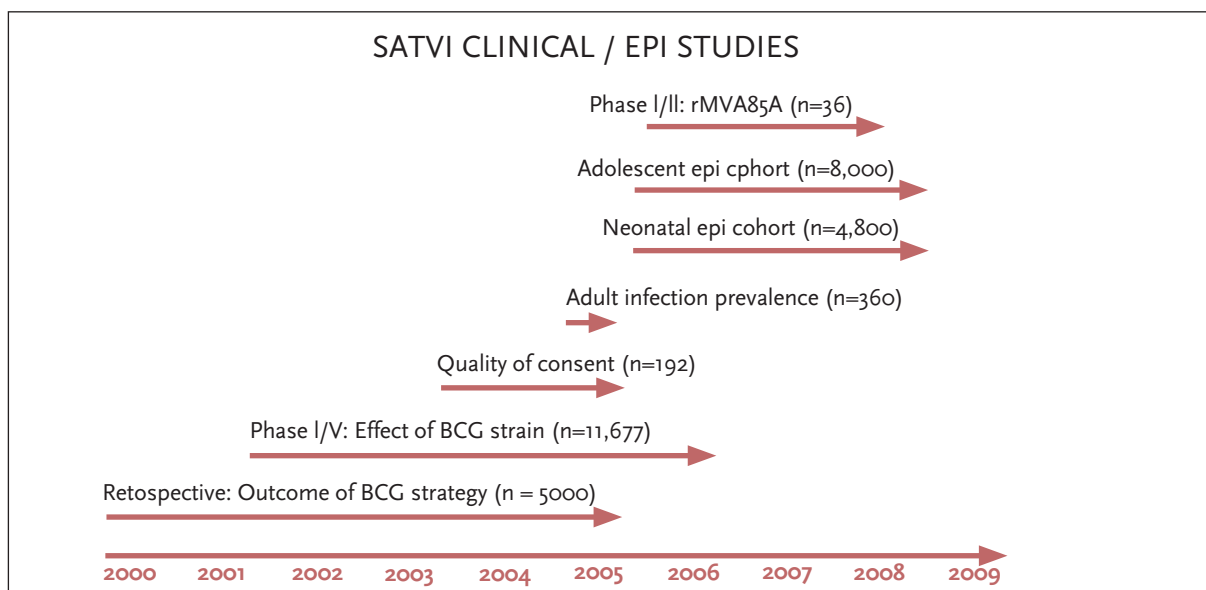
TRIAL COMMITTEES

- The trial will be overseen by a Trial Steering Committee with an independent chairperson.
- A Data Monitoring Committee (Chair Professor Tim Peto) will oversee safety aspects of the trial by reviewing data at regular intervals.
- A trial management group will meet monthly in London.
- Each site will have its own trial management committee which should meet weekly to review progress.

3.7. BCG-induced immune correlates of protection against tuberculosis – Dr Willem Hanekom, South Africa

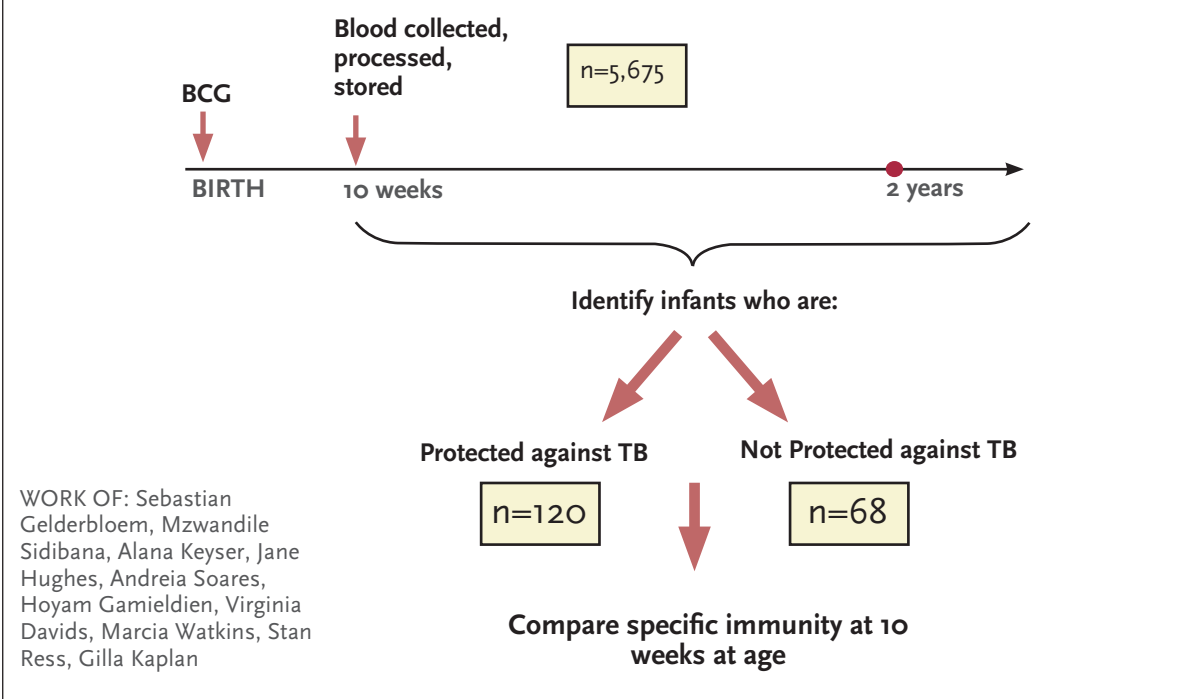
THE SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE (SATVI), AT UCT

- Clinical, epidemiological, immunological research critical for TB vaccine development





TO IDENTIFY BCG-INDUCED IMMUNE CORRELATES OF PROTECTION AGAINST TB



■ Immune correlates analysis plan:

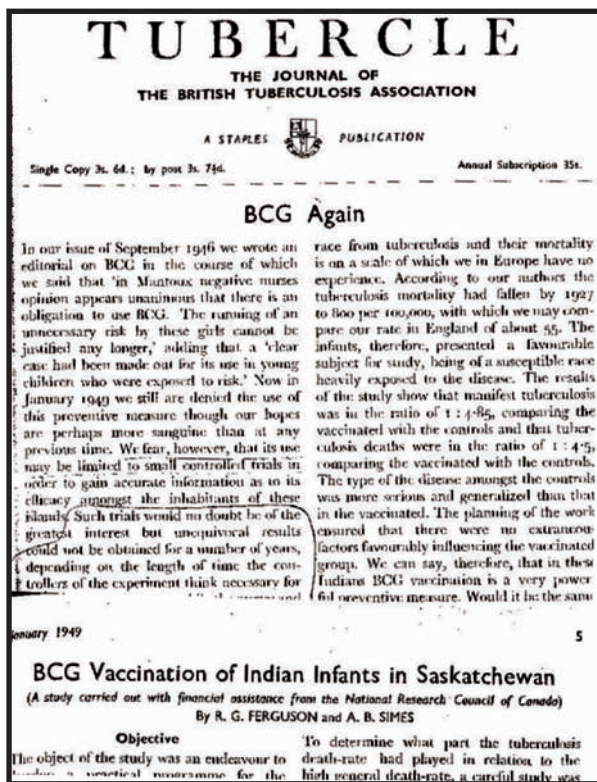
- Now: Plasma cytokine profiles
- 2006: T cell profiles
- 2006-7: mRNA profiles
- 2006-7: T cell functional capacity
- 2006-7: Innate immunity profiles
- 2006-7: Antibody profiles

■ SATVI: challenges to site development

- No infant TB vaccine trial blueprint
- Diagnosing TB in infants in a rural area
- Absence of an immunological endpoint
- Ethical concerns
- Constraints within the health service
- Human resources capacity issues



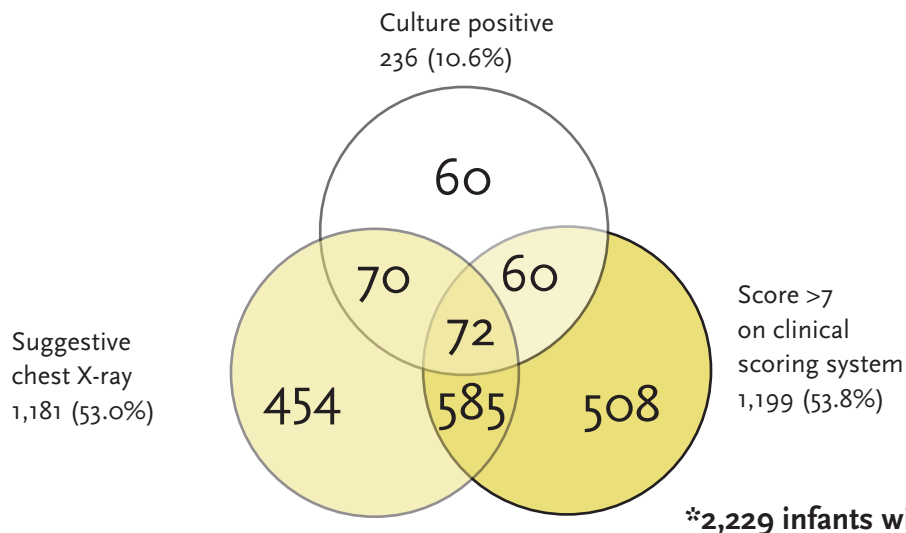
CHALLENGE 1: NO INFANT TB VACCINE TRIAL BLUEPRINT



SOLUTIONS:

- Consultation with local and international experts
- Pilot studies
- Monitoring and evaluation
- Protocol modifications

CHALLENGE 2: DEFINITIVE DIAGNOSIS OF INFANT TB



- Challenge 2: Definitive diagnosis of infant TB
 - Solutions:

| | Patients | Culture positive | Smear Positive | Culture or smear positive | Cumulative yield |
|-----------------------------|----------|------------------|----------------|---------------------------|------------------|
| Total Induces sputum | 250 | 58(23%) | 29(12%) | 62(25%) | 100% |
| Total | 250 | 51(20%) | 25(10%) | 54(22%) | 87% |
| First specimen | 250 | 37(15%) | 19(8%) | 41(16%) | 66% |
| Second specimen | 255 | 27(11%) | 13(5%) | 30(12%) | 79% |
| Third specimen | 227 | 29(13%) | 11(5%) | 31(14%) | 87% |
| Gastric lavage | | | | | |
| Total | 250 | 38(15%) | 17(7%) | 40(16%) | 64% |
| First specimen | 250 | 19 (8%) | 8(3%) | 20(8%) | 32% |
| Second specimen | 244 | 22(9%) | 12(5%) | 26(11%) | 56% |
| Third specimen | 234 | 18(8%) | 10(4%) | 22(9%) | 64% |

Dates are number or %

**ZAR, et al. Lancet 2005; 365:130*

- Challenge 3: Ethics
 - Poor, historically oppressed, research naïve population
 - How do we prevent coercion and exploitation of participants and institutions?
 - How do we ensure that the rights, safety and well-being of participants are protected?
- Solutions:
 - Advocacy
 - Consultation: community, trade unions, school structures
 - Dedicated ethics person at SATVI
 - Training of counsellors
 - Audits of process
- Challenge 4: Engaging the health services
- Solution:
 - Partnership (SATVI and health services)
 - No poaching
 - Health services
 - Support research
 - Provide facilities
- Challenge 5: Human resource capacity
- Solution:
 - SATVI personnel development
 - Academic
 - Non-academic
 - Professional development program
- Development of health services personnel



DCCC members provided support of capturing the needs of African researchers and their collaborators (above: three DCCC members with the Executive Director)

What we have learnt too is that infrastructure, and trained and skilled personnel are critical and therefore, for in case this is not absolutely clear yet, loads of money is required

- SATVI support structures include dedicated:
 - Data management team
 - IT person
 - Regulatory/ethics person
 - Monitors
 - Admin/grant management team
- SATVI networks/collaborators
 - Local:
 - IIDMM
 - University of Stellenbosch
 - SATRI
 - Rest of Africa:
 - New TB vaccine site initiatives (Uganda and Kenya)
 - Gates Global Challenge 6 (Uganda, Ethiopia, Malawi and Gambia)
- WHO initiatives
- Europe/United States:
 - Aeras Global TB Vaccine Foundation
 - Public Health Research Inst
 - BD Biosciences
 - University of Oxford
 - University of Washington
 - New York University
 - Karolinska Institute
 - Case Western University
 - Gates Global Challenge 6+12 (SSI, Stanford, University of Pittsburgh, Max Planck Institute and LUMC)

4.0 PRESENTATIONS BY EDCTP GRANTEES – DAY 2

Tuesday, 25 July

Presentations by EDCTP grantees

Chair: Mr Niresh Bhagwandin, Medical Research Council (South Africa)

Rapporteur: Dr Christine Manyando, DCCC member (Zambia)

4.1. EDCTP funded clinical trials registry

– Professor Jimmy Volmink, South Africa

EDCTP CLINICAL TRIALS REGISTRY

- SACC with support from the EDCTP has begun to establish a registry of HIV/AIDS, TB and Malaria trials conducted in sub-Saharan Africa
- Will serve as a global resource for researchers, clinicians, policy makers and the lay public
 - Keep track of on-going clinical trials
 - Access reliable information on the efficacy and safety of prevention and treatment measures
 - Identify evidence gaps to be addressed in trials
 - Provide a 'laboratory' for studying the coverage, quality, ethics and funding patterns of trials

TWO COMPONENTS OF TRIAL REGISTRY

- Prospective registry - infrastructure for registration of trials with capture of relevant information as it becomes available
- Retrospective registry - database of information on completed trials

PROSPECTIVE REGISTRATION OF TRIALS

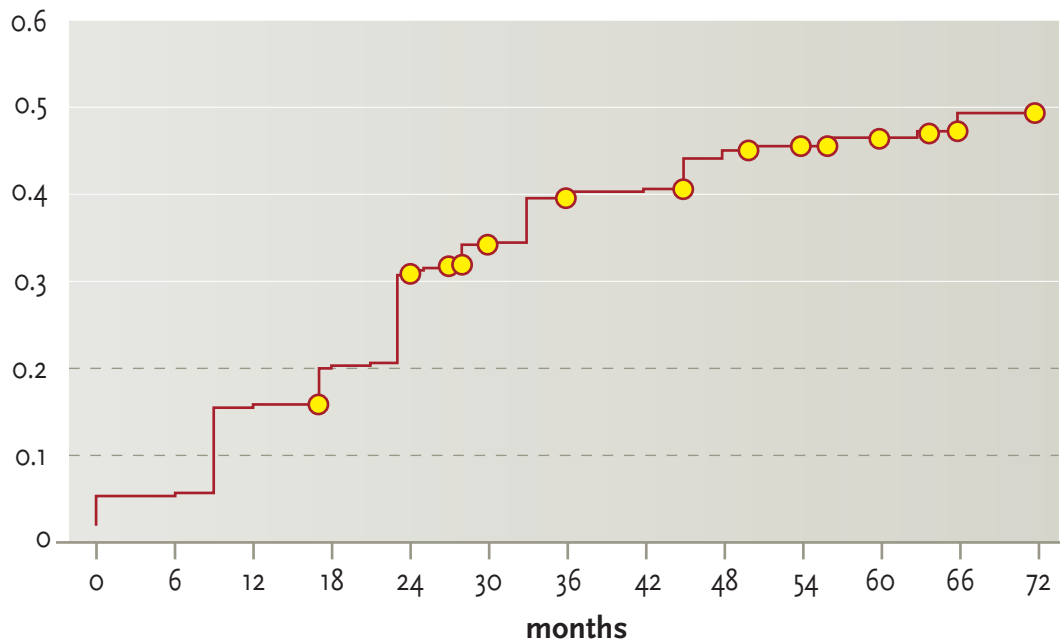
- Recent global developments
 - International Committee of Medical Journal Editors (ICMJE) statement
 - Research funders – Canadian Institutes for Health Research (CIHR), Wellcome Trust
 - New York lawsuit against Glaxo Smithkline; GSK (Paxil)
 - WHO Clinical Trials Registry Platform

WHY THE FUSS ABOUT PROSPECTIVE REGISTRATION?

- Many trials remain unpublished

| POPULATION | IDENTIFICATION | FOLLOW-UP | % UNPUBLISHED |
|------------------|----------------|-----------|---------------|
| JHU-MED | 1980 | 1988 | 19 |
| JHU-PH | 1980 | 1988 | 34 |
| NIH trials | 1979 | 1988 | 7 |
| Oxford | 1984-87 | 1990 | 27 |
| Sydney | 1979-88 | 1992 | 41 |
| NIH AIDS trials | 1986-96 | 1996 | 45 |
| Barcelona trials | 1997 | 2001 | 79 |

Cumulative time to full publication of abstract results



Scherer and Langenberg 2000. Systematic review of 46 reports. Cochrane Library

The right to search for truth implies also a duty; one must not conceal any part of what one has recognized to be true. (Albert Einstein)

CONSEQUENCES OF UNDER-REPORTING

- Studies with 'non-significant' results less likely to be published leading to over-optimistic conclusions
- 'Unwelcome' findings may be suppressed causing harm to patients
- Unethical exploitation of trial participants
- Wasteful duplication of research
- Public confidence in science is undermined

CLINICAL TRIALS REGISTRIES: A STEP IN THE RIGHT DIRECTION

- Existing Clinical Trials Registries
 - USA – Clinicaltrials.gov
 - UK – Current Controlled Trials
 - Europe – European Clinical Trials Database (EudraCT)
 - Other

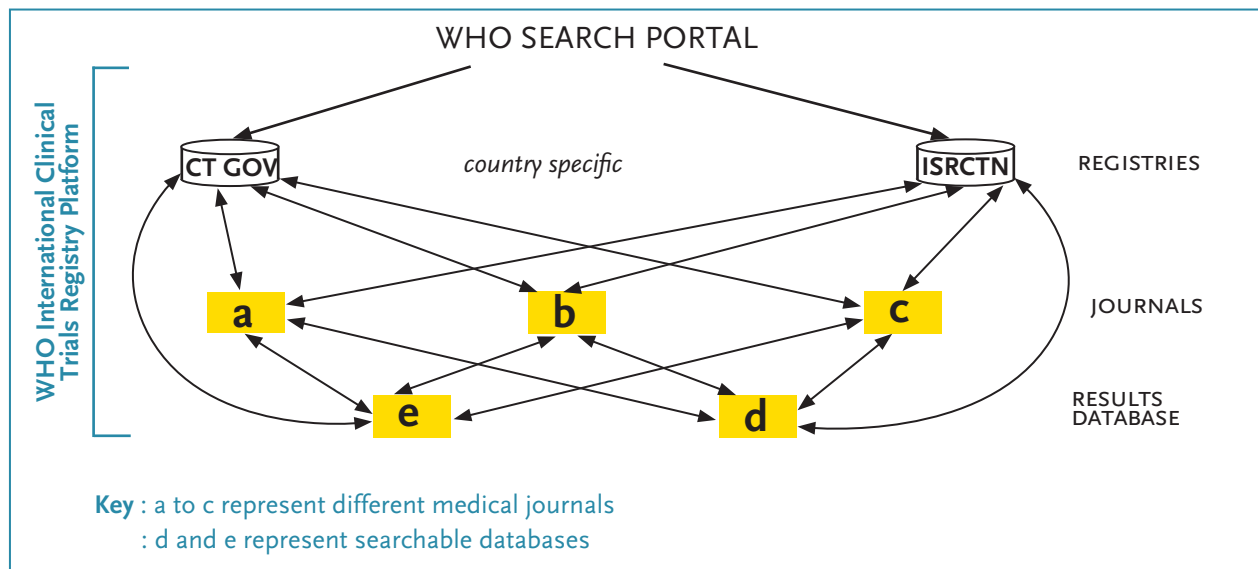
LIMITATIONS

- Incomplete and fragmented
- Duplication
- No standardization or coordination
- Inaccessible



WHAT IS NEEDED?

- A global unified registry (may be virtual)
 - Unique trial identifications
 - Comprehensive
 - Minimum protocol information
 - Minimum results
 - Standardization across registers
 - Quality assurance
 - Universal access



EDCTP PROSPECTIVE REGISTRY

- WHO Compliant
 - Collect full 20 item WHO Registration Data Set
 - Request universal trial reference number (UTRN)
 - Able to upload to WHO following technical standards
 - Processes for authenticating and validating input
 - Searchable by public at no charge

EDCTP PROSPECTIVE REGISTRY

- Cooperation essential
 - Trialists
 - Other registries e.g. SANRR
 - Governments
 - Pharmaceutical Industry
 - Funders



EDCTP RETROSPECTIVE REGISTRY

- Compile database of completed HIV/AIDS, TB and Malaria trials
- Continuity with prospective registry
- Coding system for ease of searching
- Ensure that all trials are included in Cochrane systematic reviews
- Employ GIS to map and visualise trials

EDCTP CLINICAL TRIALS REGISTRY

- Three year project
 - Year 1 (Pilot phase)
 - Prospective registration of all HIV/AIDS and Malaria trials conducted in SA along with all EDCTP funded trials conducted elsewhere in Africa
 - Prospective registration of all trials investigating artemisin-based combination treatments or malaria.
 - Year 2
 - Evaluate pilot projects, streamline initiative and begin prospective registration of all HIV/AIDS and Malaria trial conducted in sub-Saharan Africa
 - Year 3
 - Compile comprehensive review of the scope, characteristics, ethics and funding sources of HIV/AIDS and Malaria trial conducted in sub-Saharan Africa

4.2. A controlled clinical trial to evaluate high dose rifapentine and moxifloxacin in the treatment of pulmonary tuberculosis – Dr Amina Jindani, United Kingdom

STRATEGIES TO IMPROVE COMPLIANCE IN TB TREATMENT

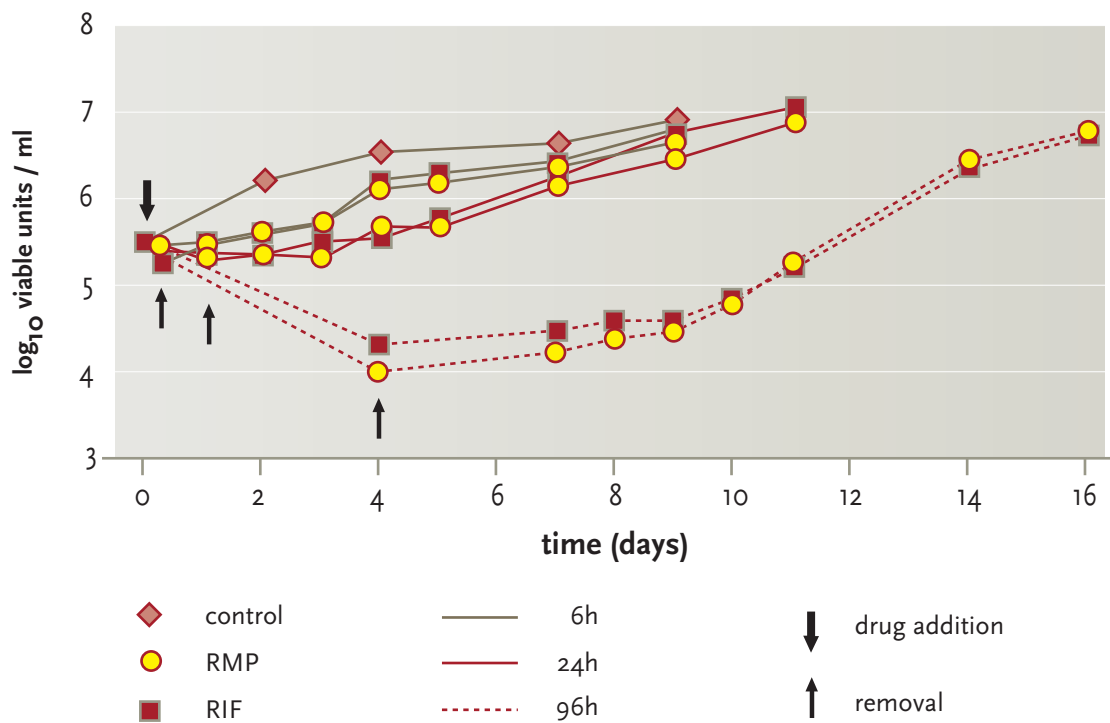
- Shortening of the continuation phase
- Simplification of the continuation phase

DRUG DEVELOPMENT

- New drugs
- Existing drugs
 - Isoniazid
 - Ethambutol
 - Pyrazinamide
 - Rifamycins
 - Rifampicin
 - Rifapentine
 - Rifabutin

BACKGROUND

- Exposure of *M. tuberculosis* to rifampicin or to rifapentine for 6, 24 or 96 hrs



Dickinson J and Mitchison DA. 1987. *Tubercle*; 68:113-118

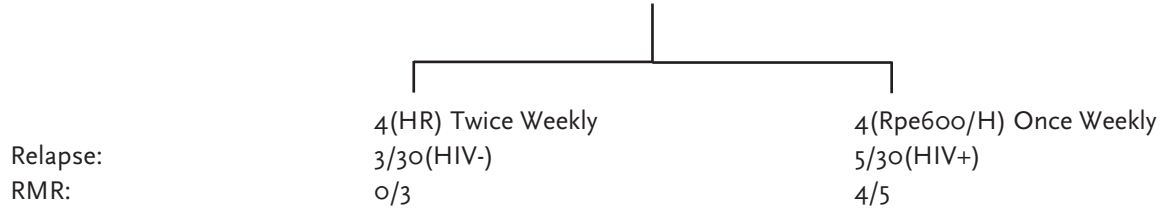


■ 24-month outcomes in three rifapentine trials

| REGIMEN | HR ₃ | HP ₁ | HP _{2/3} | PLACE |
|-------------------|-----------------|-----------------|-------------------|-----------|
| Crude relapse rt. | 3.7% | 9.0% | 9.9% | Hong Kong |
| Completed RR | 4.1% | 10.1% | 10.9% | |
| Life Table F/R Rt | 4.2% | 10.2% | 11.2% | |
| Crude relapse rt. | 5.3% | 10.8% | | HMR 008 |
| Completed RR | 6.6% | 12.4% | | |
| Life table RR | 8% | 14% | | |
| Crude relapse rt. | 4.2% | 8.4% | | TBTC 22 |
| Completed RR | 4.5% | 9.2% | | |
| Life table RR | 4.6% | 10.1% | | |

USPH STUDY 22

TRIAL DESIGN
2(EHRZ) DAILY OR 2X WEEKLY OR 3X WEEKLY.



Vernon A, Burman W, Benator D, Khan A, Bozeman L and TBTC. 1999. *Lancet*; 353: 1843-1847

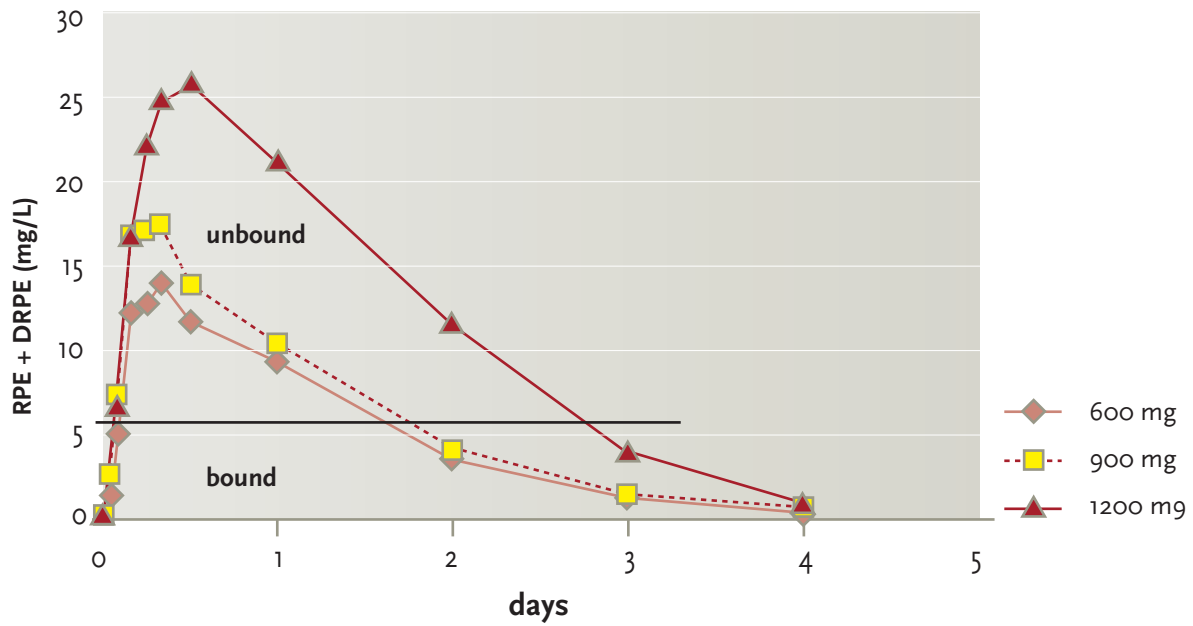
■ Isoniazid acetylation

- Relapse linked to acetylation rates in TBTC Trial* but not in Hong Kong Trial# (*Weiner M, Burman W, Vernon A, Benator D, Peloquin CA, Khan A et al and the Tuberculosis Trials Consortium. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. *Am J Respir Crit Care Med.* 2003; 167:1341-1347. #Tam CM, Chan SL, Kam KM, Sim E, Staples D, Sole KM, Al-Ghusein H, Mitchison DA. Rifapentine and isoniazid in the continuation phase of a 6-month regimen. Interim report: no activity of isoniazid in the continuation phase. *Int J Tuberc Lung Dis* 2000; 4: 262-267)

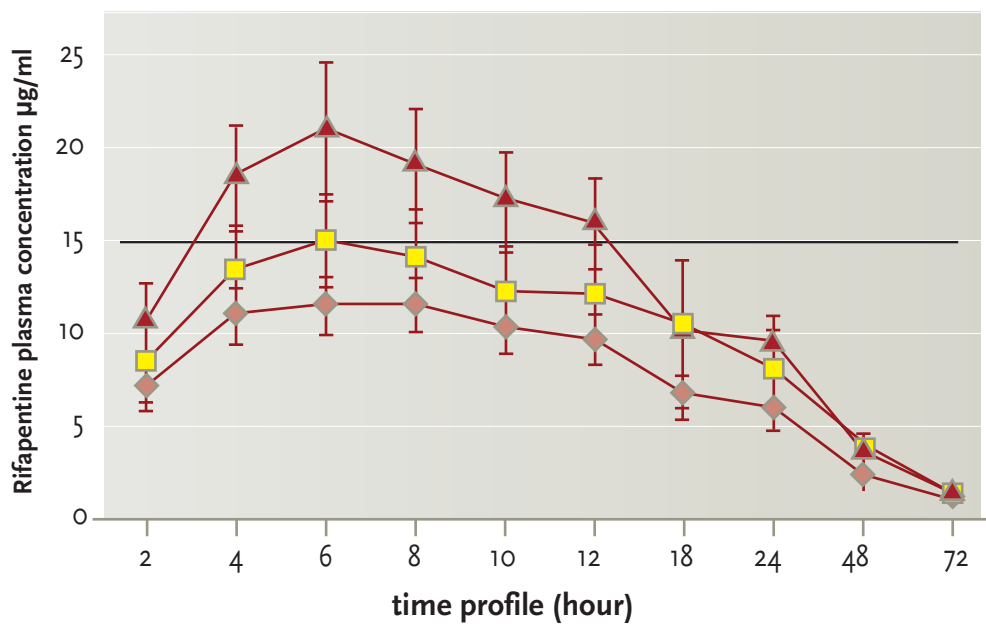
■ Plasma binding

- Rifampicin – 85%
- Rifapentine – 97%

Blood levels of rifapentine + desacetylrifapentine



Background IV: USPHS study 23



Weiner M, Bock N, Peloquin CA, Burman WJ, Khan A, Vernon A, Zhao Z, Weis S, Sterling T, Hayden K, Goldberg S, and TBTC. 2004. Am J. Resp. Crit Care Med; 169: 1191-1197

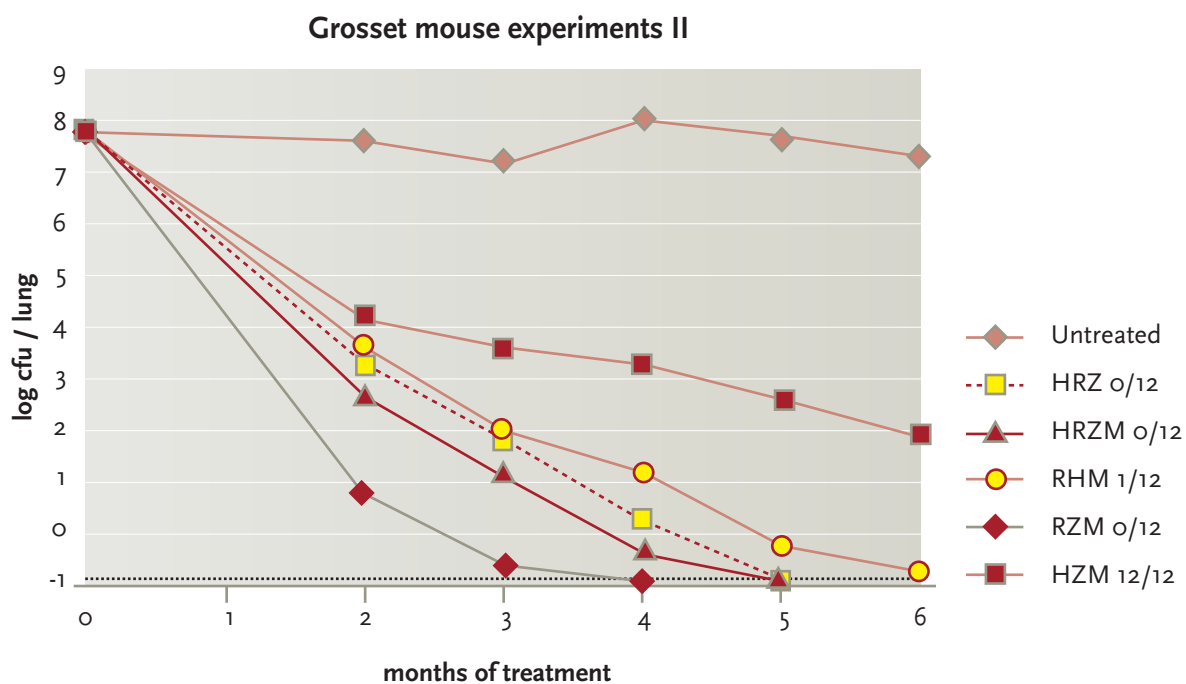
■ Rifapentine pharmacokinetics

| | 600mg | 900mg | 1200mg | p Value |
|------------------|-------|-------|--------|---------|
| No. of patients | 15 | 7 | 13 | |
| AUC ₀ | 296 | 410 | 477 | 0.02 |
| C _{max} | 12.2 | 14.6 | 18.6 | 0.03 |
| Half-life | 14.4 | 16.4 | 14.4 | 0.90 |

Weiner M, Bock N, Peloquin CA, Burman WJ, Khan A, Vernon A, Zhao Z, Weis S, Sterling T, Hayden K, Goldberg S, and TBTC. 2004. *Am J. Resp. Crit Care Med*; 169:1191-1197

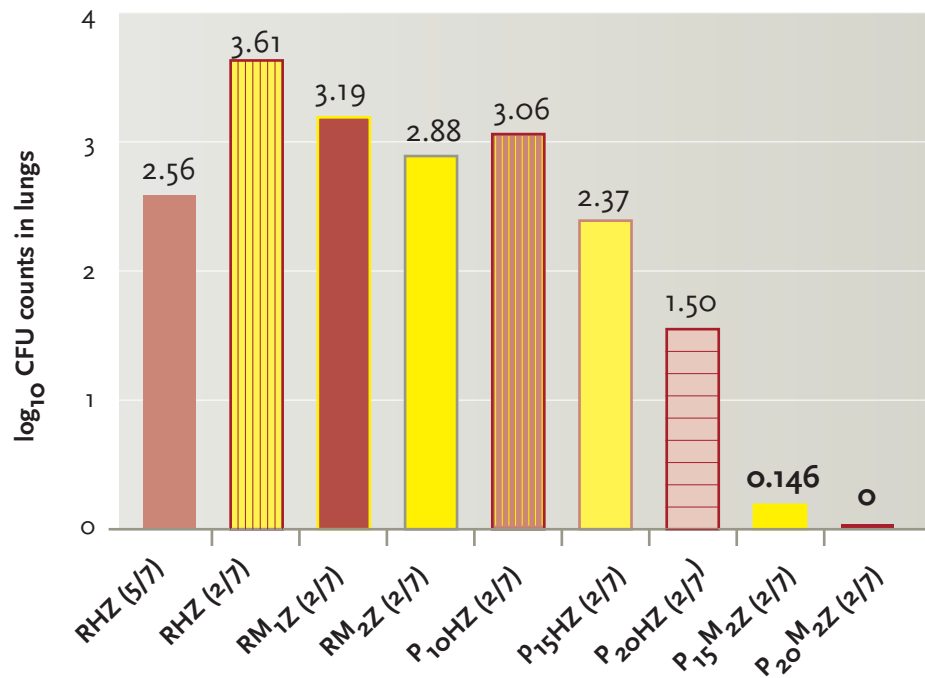
■ Half life of drugs

- Isoniazid (RA) – 1.3 hours
- Isoniazid (SA) – 3 hours
- Rifampicin – 3 hours
- Rifapentine – 14 hours
- Moxifloxacin – 12 hours





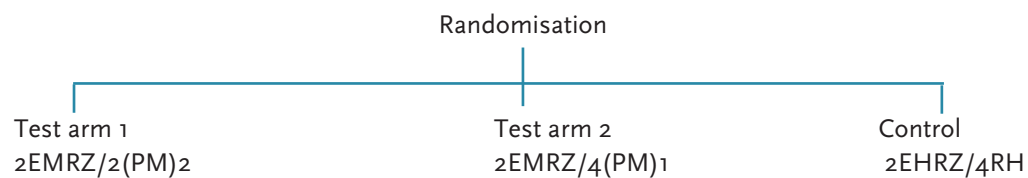
Lung CFU counts after 2 months of treatment



RIFAQUIN TRIAL

- An international multicentre randomised controlled clinical trial to evaluate high dose rifapentine (Rpe) and a quinolone in the treatment of pulmonary tuberculosis

TRIAL DESIGN



(PM)₂ = Rpe 15 mg/kg + Moxifloxacin 500 mg (twice weekly)

(PM)₁ = Rpe 20/kg mg + Moxifloxacin 500 mg (once weekly)

RH = Rifampicin 600 mg + INH 300 mg

OBJECTIVES

- To evaluate the effect of an increase in Rpe dose size in reducing or eliminating the risk of RMR in relapse cultures in HIV positive patients.
- To evaluate the effect of an increase in Rpe dose size in decreasing the relapse rate so that it would be equivalent to the rate found in a control regimen of rifampicin/isoniazid.
- To assess whether substitution of moxifloxacin for isoniazid will achieve either of the aims 1 and 2, above.



PRIMARY END POINTS

- Presence of Rpe and moxifloxacin resistance in relapse cultures
- Combined rate of failure at the end of treatment and relapse by 24 months
- Drug related adverse events occurring during chemotherapy

SECONDARY END POINTS

- Sputum culture results at two months (after initiation of chemotherapy)
- Sputum smear results at two months (after initiation of chemotherapy)
- Rate of completion of chemotherapy according to the protocol
- Number of observed doses of chemotherapy ingested

SUB-STUDIES

- Interaction between rifapentine and moxifloxacin such that the blood levels of moxifloxacin are sub-optimal
- Effect of fatty meal
 - Rifapentine absorption is significantly enhanced if taken with a high-fat meal.
 - In pharmacokinetic studies of rifapentine conducted by the MRC and the University of Cape Town in South Africa (Helen McIlleron, unpublished), different types of meals produced similar results. Maize porridge with and without lard, and chicken soup, all resulted in significant increases in rifapentine blood levels compared to water.
 - In a further study of the pharmacokinetics of consecutive doses of rifapentine in tuberculosis patients, chicken soup was used as an accompanying meal (Langdon et al. In J Tuberc Lung Dis 2004; 8:862-867), with good results.

PROBLEMS ENCOUNTERED AND HOW THEY ARE SOLVED

- Staffing
- Laboratory
- Training
- Patient numbers
- Data management
- Quality assurance
- Serious adverse events (SAEs)

EXISTING GAPS IN HUMAN RESOURCES AND INFRASTRUCTURE

- Staffing levels and numbers
- Laboratories
- IT and trained staff

EQUIPMENT IN THE CENTRES

- A deficiency at all centres in laboratory and IT equipment.

DATA MANAGEMENT

- Questionnaire regarding computing facilities
- Appointment of data manager

- Installation of software
- Training of local data entry personnel
- Regular data checks
- Regular site visits

ETHICS AND REGULATORY ISSUES

- Patient information system
- Two stage consent form
- Investigators brochures
- Approval by Ethics Committees of each country
- Trial Steering Committee
- Independent Data Monitoring Committee

QC/QA, ACCREDITATION

- Sample of cultures checked centrally
- All resistant cultures checked centrally
- Data entry monitoring and verification

EXISTING NETWORKS

- International Consortium for trials of chemotherapeutic agents in tuberculosis (INTERTB)
- South African Medical Research Council (SAMRC)
- South Africa TB vaccine initiative (SATVI)
- Aurum Institute for Health Research in South Africa
- London School of Hygiene and Tropical Medicine (LSHTM)
- Malaria Institute at Macha (MIAM) in Zambia
- National TB Control Programmes (NTPs)

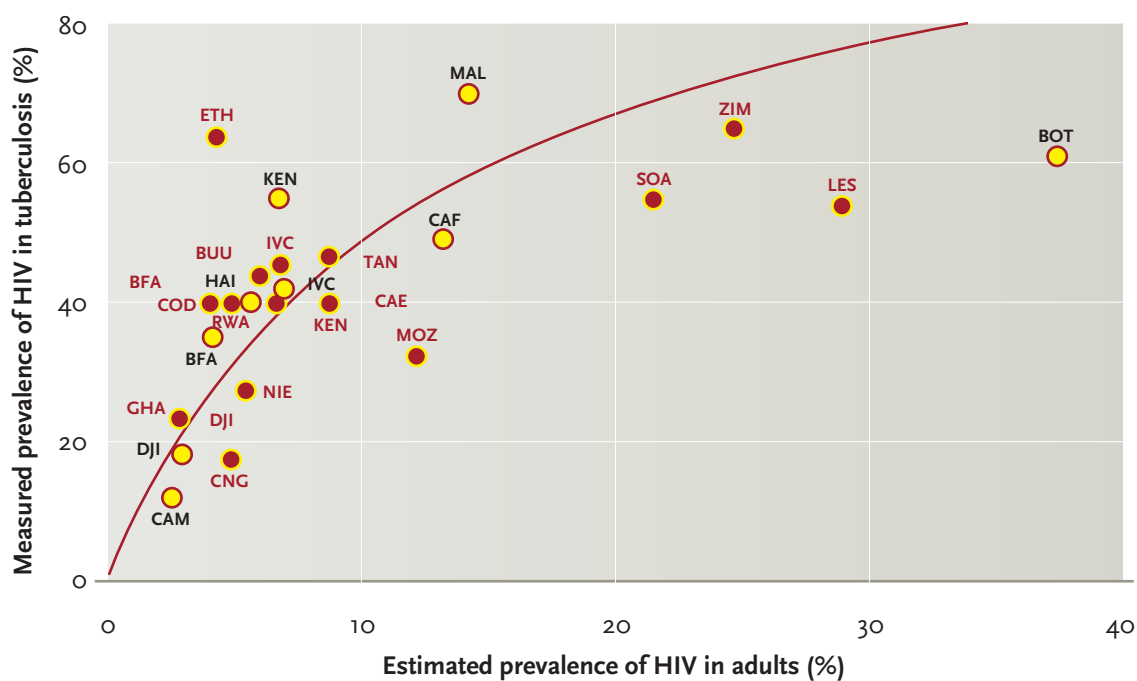
PARTICIPATING CENTRES

| CENTRE | NUMBERS ALLOCATED |
|---------------|--------------------------|
| Cape Town | 210 |
| Johannesburg | 310 |
| Harare | 210 |
| Marondera | 210 |
| Maputo | 200 |
| Macha | 110 |
| TOTAL | 1250 |

4.3. 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 Helen McIlleron, South Africa

EPIDEMIOLOGY OF TB/HIV CO-INFECTION

- TB/HIV is common in Africa ~ 40% (up to 75%) of TB patients
- Many patients presenting with TB have advanced HIV: HAART indicated to reduce early mortality
- Although reduced, risk of TB remains high in patients established on HAART



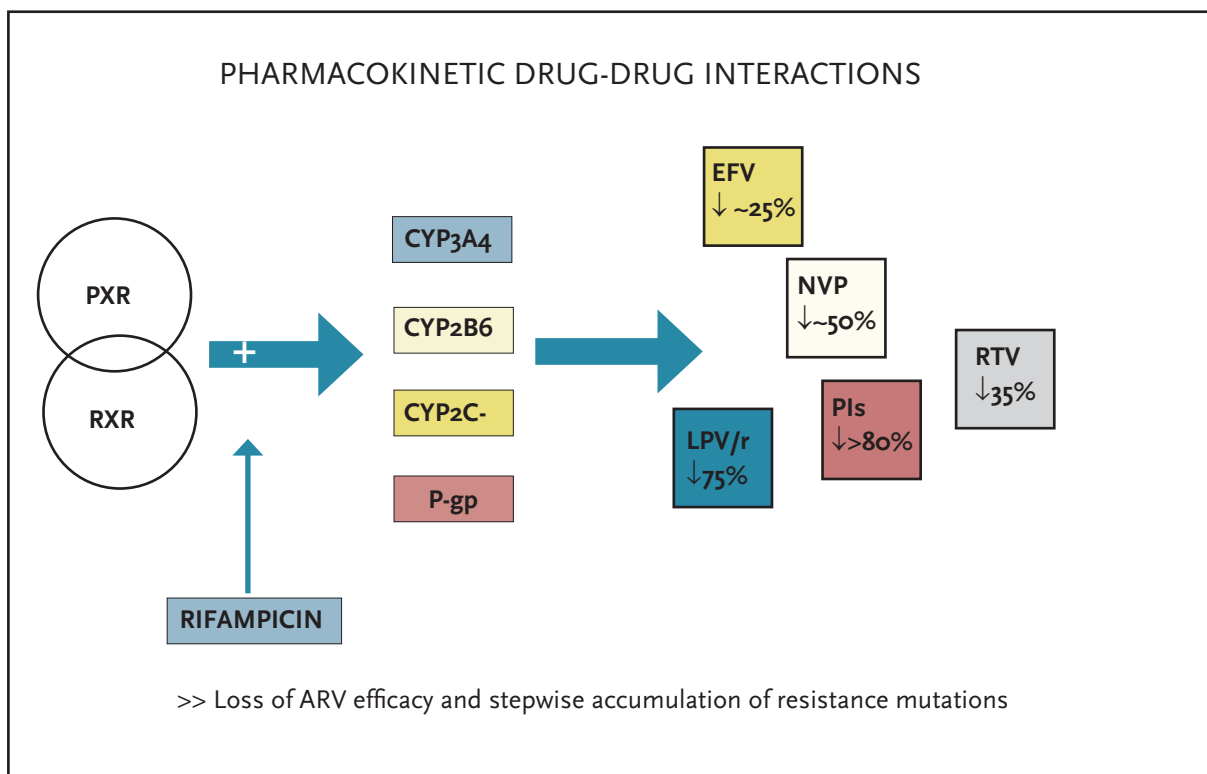
Corbett et al. Lancet 2006; 367:296–37

COMPLICATIONS OF CO-TREATMENT

- PK interactions
- Overlapping toxicity
- Immune reactivation inflammatory syndrome (IRIS)
- Challenged treatment adherence

AFRICAN SETTING

- Rifampicin-based TB treatment
- Limited ARV regimen options



CO-TREATMENT OPTIONS

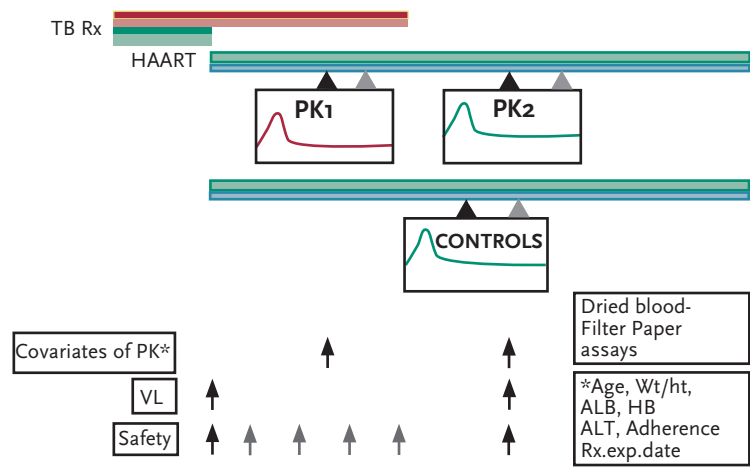
- Serious concerns about safety and efficacy of available regimens; limited evidence base for current guidelines
 - Small studies in healthy normal volunteers from developed countries
 - environmentally, genetically, pathologically, nutritionally, demographically different to patients who need co-treatment
- Need bigger studies in relevant patient populations:
 - People with TB/HIV
 - Africans
 - Children
 - Women
 - PK, efficacy and safety

PROPOSED STUDIES

- ARV levels in HIV-infected patients with and without rifampicin-based TB treatment
- Efavirenz (EFV), niverapine) NVP, Kaletra®
- Adults and children



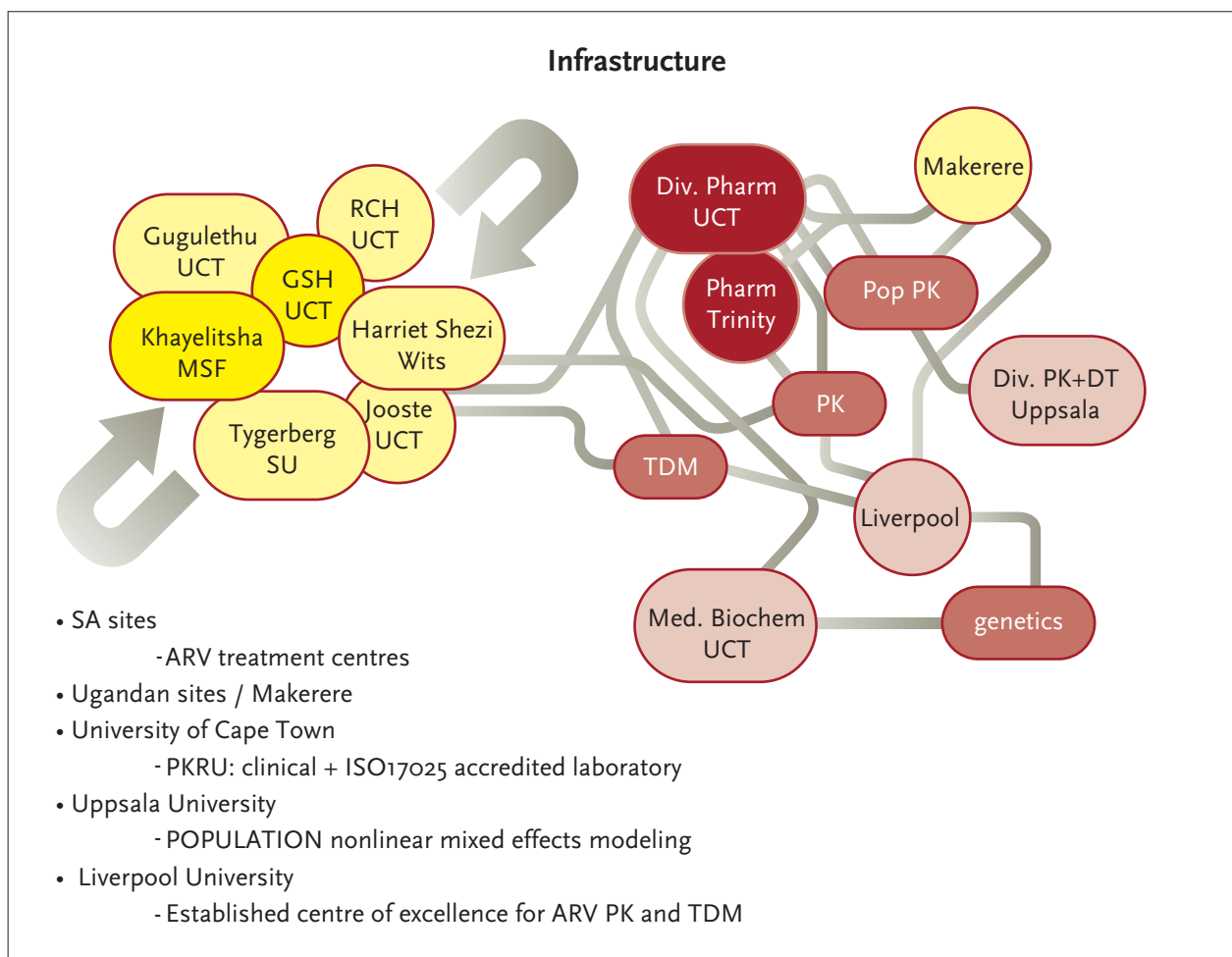
basic study design



| | With RIF | | Without RIF |
|----------------------|--------------------------------------|--|---------------------------------------|
| | | ["Consider ↑ dose – 800 mg"] | |
| EFV: (Children) | Std. dose/wt (Daily) | vs. | Std. dose/wt (Daily) |
| | | ["Safe and effective dose of LPV/r not established"] | |
| LPV/r: (Children) | 460/115 mg/m ² (/12 h) | vs. | 230/57.5 mg/m ² (/12 h) |
| LPV/r: (Adults) | 800/200 mg (/12 h) | vs. | 400/100 mg (/12 h) |
| | | ["Not recommended" / "careful monitoring"] | |
| NVP: (Children) | Std. dose*1.5/wt (/12 h) | vs. | Std. dose/wt (/12 h) |
| NVP: (Adults) | 300 mg /12 h (/12 h) | vs. | 200 mg / 12 h (/12 h) |

ADDING VALUE

- SA Department of Health
 - Pilot studies (EFV, LPV in children; NVP in adults)
 - Expand sample size and enrich data
- University of Cape Town's equipment committee
- International Maternal Paediatric Adolescent AIDS Clinical Trials (IMPAACT)
 - Intracellular and free drug concentrations
 - Study experience, knowledge of study population
 - Population models
 - Expanded description of PK in children
 - Unbound + intracellular fractions
 - Genetic polymorphisms



GAPS: STUDY SPECIFIC INFRASTRUCTURE AND CAPACITY

- Additional study staff: administrator, counsellor, research nurses
- PhD student; post-doctoral student
- International expertise / supervision: Dr C Merry, Prof. D Back, Prof. M Karlsson
- API 3200 QTRAP MS/MS mass spectrometer
- Data management and storage
- Study monitor

POTENTIALLY PROBLEMATIC AREAS

- Ethical and regulatory
 - Children
 - Unregistered use (double dose Kaletra®; increased dose EFV)
- Dosing issues
 - accuracy of dosing
 - practical dosing strategies
- Formulation issues
 - availability of EFV syrup
- Sample handling and storage
 - Infrastructure/organization, good SOPs, training

QA/QC ACCREDITATION

- Established centres operating according to GCP and conducting studies of international standing
- Study specific monitor
- Laboratory ISO17025 accredited – ongoing evaluation programme
- International Inter-laboratory Quality Control Program for Therapeutic Drug Monitoring in HIV Infected patients

EXISTING NETWORKS

- Collaboration with Uppsala University - nonlinear modelling PK-PD (South Africa – Sweden Programme on Research Co-operation)
- International Inter-laboratory Quality Control Program for Therapeutic Drug Monitoring in HIV Infected patients
- WHO collaborating centre for drug policy
- WHO recommended centre for QA/bioequivalence of TB drugs
- Medicines Information Centre (MIC) HIV hotline
- International Maternal Paediatric Adolescent AIDS Clinical Trials (IMPAACT)

4.4. The burden of tuberculosis in eastern Sudan: epidemiology and drug resistance patterns of *Mycobacterium tuberculosis* isolates

– Professor Maowia Mukhtar, Sudan

BACKGROUND AND RATIONALE

Although tuberculosis is known to be endemic in Sudan, no data is available on its burden, epidemiology, health seeking behaviour of TB patients, risk factor for TB and the extent of drug resistance (El Sony et al; 2000). The annual risk of infection (ARI) was estimated in Sudan at 1.8% in 1986, which translates to an estimated annual incidence rate of smear-positive TB of 90 per 100 000 person-years. It is often said that the eastern Region of Sudan might have higher rates, and recent public health records showed that >50% of the hospital admissions in Gadarif hospital were TB patients. Since 1986, no more recent surveys were conducted in Sudan on annual risk of infection.

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 Program for free treatment.

OBJECTIVE

The main objective of this proposal is to identify suitable sites for future diagnostic, treatment and vaccine trials on tuberculosis.

SPECIFIC AIMS

- TB diseases related:
 - To estimate the frequency of pulmonary TB in patients with cough
 - To map and determine the burden of TB disease at community level in Kassalla and Gadarif states in eastern Sudan
 - To document the health seeking behaviour of patients with long lasting cough in this region.
- Health system related:
 - To document the available system for TB care in the two states
 - To Determine the health seeking behaviour of suspected TB patients
- TB infection related:
 - To study the incidence rate of TB infection in selected study areas in eastern Sudan
 - To map and determine the frequency of Mycobacterium drug resistance to anti-tuberculous treatment in isolates from enrolled patients.
 - To determine the genetic diversity of those Mycobacterium isolates
 - To study risk factors for the development of overt TB disease in infected persons

WORK PLAN

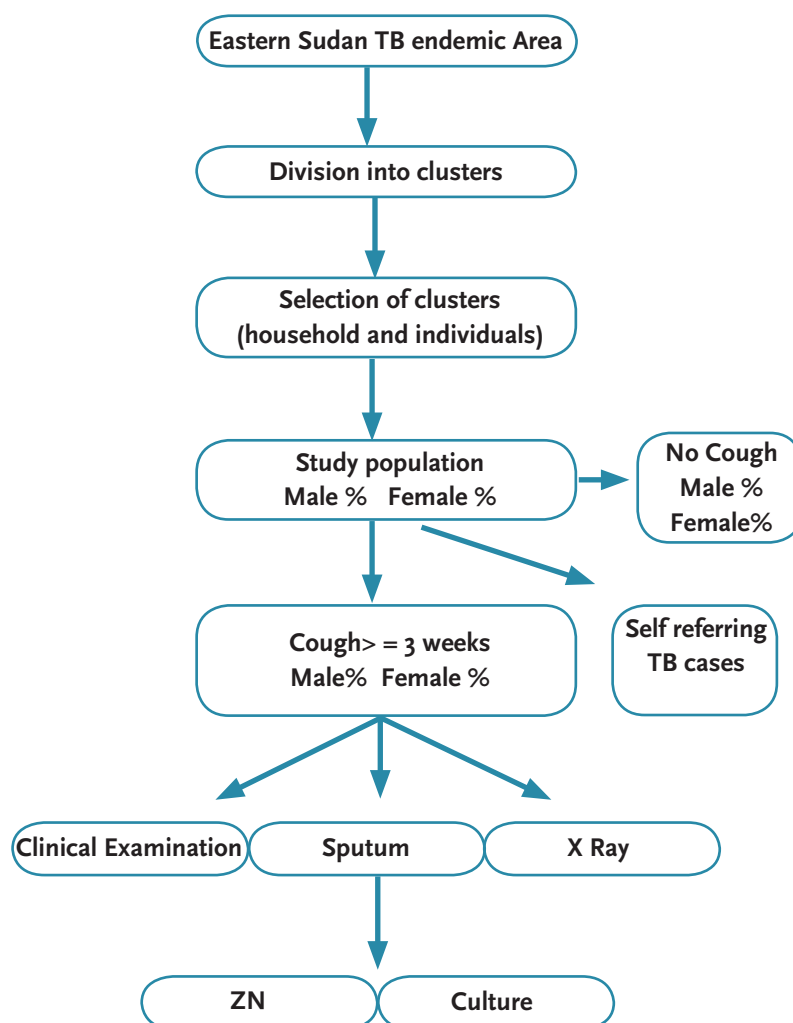
- The project is carried out in two phases:

- **Phase 1**

- concentrates on the TB disease-related objectives (A) as well as on the health system (B), to get the general (global) picture. Based on the findings in Phase 1, we will be able to identify areas within the States of Kassalla and Gedarif with a high burden of TB disease, and operational TB health facilities. Both criteria are important for the identification of suitable trial sites.

- **Phase 2**

- further documents those high-burden areas, and go more in-depth, to study the incidence rate of mycobacterium infection as well as risk factors for TB diseases. Extensive data will be collected at household level, by repeated cross-sectional surveys or longitudinal cohort studies.





RESULTS 1

- Gadaref State
 - Selection of villages:
 - 50 villages were selected in Gadaref State
 - 100 household/ village were randomly selected
 - Cough rate survey is completed
 - Clinical survey is completed
 - Treatment seeking behaviour is completed

- Gadaref cough rate

| NO. SCREENED VILLAGES | NO. SCREENED INDIVIDUALS | NO. COUGHING INDIVIDUALS | COUGH RATE % |
|-----------------------|--------------------------|--------------------------|--------------|
| 50 | 16080 | 904 | 5.62% |

- Result Kassalla State

| NO. SCREENED VILLAGES | NO. SCREENED INDIVIDUALS | NO. COUGHING INDIVIDUALS | COUGH RATE % |
|-----------------------|--------------------------|--------------------------|--------------|
| 30 | 14118 | 284 | 2% |

PCR Characterization of isolates will be conducted.

RESULTS 2

- Completed forms are currently used for data entry
- Data analysis is currently done at the School of Mathematics University of Khartoum
- Village coordinates are recorded and maps are under development

DATA MANAGEMENT

- The TB data bases will be maintained at a data management centre at the Mathematical Sciences. It will be web-based server database allowing different counterparts to access to needed information; such required data can be abstracted from different sub-databases and merged. The information in these databases will enable TB programs to easily identify patients and their follow up records.

QUALITY ASSURANCE AND QUALITY CONTROL

- All forms were pre-tested and compared
- Laboratory specimens were kept and checked by experts
- Surveys were repeated in selected villages
- All teams attended training courses before the start of the project



RESEARCH CAPACITY IN THE INSTITUTE

- Field survey teams (medical teams, field transportation)
- Molecular Biology facilities (PCR and DNA sequencing)
- Microbiology field lab facility
- Immunology facilities (antibody and cell mediated immune response analysis)
- Isolate bank storage facilities
- Biostatistics and data management personnel

FACED DIFFICULTIES

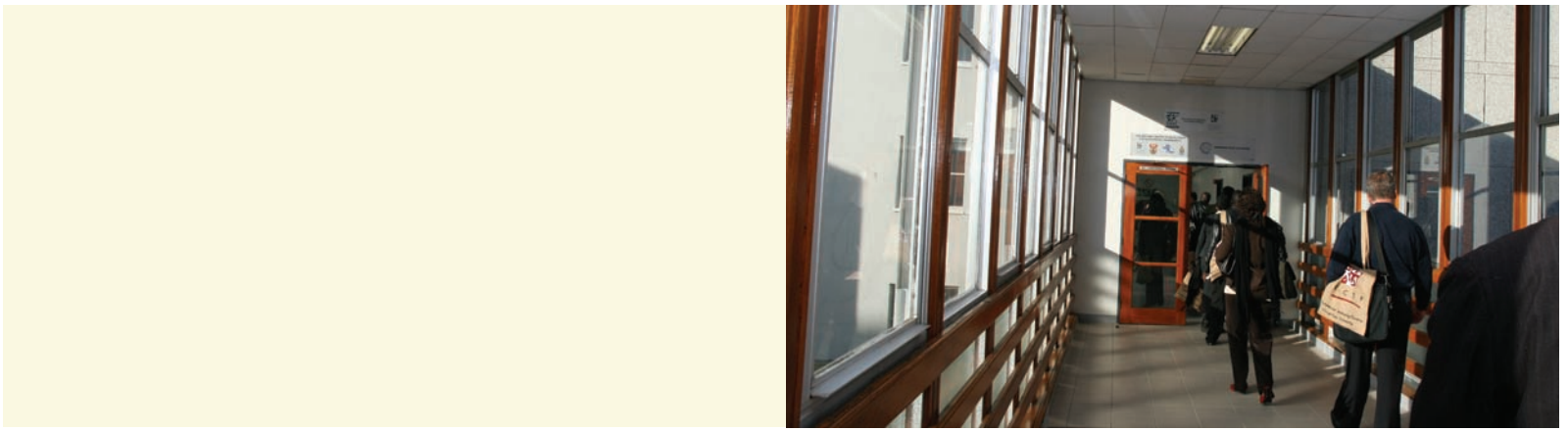
- Weakness of health system
- Social stigma of TB
- Community marginalization
- Lack of well-trained survey personnel in the study states
- Lack of infrastructure for data management

NEEDED CAPACITY

- Data management
- Field facilities for lab investigation
- Personnel training on epidemiology and clinical trials

COLLABORATORS

- Prince Leopold Institute of Tropical Medicine:
- Professor Patrick Van der Styft
- Dr Greet Dieltiens
- Kassalla Faculty of Medicine
- Kassalla State Ministry of Health
- Gadarif Ministry of Health
- Central Health Laboratory
- Federal Ministry of Health
- National TB control Program



4.5. Understanding the mechanism of piperazine resistance – *Dr Alexis Nzila, Kenya*

ARTEKIN (ATK): PIPERAQUINE (PQ) AND DIHYDROARTEMESININ (DHA)

- Used in Asia (China, Vietnam)
 - Efficacious
 - Cheap
 - Easy to administer
 - Potential alternative to chloroquine (CQ) and Fansidar
- Problem:
 - Use as monotherapy (South East Asia):
 - Rapid selection of resistance to PQ
 - May compromise ATK life span

PROJECT: Understanding the mechanism of PQ resistance: identification of the molecular markers of PQ resistance.

PEOPLE AND LABORATORIES

- Dr. A. Nzila (KEMRI/Wellcome Trust Nairobi)
- Leah Mwai, student (KEMRI/Wellcome Trust Nairobi)
- Abdurahman Abdi
- Steven Kiari
- Dr X. Su (NIH, Rockville US)
- Prof. Steve Ward (Liverpool Tropical School, UK)
- Dr Steffen Borrmann (KEMRI/Wellcome, Kenya)
- Dr Philipp Sassy (KEMRI/Wellcome, Kemri)

THE TWO HYPOTHESES

- PQ is a long active drug, half-life of 15-20 days
 - Strong selective pressure
- PQ is a bisquinoline drug
 - Two chloroquines molecules linked with piperazyl ring
 - Same mode of action than CQ
 - Some CQ markers may have an impact of PQ activity: Use CQ-resistance as framework

PROGRESS

- Problems at the beginning in building up of my research group
 - Mid 2005: there were funding problems and many staff left
- January 2005: recruited 3 students:
 - L. Mwai (been awarded a PhD studentship)
 - Abdurahman Abdi
 - Steven Karia
- January 2005 to April 2005
 - Training of students was done in:

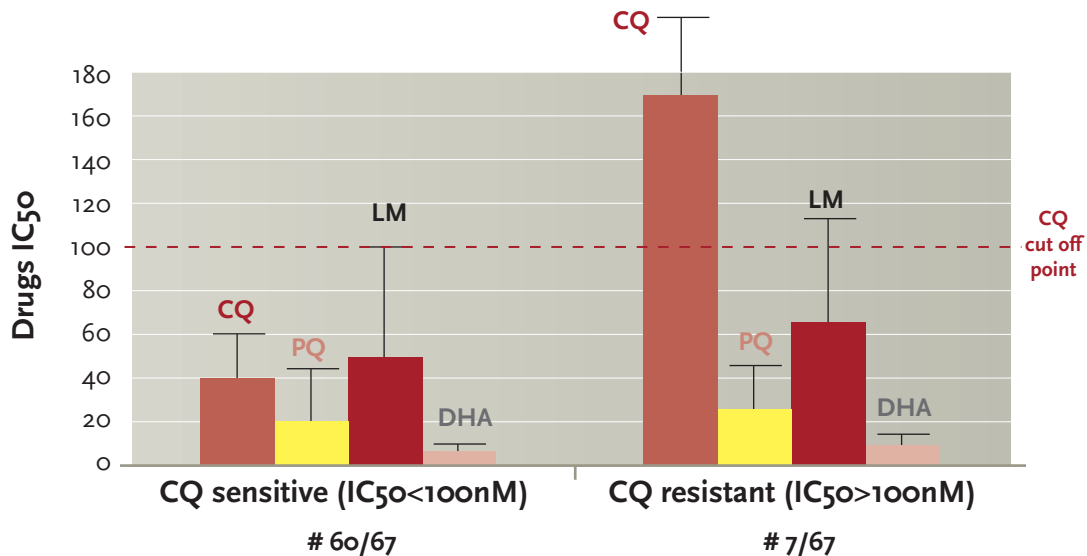


- In vitro culture
 - Molecular analyses (molecular biology techniques)
- November 2005 to January 2006
 - Drug testing Unit was not ready and there was lack of facility of radioactive waste disposal
 - November 2006 to December 2006
 - Settling up a the new laboratory
 - Overall: 6 out of 18 months of the project were spent on training and setting up the new lab

STUDY IN KILIFI (STUDY I): CLINICAL TRIAL ON EFFICACY OF ARTEKIN (PQ/DHA) VERSUS COARTEM (LUMEFANTRINE; LM/ARTEKIN; ART) IN KILIFI [PINGILIKARNI].

- Clinical results: 240 (PQ/DHA) and 180 (LM/ART) patients enrolled about 20% of failure after 42 days treatment
- Lab work: Samples collected before and after treatment; adapted in vitro drug assays

1. In vitro activity of PQ in relation to CQ, LM and DHA



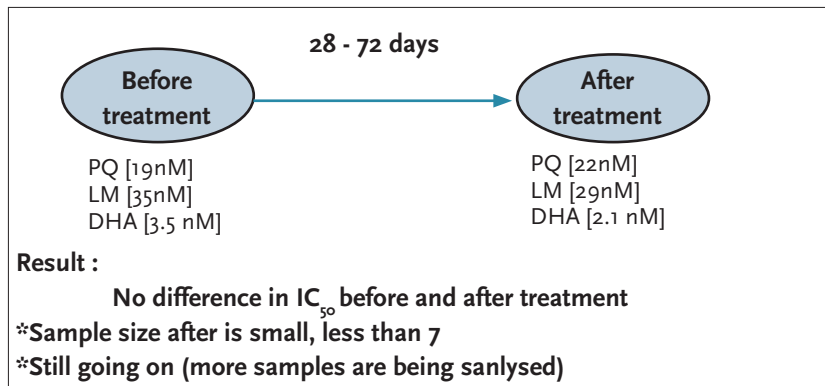
Conclusion:

- High rate of CQ sensitive (reversal of resistance?)
- PQ, LM, DHA retains sensitivity against CQ resistant strains
- Slight increase of LM and DHA IC₅₀ in CQ resistant but not significant

The results are in agreement with reports from other endemic areas



2. SELECTIVE PRESSURE OF PQ



PLANNED STUDIES ON THESE SAMPLES

- Analysis of molecular markers of chloroquin resistance (CQR)
 - pfcr1
 - pfmdr
 - and selected transporters

SIMILAR STUDIES

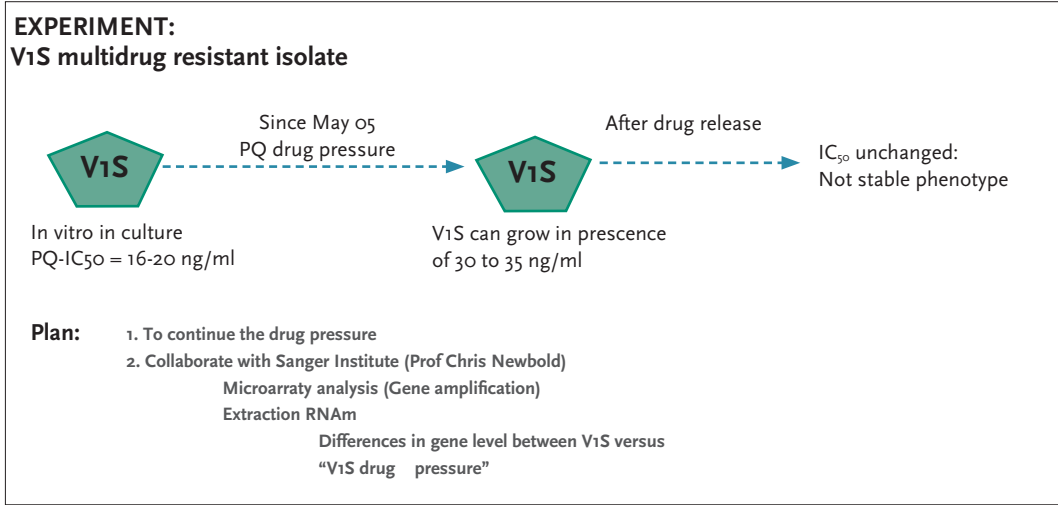
- In vitro PQ versus CQ, LM and other anti-malarial on fresh isolates
 - In western Kenyan (along Lake Victoria): Endemic area in Kenya
 - Collaborations:
 - Walter Reed Institute, US army (Kenya)
 - University of Liverpool
 - KEMRI; Wellcome Trust
 - Gate Foundation sponsored student (Ms Rubia Mukadam) assigned to work in our Unit in Nairobi (1 year).
 - Data are not available yet

MILESTONES AND DELIVERABLES OF ALL THESE STUDIES

- Relationship between the activity of PQ, CQ, LM, amodiaquine (AQ), DHA
- Existence of selective pressure of PQ and LM for resistance after
- Artkin and Co-artem
- Impact of CQR markers on the activity of PQ, LM

STUDY 2: IDENTIFICATION OF RESISTANCE MARKERS

- Method
 - Comparison of the genetic differences (micro-satellite, sequencing) : between sensitive and resistant isolate
- Problem:
 - No established PQ resistant strain so far
- Solution:
 - Selection of resistance by in vitro drug pressure
 - Continuous in vitro culture in presence of increasing drug concentration



ALTERNATIVE APPROACH

- Drug pressure in *P. falciparum*:
 - Challenging, time consuming, not guaranty for a stable marker
- What about selecting resistance in animal model?
 - In vivo in mouse with *Plasmodium berghei* (with Swiss Trop, Reto Brun)
 - PQ ED₅₀ (Effective dose): 15 mg/L
 - Drug pressure for 3 to 6 months: ED₅₀ = 125 mg/L
 - Resistance strain?

STABILITY OF THE PHENOTYPE:

- Cryopreservation
 - successive passages in mouse
 - ED₅₀= 15 mg:L; not stable

PLAN:

- To continue drug pressure in vivo
- To discuss with Sanger Institute: on use of berghei RNA to identify amplified genes by microarray

EXPECTED MILESTONES AND DELIVERABLES OF STUDY II

- Selection of stable PQ resistant strain in falciparum and/or berghei
- Use of these strain to search for markers of PQ resistance
- Information on the use of microarray and gene amplification associated with PQ resistance in falciparum and berghei.

SUMMARY OF THE PROJECT

- PQ activity versus other anti-malarial: well advance, completed by October 06
- PQ selective pressure: going on, completion October 06
- Analysis of CQ resistant markers: to start in August 06 up to January 07



- Selection of falciparum and berghei resistant strains, resistant phenotype: not stable yet
 - Microarray analyses to be initiated soon Isolation of RNA September to Deco6

ANOTHER AREA OF RESEARCH: LUMEFANTRINE RESISTANCE

DR LEAH MWAI EDCTP PhD STUDENTSHIP (JULY 06 TO JULY 09)

- Coartem: first line of treatment concern about LM resistance
- Major studies
 - LM and the activity of the other anti-malarial: already going on
 - LM selective pressure: going on
 - Selection of LM resistance in vitro: has started
 - Selection of LM in vivo with berghei: to start soon
 - Identification of LM markers of resistance: to use the same methodology as in PQ resistance

DISSEMINATION AND COMMUNICATION (EDCTP FELLOWSHIP) – EDCTP WAS ACKNOWLEDGED

- Participate to MIM meeting in Yaoundé, Nov 06: Preliminary data were presented
- Workshop participation (L Mwai)

COMPLETED MANUSCRIPT ION WRITING FROM PREVIOUS PROJECTS

- Nzila Alexis. The past, the present and the future of antifolate in the treatment of Plasmodium falciparum infection. *J. Antimicrobial Agent*, 2006.
- Nzila Alexis. Why pteridin analogs are not used as potentiator of anti-dihydrofolate reductase agents against malaria parasite. *Submitted for publication*.
- Nduati E. W., Leah Mwai, S. Ommeh, Kokwaro G.O and Nzila Alexis. The anti-malarial activity of the antifolate anticancer methotrexate and aminopterin in P. falciparum. *Submitted for publication*.
- C. Ochong E, Alexis Nzila, Eunice Nduati, Sera Kimanu, Isabelle Ochola and Carol Sibley. Longitudinal analyses of dihydrofolate folate reductase and dihydropteroate genotypes in Plasmodium falciparum isolates from different sites in Kenya. *Submitted for publication*.

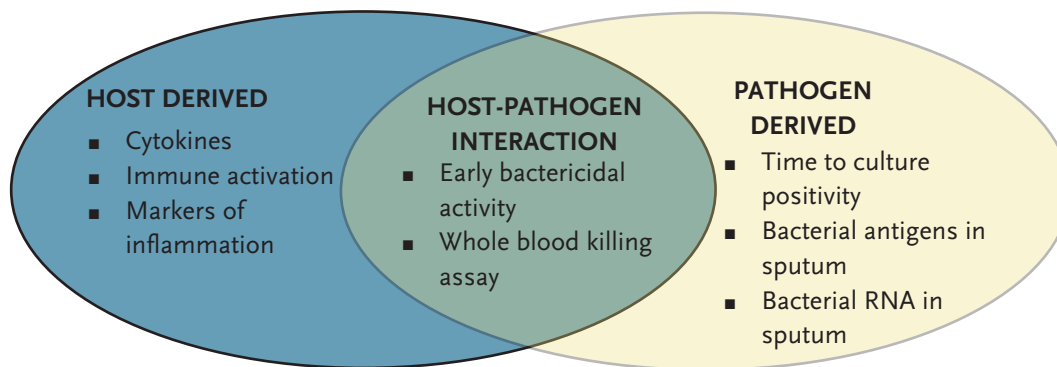


4.6. Surrogate markers to predict the outcome of anti-tuberculosis therapy – Professor Paul van Helden, South Africa

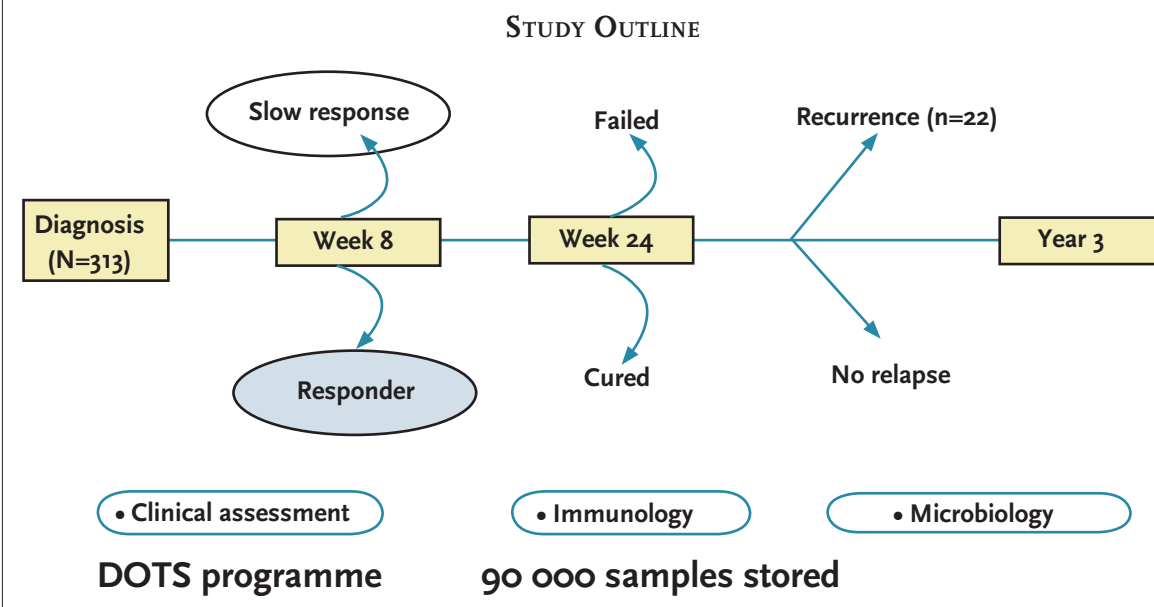
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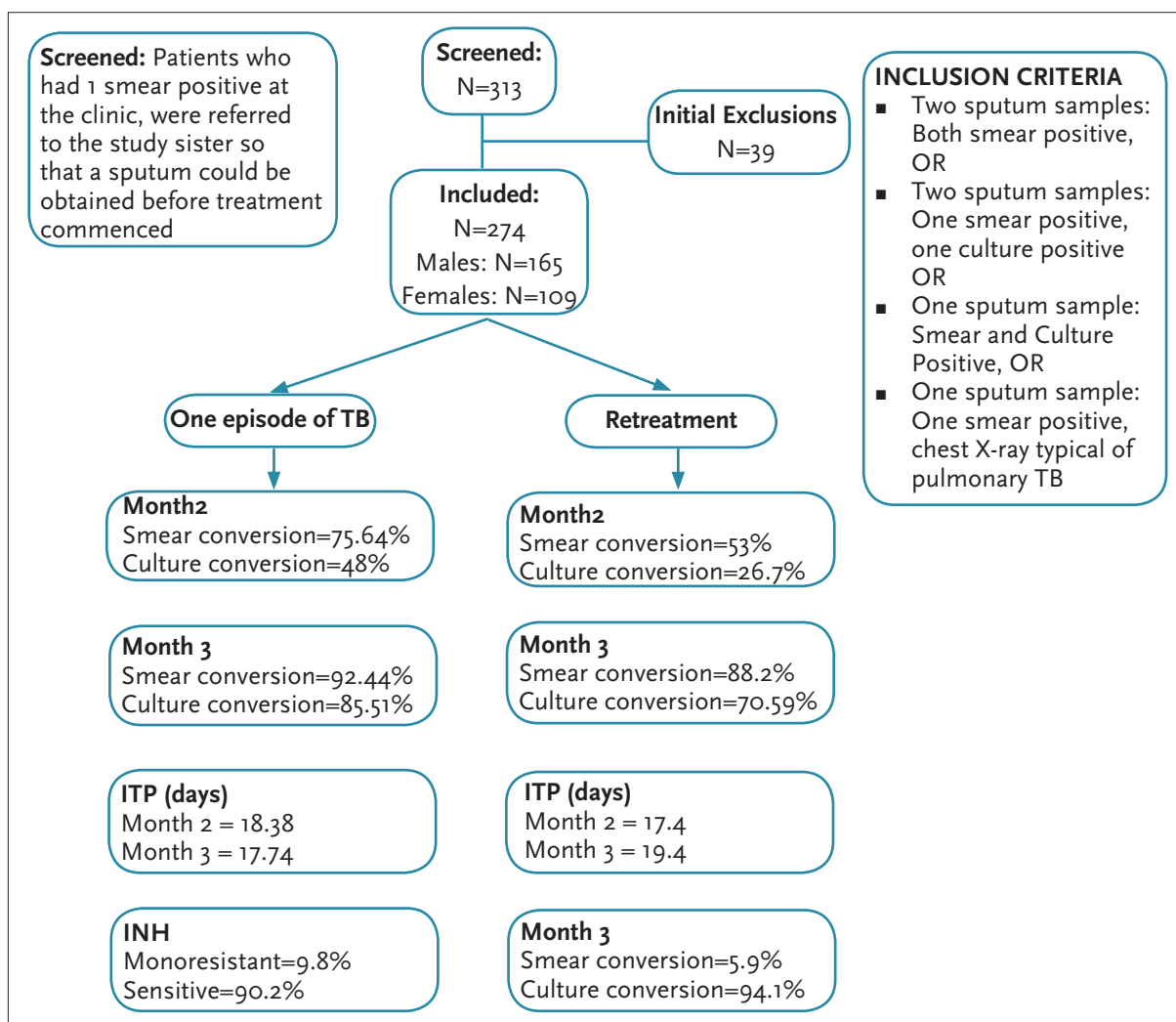
- This programme is concerned with a search for surrogate biomarkers for chemotherapeutic cure of tuberculosis (TB) in order to shorten drug trials and treatment.
- The hypothesis is that by studying a range of factors from both host and pathogen in matched individuals having a different clinical outcome, a biomarker or algorithm describing a set of biomarkers, measured early during chemotherapy, will predict outcome prospectively.

SURROGATE MARKERS - WHY AND WHICH?



SURROGATE MARKERS - LONGITUDINAL STUDY





EXCLUSIONS

- Gender: male: 24 and female: 15
- Reasons for Exclusion (n=39)
 - HIV (N=14), Immunological (N=4), multi-drug resistant TB; MDR (N=8), Mycobacterium other than TB; MOTT (N=2), Non-tuberculous; NTB (N=5), Other (N=1), Previous TB (N=2) and Protocol Violator (N=3).

SPECIFIC OBJECTIVES

- To complete the follow-up of the patient cohort (funded by GSK)
- To analyse samples stored from TB patients, particularly those samples collected before initiation of therapy and during the early phases of treatment from recurrent/relapse patients, using microbiological, serum, blood parameters, immunological and genetic markers
- To develop a test (algorithm) based on the findings that these parameters can be used to

discriminate between disease states, enabling selection of specific patient type for PoC study and detection of “cured” patients early during treatment and detection of relapse patients much sooner than the standard two-year follow up.

PROBLEMS

- Clinical/field: not funded, need for extra samples to establish assays. Own reserve funds
- Sample storage: power failures-Stellenbosch University (SU) installed emergency generators (two spares needed)
- Sample quantity: ideas/demands exceed supply-3 Senior local PIs decide based on formal motivation
- Lab/technical: scientific approach and solve as and when needed. Use of pilot studies. Equipment shortage.

EXISTING GAPS: HUMAN RESOURCE (HR) AND INFRASTRUCTURE

- HR: Inadequate funding to support all that is needed, e.g. sample management (>90 000 samples) and data management. Cross funded. Stats by SU and MRC at no cost to us. Hiring subject to labour laws- assistance from HR departments.
- Infrastructure: supplied from other sources

EQUIPMENT

- LSHTM: Microarray and associated equipment
- University of Pretoria: Surface Plasmon Resonance Biosensor
- Stellenbosch University: BL3 lab, polymerase chain reaction (PCR), FACS, enzyme linked immunosorbent assay (ELISA), cell culture etc

DATA MANAGEMENT

- Clinical: Access dBase, input controlled by clinical team. No direct access. Compact discs printed for lab use
- Laboratory: depends on nature of result. Some goes to main clinical dBase, some to smaller subsets. Some on specialised dBase e.g. strain genotype on Gelcompar, microarrays. At SU, all backed up each day on own server.

ETHICS AND REGULATORY ISSUES

- All studies approved by SU Institutional Review Board; IRB (Office for Human Research Protections; OHRP accredited). Partners have own IRBs as required.
- No drug regulatory issues, as patients on standard DOTS treatment.
- Biosafety: according to institution rules. BL3 at SU.

QC/QA/ACCREDITATION

- None specifically. No requirement, as not a formal registered trial. Standard GCP/GLP. SU had independent audit in June to identify gaps. All gaps can be closed, but not with existing funds.
- Ethics: SU IRB is OHRP (USA) accredited
- CDC assessment of Microbiology assays

EXISTING NETWORKS

- Numerous (London School of Hygiene and Tropical Medicine, GSK, City of Cape Town Health Department, Stellenbosch University and University of Pretoria)



5.0 SUMMARY OF THE RECOMMENDATIONS

PARTICIPANTS RECOMMENDED THE FOLLOWING TO EDCTP:

- Extension of senior fellowships
- Enhancing capacity building in Africa by strengthening the regulatory framework, ethics review mechanisms, infrastructure and training of personnel
- Fostering closer collaboration between investigators and policy makers and other regional organizations in Africa
- Promoting and strengthening of south-south and north-south networking
- Devising strategy for accreditation of clinical trial sites
- Revisiting co-funding and budget cuts associated with EDCTP grant



6.0 CLOSING REMARKS,

- *Dr Pascoal Mocumbi, High Representation – EDCTP, Netherlands.*

In his closing remarks Dr Pascoal Mocumbi expressed his appreciation to the organisers of meeting for quality meeting arrangements, facilities and hospitality that made it possible for a successful meeting. He also was appreciative of the active participation of all participants and that the opportunity to bring together investigators and representatives of national health research authorities enabled the beginning of a sustainable collaboration toward establishment of African networks according to discipline and activities. He urged all investigators participating in this first meeting to take the lead in forming networks in their respective institutions whose representation ranged from their peers to investigators in other fields. This, he said, should first aim at establishing national research forums to contribute to setting of national research agendas since sustainability of clinical research activities depend on their integration in national research and development strategies. He encouraged participants to undertake the lead in the initiatives of publishing papers as a way of sharing science and experiences. Dr Mocumbi reminded the participants of the importance of acquiring new skills and ability to attract more research funding to their clinical trial centres. With those remarks Dr Mocumbi wished all the participants safe travel back to their respective countries.



Site visits to research sites receiving grants from EDCTP was part of the programme (above: Prof Paul van Helden shows participants one of his laboratories

LIST OF PARTICIPANTS

LIST OF PARTICIPANTS TO EDCTP INVESTIGATORS MEETING – 24 TO 25 JULY 2006 – CAPE TOWN

| | | |
|--|---|--|
| <p>Abraham Alabi MRC Laboratories P O Box 273 Banjul aalibi@mrc.gm +2209988589</p> | <p>Aissatou Toure Balde Institute Pasteur Dakar/DCCC BP 220, Dakar atoure@pasteur.sn +221 839 9241</p> | <p>Al Hassan Alansary TB Research Centre Kassala, Sudan alansaryal@yahoo.com +249 912928455</p> |
| <p>Alexander Pym MRC P O Box 70380 Overport Durban South Africa alexander.pym@mrc.ac.za +273 12034747</p> | <p>Alexis Nzila Kemri/Wellcome Trust Research Program P.O.Box 230, 80108, Kilifi, Kenya anzila@kilifi.mimcom.net +254 41 522535 / 522063 / 525043 Fax: (+254) 41 522390</p> | <p>Aline Uwimana Pnilp/ Rwanda Kigala/ Rwanda rwauza@yahoo.fr (08) 460895</p> |
| <p>Ambrose Talisuna Ministry of Health, Uganda P O Box 7272, Kampala atalisuna@gfsat.com +256 712 506-275</p> | <p>Amina Jindani St. George's, University of London, London SW17 0RE, United Kingdom. ajindani@sgul.ac.uk Tel: 44 020 8725 2810 (direct) Fax: 44 020 8672 0234</p> | <p>Andreas Diacon University of Stellenbosch Cape Town ahd@sun.ac.za</p> |
| <p>Andrew Nunn MRC Clinical Trials Unit 222 Euston Rd, London NW1 2DA ajn@ctu.mrc.ac.uk (44) 207 670 4703</p> | <p>Anthony MBewu President MRC, SA P O Box 19070, Tygerberg South Africa, 7505 anthony.mbewu@mrc.ac.za +27219380319</p> | <p>Bakery Fofana University of Bamako P O Box 1805, Bamako, MRTC/DE bfofana@mrtcbko.org (223) 678 9450</p> |
| <p>Bart Jordi EDCTP Secretariat P O Box 83015 The Hague Netherlands jordi@edctp.org +31-70-3440884</p> | <p>Bernice Mwale Pharmaceutical Regulatory Authority P O Box 31890 Lusaka, Zambia mwalebc@yahoo.com (260) 1-220429</p> | <p>Carl Reddy MRC, Tb Unit, Durban 491 Ridge Rd, Durban, 4091 carl.reddy@mrc.ac.za 031-203 4745</p> |
| <p>Carolyn Nabasumba EPI Centre – Uganda P O Box 1956, MBRA nabasumba.carolyn@gmail.com +256 071-2369163</p> | <p>Charles Mgone EDCTP MRC Cape Town P. O. Box 19070 Tygerberg, Cape Town, RSA mgone@edctp.org +27219380839</p> | <p>Chifumbe Chintu CHAPAS School of Medicine P O Box 50110, Lusaka Zambia cchintu@zammet.zm 260 1 254681</p> |
| <p>Christine Manyando Tropical Diseases Research Centre P. O. Box 71769, Ndola Zambia. Manyando@zamnet.zm orcmanyando@yahoo.com</p> | <p>Clayton Onyango MRC Laboratories Box 273, Banjul, The Gambia conyango@mrc.gm +220 7713344</p> | <p>Clement Mwakamui University Teaching Hospital P O Box UTH 63, Lusaka Zambia clemwa2003@yahoo.com 260-97799949</p> |

| | | |
|--|---|--|
| <p>Concepta Merry Uganda cmerry@tcd.ie</p> | <p>Dan Mwahlé Director of Research Department of Science and Technology Pretoria South Africa</p> | <p>Daan du Toit Manager: Strategic Partnerships Department of Science and Technology (South Africa) daan.dutoit@dst.gov.za +27 12 843 6336 Fax: + 27 12 349 1058</p> |
| <p>Dario Zanon European Commission dario.zanon@cec.eu.int</p> | <p>Deidre Abrahams EDCTP MRC Cape Town P. O. Box 19070 Tygerberg, Cape Town, RSA deidre.abrahams@mrc.ac.za +27219380819</p> | <p>Diana Gibb MRC Clinical Trials Unit 222 Euston Rd, London, NW1 2DA d.gibb@ctu.mrc.ac.uk 44 2076704894</p> |
| <p>Elise Levendal SAAVI, MRC, SA P O Box 19070, Tygerberg South Africa, 7505 elise.levendal@mrc.ac.za +27219380262</p> | <p>Didier Koumavi Ekouevi ZACCI/ACOMDA P8 BR B54, Abidjan 18 Cote d'Ivoire ekouevi@aviso.ci kristoli@yahoo.com 4894 +225 07780845</p> | <p>Eusebio V. Macete Centro de Investigação em Saúde da Manhiça eusebiomacete@yahoo.com C. Postal 1929 Maputo Mozambique + 258 21 810002 Centro de Salud Internacional, Hospital Clínic, Rosselló 132 2ffl, 2ffl Barcelona Spain + 34 93 227 5706</p> |
| <p>Francine Ntoumi EDCTP Secretariat P O Box 83015 The Hague Netherlands ntoumi@edctp.org +31-70-3440891</p> | <p>Gerhard Walzl University of Stellenbosch Cape Town South Africa gwalzl@sun.ac.za</p> | <p>Getachew Desta Addis Ababa, University Medical P O Box 2380 Addis Ababa, Etiópia getadera@yahoo.com 257-0115510653</p> |
| <p>Gilla Kaplan Public Health Research Institute/UMDNJ, 225 Warren Street Newark, NJ 07103-3535 USA dalton@phri.org / Kaplan@phri.org +973 854-3223 Fax: +973 854-3221</p> | <p>Hazel Dockrell London School of Hygiene & Tropical Medicine Keppel St, London, WC1E 7HT hazel.dockrell@lshtm.ac.uk +44 207 927 2637</p> | <p>Havana Chikoto University of Cape Town Clinical Pharmacology, GSH hchikoto@uctgh1.uct.ac.za</p> |
| <p>Helen McIlleron Division of Clinical Pharmacology, University of Cape Town (UCT), K45 OMB, Groote Schoor Hospital, Observatory 7925, South Africa hmciller@uctgh1.uct.ac.za</p> | <p>Helen McShane Oxford University United Kingdom</p> | <p>Herman Awono Ambene .C.E.A.C./ IRY Yaounde- Cameroon contact@oceac.org +237 2232232</p> |
| <p>Innocent Valea Centre Nuraz 01 BP 390 Bobo-Dionlasso Burkinafo valinno@yahoo.fr (226) 70138271</p> | <p>Jimmy Volmink Deputy Dean (Research) Faculty of Health Sciences Stellenbosch University jvolmink@sun.ac.za +2721938-9098 Fax : +2721938-9558</p> | <p>Jackie Cliff London School of Hygiene & Tropical Medicine Keppel St WC1E 7HT London jackie.cliff@lshtm.ac.uk +44 207 612 7833</p> |

| | | |
|---|--|---|
| <p>Janneke van Dijk MACHA/ MIAM P O Box 630166, Zambia janneke.vandijk@macha.org.zm</p> | <p>Kobus Herbst Africa Centre, UKZN P O Box 198, Mtubatuba 3935 South Africa kherbst@africacentre.ac.za +273 555507503</p> | <p>Lahouari Belghardi WHO WHO/IVB 20, AV APPA 1211 Geneva, Switzerland belgharbil@who.int +412 27913925</p> |
| <p>Lakhi Shabir UTH/ Lusaka Remox P/bag RW1x, Ridgeway, Lusaka Zambia UTH Lusaka Zambia lakhisr@coppernet.zm +26095816482</p> | <p>Laura Brum Instituto Nacional de Saúde Dr. Ricardo Jorge, Av. Padre Cruz 1649-016 Lisboa Portugal Laura.Brum@insa.min-saude.pt Tel:+351 217519235 Fax: +351 217526452</p> | <p>Leah Mwai KEMRI/ Wellcome Trust Research P O Box 230-30108, Kalifi, Kenya lmwai@kilifi.kemri-wellcome.org +254222883049</p> |
| <p>Liesl Grobler MRC, SA P O Box 19070, Tygerberg South Africa, 7505 liesl.grobler@mrc.ac.za +27219380506</p> | <p>Lizeka Xiphu MRC – South Africa lizeka.xiphu@mrc.ac.za 021-938 0525</p> | <p>Lynn Zijenah Immunology Department University of Zimbabwe Medical School, P.O BOX A 178 Avondale Zimbabwe. E-mail: lzienah@healthnet.zw sodai@mweb.co.zw +263 4 791631 Fax: 263 4 724912</p> |
| <p>Mamohloding Tlhagale Department of Science and Technology Pretoria South Africa Mamohloding.Maahlo@dst.gov.za</p> | <p>Mark Hatherill SATVI University of Cape Town South Africa mark@rmh.uct.ac.za +27-21-4066990 Fax : +27-21-4066081</p> | <p>Martin Meremikwu University of Calabar P O Box 1211, Calabar, Nigeria mmeremik@yahoo.co.uk +2348036742377</p> |
| <p>Michael Makanga MRC Cape Town P. O. Box 19070 Tygerberg, Cape Town, RSA makanga@edctp.org +27219380509</p> | <p>Michael Nambozi Tropical Disease Research Centre P O Box71769, Ndola, Zambia michaelnambozi@yahoo.com +26 097835721</p> | <p>Michel Klein EDCTP PB 54 Strathgowan AV. Toronto ON, Canada, M4N1BS +14164813549</p> |
| <p>Moiwa Mukhtar University of Khartoum, Inst- Enden P O Box 11463, Khartoum mmukhtar@iend.org +29991223426</p> | <p>Ndekya Maria Oriyo Kilimanjaro Christian Medical Centre P O Box 3010, Moshi, Tanzania ndekya@yahoo.com +255-784-417771</p> | <p>Niresh Bhagwandin MRC, SA P O Box 19070, Tygerberg South Africa, 7505 niresh.bhagwandin@mrc.ac.za +27219380207</p> |

| | | |
|---|--|---|
| <p>Nulda Beyers University of Stellenbosch Cape Town South Africa nb@sun.ac.za</p> | <p>Odile Leroy EDCTP Secretariat P O Box 83015 The Hague Netherlands leroy@edctp.org +31-70-3440890</p> | <p>Mary Edwards Reproductive Health & HIV Research Unit University of Witwatersrand Department of Obstetrics & Gynaecology Chris Hani Baragwanath Hospital Soweto, Johannesburg P O Bertsham 2013 m.edwards@rhrujhb.co.za +27 (11) 989 9200 +27 (0)82 374 1157</p> |
| <p>Ndounga Nothilu CERVE BP 124 9, Brazzaville ngonalandounga@yahoo.fr 242-5260505</p> | <p>Patrick Coffie PACCI/ ACONDA 18 BP 1954, Abidjan 18 patrick.coffie@pacci.ci 225 21755960</p> | <p>Patrice Piola Epicentre Epicentre Mberara Uganda uganda@epicentre.msfi.org +256 772 721 746</p> |
| <p>Pascoal Mocumbi EDCTP Secretariat P O Box 83015 The Hague, Netherlands mocumbi@edctp.org +31-70-3440883</p> | <p>Paul van Helden Stellenbosch Univ. Health & Science P O Box 19063, Tygerberg South Africa, 7505 pvh@sun.ac.za +27219389401</p> | <p>Peter Manyike SAAVI, MRC, SA P O Box 19070, Tygerberg South Africa, 7505 peter.manyike@mrc.ac.za +27219380262</p> |
| <p>Peter Ndumbe Centre for the Study and Control of Communicable Diseases (CSCCD), Faculty of Medicine and Biomedical Sciences (FMBS), Melen Street, University of Yaounde I, BP 8445 Yaounde, Cameroon. pndumbe@yahoo.com</p> | <p>Pierre-Blaise Matsiegui Albert Schweizer Hospital BP U8 , Lamberene-Gabon matsiegui@yahoo.fr +241 07840459</p> | <p>Quique Bassat Centro de Investigação em Saúde da Manhica, Manhica, Maputo, Mozambique quique.bassat@manhica.net quique.bassat@teleline.es +258 21 81 0002 Fax: +258 21 81 0002</p> |
| <p>Roma Chilengi AMANET Box 33207, Dar-Es-Salaam Tanzania chilengi@amanet-trust.org +255222700018</p> | <p>Roxana Rustomjee MRC P O Box 70380, Overport South Africa, 4067 rustomjee@mrc.ac.za 27312034745</p> | <p>Simon Agwale Innovative Biotech Limited, 1 Abdu Abubakar Street, P. O. Box 30, Keffi, Nasarawa State Nigeria. sagwale@innovativebiotechng.com. +234 47 62593 or +234 80 5615 7867.</p> |
| <p>Simukai Zizhou Ministry of Health & Child Welfare P O Box 10, Marondera Zimbabwe szizhou@healthnet.org.zw +263 792 4570</p> | <p>Sodiomon Sirima CNRFP BP 2208, Obaya s.sirima.cnlp@fasonet.bf +22650305220</p> | <p>Souleymane Mboup Université Cheikh Anta DIOP, Laboratoire de Bacteriologie Virologie, CHU Le Dantec, BP 7325, Dakar, SENEGAL mboup@rarslbv.org or virus@sentoo.sn +221-8216420 et 8225919 Fax : 221-8216442</p> |

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| <p>Stanley Mungofa Harare City Health Dept. Box 596, Harare, Zimbabwe smungofa@healthnet.org.zw 263-11860733</p> | <p>Thomas Nyirenda EDCTP MRC Cape Town P. O. Box 19070 Tygerberg, Cape Town, RSA nyirenda@edctp.org +27219380346</p> | <p>Tinto Halidou Centre Muraz 01 BP 390 BoboD550 01 (BF) tintohalidou@yahoo.fr +22676541180</p> |
| <p>Thuli Mthiyane MRC P O Box 70380 Overport,4067 Durban mthiyant@mrc.ac.za</p> | <p>Umberto d'Alessandro Institute of Tropical Medicine National Street 155, B2000 Antwerp udalessandro@itg.be +3232476354</p> | <p>Veronica Mulenga University Teaching Hospital Dept. of Paediatrics Lusaka Zambia veromulenga@yahoo.co.uk +260 96953792</p> |
| <p>Victor Chalwe Population Based Field Epidemiology TDRC, P O Bo x 71769, Ndola victorchalwe@yahoo.com +26096601830</p> | <p>Walter Jaoko University of Nairobi, KAVI Dept. of Microbiology Box 19676, Nairobi wjaoko@kaviuon.org +254733752468</p> | <p>Willem Hanekom University of Cape Town Health Science, Anzio Rd Observatory, SA, 7925 willem@rmh.uct.ac.za +27 214 066080</p> |
| <p>Zacherie Kashongwe Catholic University, BV KAV P O Box 2 Rwanda zkashongwe@yahoo.fr +211 381 317 8240</p> | | |

CORRESPONDENCE:

European & Developing Countries Clinical Trials Partnership (EDCTP), Africa Office,
Medical Research Council, P.O. Box 19070, Francie van Zyl Street, Tygerberg, Cape Town, South Africa.
Tel: +27 21 938 0819. Fax: +27 21 938 0569. Website: www.edctp.org

