EDCTP

European & Developing Countries Clinical Trials Partnership

Annual Report 2014

Starting EDCTP2

EDCTP activities 2003 - 2014

65 calls for proposals

600+ scientific publications

516 Senior Fellows and students (BSc, MSc, PhD, MD)

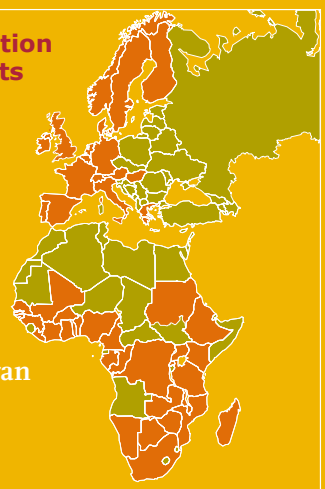
€ 211.98 million grant value

254 grants awarded

Participation in projects

16 European countries

30 sub-Saharan African countries



Project portfolio

HIV/AIDS
56 projects
€ 62.5M

Drugs	Vaccines	Diagnostics	Microbicides	Cross-cutting*
20 projects	12 projects	1 project	5 projects	18 projects
€ 25.08M	€ 23.39M	€ 0.29M	€ 9.39M	€ 4.37M

Tuberculosis
36 projects
€ 70.68M

Drugs	Vaccines	Diagnostics	Cross-cutting*
10 projects	8 projects	10 projects	8 projects
€ 30.10M	€ 23.25M	€ 13.32M	€ 4.01M

Malaria
42 projects
€ 50.69M

Drugs	Vaccines	Diagnostics	Cross-cutting*
22 projects	6 projects	2 projects	12 projects
€ 30.13M	€ 17.36M	€ 0.59M	€ 2.61M

HIV/TB co-infection
12 projects
€ 7.23M

Drugs	Cross-cutting*
8 projects	4 projects
€ 6.71M	€ 0.52M

Ethics and regulatory, and other cross-cutting activities*
108 projects
€ 20.86M

**Cross-cutting activities: projects not linked to a particular intervention; epidemiological research looking at disease prevalence and incidence; capacity building and infrastructure improvement; ethics and regulatory; as well as networking grants.*

Contents

Message from the Executive Director

As we come to the end of the first EDCTP programme, which has been extended to 31 December 2015, the 2014 Annual Report covers achievements of the programme over the years since its inception in 2003. These include outcomes of the finished clinical trials and preliminary results, of some that are coming to an end soon, as well as reports of various high-profile capacity development and networking projects. By the end of 2014, the programme had released 65 calls and awarded 254 grants involving researchers from 30 African and 16 European countries. Many of these trials have contributed towards policy and international treatment and prevention guidelines as pointed out in the annual report.

During 2014 a lot of efforts went into preparing ourselves for the second programme commonly known as EDCTP2. This included holding of a series of stakeholder meetings and conducting research landscape analyses that informed the drafting of the EDCTP2 strategic business plan.

The governance of EDCTP was also changed to best fit the equal ownership and partnership model where African participating states were invited to join as full members and participate in policy and decision making with their European counterparts. This required revision of the statutes and change of the legal structure from European Economic Interest Group (EEIG) to international Association under the Dutch law. These efforts culminated with the launch of EDCTP2 on 2 December. It is my sincere belief that this is the beginning of many greater things to come including a future in which Africa and Europe, along with other international partners, will work hand-in-hand to jointly invest in R&D to fight poverty-related and neglected diseases.

None of this would have been realised without the efforts and commitment of many of you who have been associated with EDCTP at one stage or another. However, I would like to extend special thanks to Dr Pascoal Mocumbi who has been our High Representative since the inception of the programme, and Prof. Hannah Akuffo who was the EDCTP General Assembly Chair for the past four years. Both stepped down in 2014. Their support to me personally as well as their selfless contribution to the programme have been very valuable. I would also like to express my sincere thanks to all members of the EDCTP constituents past and present. Special thanks also go to the very hardworking and committed members of the Secretariat who have always made what at first seemed impossible, possible.

Charles S Mgone
Executive Director

Starting EDCTP2

Preparations for the start of the second EDCTP programme (EDCTP2) commenced in 2012, when funding was received from the European Union for a programme of activities. This EDCTP-Plus project aimed to establish a strong and reliable foundation for executing the EDCTP2 programme with a bolstered EU-Africa research partnership. The activities were funded under the European Framework Programme 7 through a Coordination and Support Action Grant (FP7-304786) and were completed in 2014. Moreover, EDCTP2 received overwhelming support from the European Union, as well as the European and African Participating States, which led to the official launch of the programme on 2 December 2014.

Achievements of the first EDCTP programme

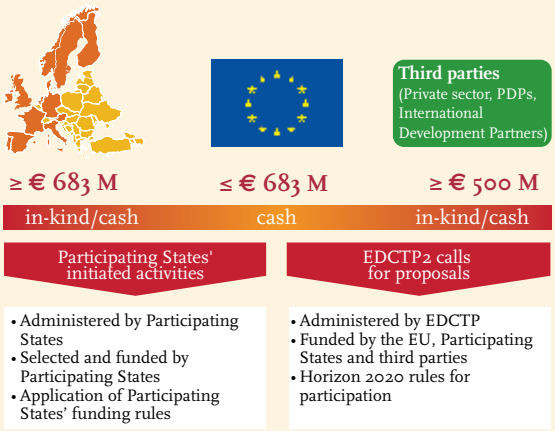
Targeting HIV/AIDS, tuberculosis and malaria, EDCTP has funded clinical trials on treatment drugs, vaccines, microbicides and diagnostics. Through its funding instruments, it has contributed to the coordination and integration of national research programmes. Results from various trials have informed national and international policies such as the WHO policy on the prevention of mother-to-child transmission of HIV and the registration of a paediatric formulation of an antiretroviral product (Pedimune) in several African countries. Furthermore, since 2003, EDCTP provided professional training to 516 African scientists and medical doctors, including 56 Career and Senior Fellows as well as more than 414 Master's and PhD students.

Overall, EDCTP represents a flagship programme for conducting sound multi-country clinical trials in sub-Saharan Africa, building a true partnership between Europe and Africa, and fostering African leadership in scientific research. Europe's strong commitment to partnership is reflected in the fact that 74% of EDCTP funding was invested in activities implemented by African research institutions. Over 70% of all EDCTP-funded projects were led by African researchers.

The EDCTP programme also contributed to networking African research which resulted in the launch of four African Regional Networks of Excellence for clinical trials. Moreover, the ethics and regulatory environment has been improved by strengthening ethics review capacity and national regulatory authorities in many African countries. EDCTP was the main funder of the African initiative to establish the Pan African Clinical Trials Registry (PACTR), an official WHO Primary Clinical Trials Registry.

The second EDCTP programme

EDCTP2 will run over a ten-year period from 2014 to 2024 with a budget of €1.36 billion in commitments. The European Union will provide a contribution of up to €683 million, on condition this is equally matched by contributions from the European Participating States. Additional funding will be sought from third parties and African Participating States.



The second programme will support all stages of clinical trials, from phase I to IV on HIV/AIDS, tuberculosis, malaria and neglected infectious diseases including emerging disease of particular relevance to Africa such as Ebola virus disease, for new or improved medical interventions, as well as advanced testing and field validation of new diagnostic tools.

The activities supported under EDCTP2 include:

- Multicentre clinical trials that are conducted by research consortia involving both European and African research teams, with integrated capacity development and networking elements
- Capacity support activities that strengthen the enabling environment for conducting clinical trials and clinical research
- Fellowships that promote career development and scientific excellence of individual researchers as well as training and mentorship of research team members.

Extended international cooperation with public and private research and development partners globally, as well as other European Union initiatives including development assistance is promoted in all these activities.

EDCTP-Plus

The EDCTP-Plus project aimed to prepare for EDCTP2 which would have an increased budget, a broader scope covering all phases of clinical trials from phase I to IV, as well as health services optimisation research, and an expanded disease remit with the inclusion of neglected infectious diseases. Additionally, a comprehensive review and revision of governance, as well as operational policies and procedures was required to ensure EDCTP2 complies with the Horizon 2020 rules of participation. The project started in 2012 and the activities were completed in December 2014. The major achievements of the EDCTP-Plus project are summarised below.

Stakeholder meetings

Six thematic stakeholder meetings were held in 2013 and 2014:

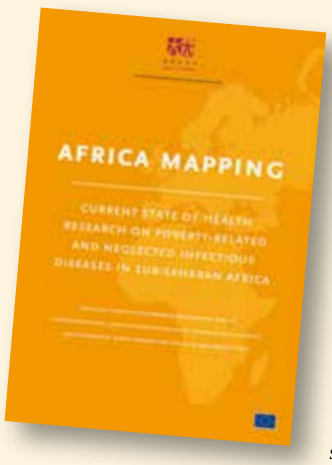
- Neglected infectious diseases (The Hague, the Netherlands, 27-28 June 2013)
- HIV/AIDS (Lisbon, Portugal, 3-4 September 2013)
- Malaria (Vienna, Austria, 19-20 September 2013)
- Tuberculosis and other mycobacterial infections (Paris, France, 28-29 October 2013)
- Health research ethics review and regulatory affairs (Antwerp, Belgium, 28-29 November 2013)
- Capacity development (Berlin, Germany, 3 July 2014).

The aim of the meetings was to highlight gaps, opportunities and barriers to progress, identify potential partners for joint initiatives, and to engage and inform stakeholders of the achievements of the first EDCTP programme, as well as the lessons learned. These meetings brought together experts from research institutions, policymaker and representatives of product development partnerships, pharmaceutical industry and international organisations. The recommendations of the stakeholder meetings have contributed towards the strategies and operation business plans of EDCTP2. The reports of these meetings are available on the EDCTP website (www.edctp.org).

Mapping research

Improving coordination and cooperation among the participating European States and enhanced engagement with the private sector and like-minded organisations are EDCTP2 objectives. The published report *Charting Research – EDCTP Participating States programmes and activities in the scope of EDCTP2* and a draft report on mapping the research programmes and relevant research cooperation activities in the newest EU Member States have informed the EDCTP2 Participating States and the Secretariat on areas of mutual interest and facilitated the submission of Participating State Initiated Activities (PSIAs) in the annual work plans.

A bibliometric analysis of African and European research programmes, partnerships, activities and capacities was commissioned in 2012 in order to analyse the fields of HIV/AIDS, tuberculosis, malaria and neglected infectious diseases over the period 2003-2011.



In collaboration with RAND Europe and Baird's CMC, EDCTP mapped sub-Saharan African health research activities and capacities and analysed how these relate to national funding commitments, health research policies and the mission of EDCTP. The report Africa mapping: *Current state of health research on poverty-related and neglected infectious diseases in sub-Saharan Africa*, published in September 2014, shows the significant regional differences in the state of health research in sub-Saharan in terms of volume, development and funding levels.

Investing in research capacity

The EDCTP-Plus project explored the consolidation and enhancement of some of the achievements of the first EDCTP programme such as optimal utilisation and retention of the invested capacity. Development of 24 laboratories – six per EDCTP Network of Excellence (CANTAM, EACCR, TESA and WANETAM) – through the Stepwise Laboratory Improvement Process Toward Accreditation (SLIPTA) was undertaken. The Pan African Clinical Trials Registry expanded the scope of trials it registers, enhanced the features and functionality of its website, and raised awareness of trial registration in Africa through advocacy and engagement with national registries. These activities may partly explain the major rise in applications for registration over the course of this project. Five finance management training workshops were held in Dakar, Senegal (2012 and 2013) for finance staff of EDCTP grantees in West and Central Africa, and in Johannesburg, South Africa (2012, 2013 and 2014) for finance staff of EDCTP grantees in Eastern and Southern Africa.

Preparation of the EDCTP organisation

In view of the second programme, EDCTP has improved its operational activities to ensure compliance with the Horizon 2020 rules for participation. This brought the successful implementation of a web-based grants management and online application system (EDCTPgrants); preparation of comprehensive and more structured financial guidelines for grant-holders; improvement of IT infrastructure capability, including IT administrative systems at the EDCTP Secretariat; and revision of policies, procedures and manuals in readiness for EDCTP2. Moreover, a comprehensive external evaluation of the first EDCTP programme was conducted by an external consultancy firm, Technopolis Group. The findings of the report *Assessment of the performance and impact of the first programme of the European & Developing Countries Clinical Trials Partnership* (September 2014) are available on the EDCTP website.

Raising private and public commitment to EDCTP

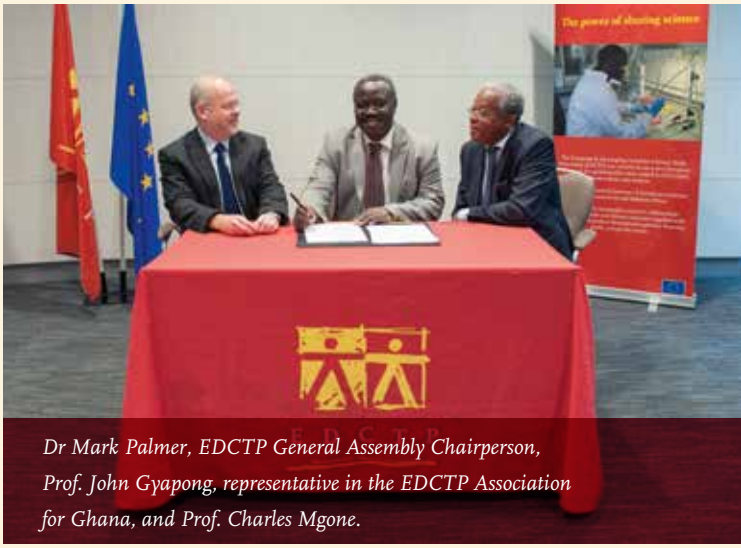
Strong foundations for future EDCTP collaboration with the private sector and product development partnerships have been and continue to be established. Key events were the 'Pharmaceutical Industry Workshop' (2012, The Netherlands), the 'Post-Registration Medicinal Products Safety Monitoring in sub-Saharan Africa' meeting (2012, South Africa), as well as individual meetings with stakeholders indicated opportunities and enthusiasm for mutually productive collaborations under EDCTP2.

EDCTP and the European Federation of Pharmaceutical Industries and Associations (EFPIA) signed in January 2013 a memorandum of understanding on a clinical research fellowship scheme that will give sub-Saharan African researchers the possibility to be placed in European-based pharmaceutical companies. In order to maximise impact and cost effectiveness, EDCTP collaborated with the WHO-TDR Career Development Programme which offers similar fellowships (but with a broader geographical scope). EDCTP and TDR launched the first call for proposals for this Clinical Research and Development Fellowship on 31 October 2014. The call will be launched annually in order to develop the necessary research capacity in this area in sub-Saharan Africa.

EDCTP Association

The EDCTP Association was established in The Hague, the Netherlands on 10 April 2014. Dr Mark Palmer, Chairperson of the EDCTP General Assembly and representing the United Kingdom, and Dr Guillaume Fusai, representing France, signed the incorporation papers. The EDCTP Association is the dedicated implementation structure for the second programme. EDCTP changed its structure from a European Economic Interest Grouping (EEIG) to an Association under Dutch law in order to enable sub-Saharan countries to become members of EDCTP, together with all countries associated to Horizon 2020, the EU Framework Programme for Research and Innovation.

On 6 May 2014, eight African and eight European countries formalised their participation in the second EDCTP programme as their representatives signed the documents of the EDCTP Association. This direct and full participation of African countries in the governance and the execution of the programme is a historic step for the African and European partnership to fight poverty-related and neglected infectious diseases. All members (or Participating States) of the EDCTP Association have voting rights in the EDCTP General Assembly, the decision-making body of EDCTP. As of 31 December 2014, 13 European countries (Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, and the United Kingdom) and 11 African countries (Cameroon, Congo, The Gambia, Ghana, Mozambique, Niger, Senegal, South Africa, Tanzania, Uganda and Zambia) had formalised their participation, while other European and African countries expressed their intention to join.



Dr Mark Palmer, EDCTP General Assembly Chairperson, Prof. John Gyapong, representative in the EDCTP Association for Ghana, and Prof. Charles Mgone.

On 15 April 2014, the European Parliament approved with overwhelming majority the participation of the European Union in the second programme of EDCTP. Following this decision, the European Council took a positive and final decision on the funding of EDCTP as part of Horizon 2020 on 6 May 2014.

The launch of EDCTP2

A high-level event held in Cape Town, South Africa marked the launch of the second EDCTP programme on 2 December 2014. The meeting was jointly organised by the European Commission and EDCTP, and was hosted by the South African Department of Science and Technology. The event was attended by 156 delegates, including African and European government representatives, major research funders, scientists, industry representatives and other experts.

The objective was to provide an opportunity to discuss the role and strategic vision of EDCTP2, and to explore possibilities for synergies with other international initiatives. Her Excellency Naledi Pandor, Minister of Science and Technology of South Africa officially opened this meeting and chaired the opening session which was followed by three keynote addresses from distinguished speakers.

Carlos Moedas, European Commissioner for Research, Innovation and Science, speaks at the welcome reception on 1 December 2014

Three roundtable sessions were later held focussing on specific challenges for the second programme: the positioning of EDCTP to address global and national health challenges; connecting the health delivery chain in order to get research results 'from bench to bedside'; and creating socially responsible partnerships for long-term investments in global health. The panellists included African ministers, African and European high-level policymakers, as well as representatives from industry, international public and private organisations and a patient organisation.

The EDCTP high-level launch event for the second EDCTP programme was the last meeting in a series of high-level meetings planned to contribute to the shaping of the strategy and funding approach of the second EDCTP programme. The first meeting took place in Cape Town, South Africa on 5 November 2012 and the second meeting was in Dakar, Senegal, on 21 October 2013. The proceedings of all three meetings were published.

2014 in a nutshell

January

Dr Mark Palmer (Medical Research Council (MRC), United Kingdom) took over from Prof. Hannah Akuffo (Swedish International Development Cooperation Agency, Sweden) as Chair of the EDCTP General Assembly. Dr Stefano Vella (Istituto Superiore di Sanità, Italy) and Dr Detlef Böcking (Deutschen Zentrum für Luft- und Raumfahrt, Germany) were elected as vice-Chairs.

Dr Pascoal Mocumbi took his leave as the EDCTP High Representative. Dr Mocumbi, Prime Minister of Mozambique from 1994 to 2004, joined EDCTP in March 2004. As the EDCTP High Representative, he has played an instrumental role in raising the profile of EDCTP, particularly with African governments and regional bodies.

February

EDCTP published the proceedings of three stakeholder meetings that were held in 2013: on health research ethics and regulatory affairs; on tuberculosis and other mycobacterial infections; and on HIV/AIDS. The recommendations from these proceedings have contributed towards the development of the EDCTP2 strategic business plan and annual work plans.

EDCTP also published a short video that captures the discussions of the Second High-Level meeting on the second EDCTP programme. The meeting took place in Dakar, Senegal on 21 October 2013 and was hosted by the Ministry of Health of Senegal, the European Commission and EDCTP. The video is available on the EDCTP YouTube channel (www.youtube.com/edctpmedia).

March

WHO-TDR, the Special Programme for Research and Training in Tropical Diseases, and EDCTP signed an agreement to harmonise and streamline their Fellowship programmes that offer pharmaceutical industry mentorship experience. TDR will offer a maximum of 8 positions per year and EDCTP up to 10 positions per year.

The EDCTP-funded PanACEA MAMS TB-01 clinical trial project completed on schedule the recruitment of patients. The multi-arm multistage (MAMS) trial aims to identify treatment combination regimens to be included in a phase III trial to achieve shorter treatment of tuberculosis.

The EDCTP-funded Pan African Clinical Trials Registry (PACTR; www.pactr.org), the first WHO-endorsed primary registry in Africa, reached an important milestone: the 300th clinical trial was registered.

July

On 3 July, the EDCTP stakeholder meeting on capacity development brought together 95 participants to discuss current and emerging capacity development gaps in Africa. The recommendations of the meeting are to inform the development of the strategy and operational plans of EDCTP2. Among the topics discussed were: EDCTP's integrated approach for capacity development in clinical trials projects; the regional Networks of Excellence; and development of African scientific leadership through different fellowship schemes.

The EDCTP-funded EARNEST trial published its results in the *New England Journal of Medicine* on 16 July. The trial has shown that the combination of a boosted protease inhibitor (lopinavir) with two nucleoside reverse-transcriptase inhibitors (NRTIs) is a feasible second-line therapy for HIV patients in Africa.

August

The EDCTP-funded project TB CHILD developed a new immunodiagnostic tool TAM-TB that has the potential to improve the diagnosis of TB in children. On 31 August, *The Lancet Infectious Diseases* published the results of a sputum-independent assay developed in Tanzania that is able to diagnose active tuberculosis in children. The T cell activation (TAM-TB) assay is the first immunodiagnostic tool which can detect active tuberculosis disease in children with sensitivity similar to culture and with excellent specificity in a tuberculosis-endemic setting.

September

REMoxTB, a phase III global clinical trial of new tuberculosis drug regimens, published its results in the *New England Journal of Medicine* on 7 September. The trial was conducted mainly in Africa where approximately 70% of the patients were recruited.

On 23 September, two large randomised controlled trials conducted in Africa that tested mefloquine, a drug for malaria prevention in HIV-negative and HIV-positive pregnant women, published their results in *PLOS Medicine*. These trials are part of the EDCTP-funded Malaria in Pregnancy Preventive Alternative Drugs (MiPPAD) study.

EDCTP, RAND Europe and Baird's CMC published a report on the current state of health research and national funding commitments for HIV/AIDS, tuberculosis, malaria and neglected infectious diseases in sub-Saharan Africa. The report, which includes an analysis of research capacity as well as health systems, was the result of a one-year study conducted in preparation for the second EDCTP programme.

On 10 April, the EDCTP Association was established in The Hague, the Netherlands. Dr Mark Palmer, Chairperson of the EDCTP General Assembly and representing the United Kingdom and Dr Guillaume Fusai representing France signed the incorporation papers. The EDCTP Association is the dedicated implementation structure for the second programme (EDCTP2).

April

Eight African and eight European countries formalised their participation in the EDCTP2 programme, as their representatives signed the documents of the EDCTP Association at the meeting of the EDCTP General Assembly on 5 May 2014. The direct and full participation of African countries in the governance and the execution of the programme is a historic step for EDCTP. All Participating States have voting rights in the EDCTP General Assembly, the ultimate and exclusive decision-making body of EDCTP.

On 6 May, the Council of the European Union in its meeting on Economic and Financial Affairs (ECOFIN) approved the participation of the European Union in the EDCTP2 programme, in accordance with the proposal approved by the European Parliament on 15 April 2014.

May

From 30 June to 2 July 2014, the Seventh EDCTP Forum took place in Berlin, Germany. The conference received 359 participants from 43 countries, mainly from Africa and Europe. Its programme consisted of 120 oral presentations on a wide range of topics including: clinical research on HIV/AIDS, tuberculosis and malaria; interactions of these three diseases with neglected infectious diseases; cross-cutting topics on health capacity development and networking, policy, ethics and regulatory affairs. The majority of the presentations were by researchers involved in EDCTP-funded projects.

The EDCTP-funded SAREN project (South African Research Ethics Network) published the first guidebook on research ethics review written by African authors. The book *Research ethics in Africa: A Resource for Research Ethics Committees* was officially launched at the Seventh EDCTP Forum in Berlin.

June

October

A novel combination of the drugs rifapentine and moxifloxacin can reduce the number of tablets to be taken by patients from 360 to 140 (administered once a week) over the six-month tuberculosis treatment period. This reduction may help patients to adhere to treatment and help to counter the growing problem of drug resistance, which occurs when patients take their medications irregularly. These are the findings of the EDCTP-funded RIFAQUIN, published in the *New England Journal of Medicine* on 23 October.

On 31 October, EDCTP published the first call for proposals under its second programme, a joint call with WHO-TDR. The EDCTP-TDR Clinical Research and Development Fellowship scheme aims to develop human resources for high quality research and development in poverty-related diseases. Fellowships are expected to strengthen the skills of the best and most promising researchers from low- and middle-income countries (LMICs), to enhance and maximise their contribution in research organisations in LMICs. Successful candidates will be placed with 'host organisations', i.e. leading pharmaceutical companies and product development partnerships for a period of up to 24 months.

November

On 17 November, EDCTP published the Proceedings of the Seventh EDCTP Forum, held in Berlin, Germany from 30 June to 2 July 2014. The report gives a detailed overview of the research results presented and the discussions that took place. The report is available on the website (www.edctp.org). The report was accompanied by a video report with highlights from a lively and successful conference where a new, young generation of African researchers made their mark. The video is available on the EDCTP YouTube channel (www.youtube.com/edctpmedia).

December

A high-level event in Cape Town, South Africa marked the launch of the second EDCTP programme (EDCTP2) on 2 December 2014. The event was jointly organised by the European Commission and EDCTP, and hosted by the South African Department of Science and Technology. It provided an opportunity to discuss the role and strategic vision of EDCTP2 as well as explore possibilities for synergies with other international initiatives.

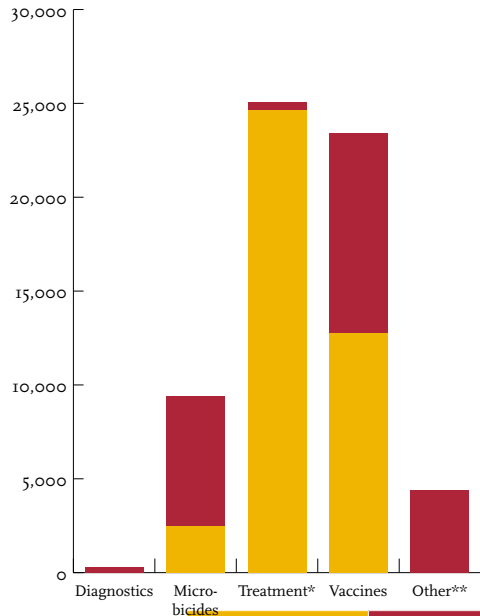
Immediately, EDCTP published two new calls under its new programme. The call for proposals on 'Diagnostic tools for poverty-related diseases' (with a budget of € 15 million for 4-8 grants) aims to fund projects that lead to rapid and simple diagnostics that can be deployed at low cost in health systems in resource-poor settings.

The call for proposals 'Maximising the impact of EDCTP research: translation of research results into policy and practice' (with a budget of € 3 million for 8-10 grants) aims to accelerate translation of research findings from EDCTP-funded activities into policy and practice in order to maximise their public health impact in sub-Saharan Africa.

HIV/AIDS

According to the UNAIDS report (2013), the annual mortality from HIV-related causes decreased with an estimated 22% from 2 million in 2009 to 1.5 million in 2013. Moreover, anti-retroviral therapy (ART) was provided to 12.9 million people globally, 11.7 million of them in low- and middle-income countries. Nevertheless, the 11.7 million people on ART represent only 36% of the estimated 32.6 million people living with HIV in these countries. The 2014 UNAIDS report 'Fast-track – ending the AIDS epidemic by 2030' sets out ambitious targets to reach and summarises the challenges to overcome in order to end the epidemic. Many of these challenges and barriers to progress are the subject of EDCTP-funded clinical trials.

HIV/AIDS funding of signed grants, 2003-2014 (€ '000)



	Clinical trial	Non trial
Diagnostics	-	€ 291
Microbicides	€ 2,455	€ 6,932
Treatment*	€ 24,659	€ 418
Vaccines	€ 12,754	€ 10,633
Other**	-	€ 4,373
Total	€ 39,868	€ 22,647

* Including funding to support projects on prevention of mother-to-child transmission of HIV

** Including immunology, epidemiology and cross-cutting issues.

HIV/AIDS research supported by EDCTP

Since 2003, EDCTP has invested € 62.5 million (29% of total EDCTP grant funding) to support 56 research projects on HIV/AIDS. The EDCTP portfolio on HIV/AIDS includes 20 treatment trials, second-line therapy and paediatric treatment and studies on HIV/TB co-infection. Six studies focus on the prevention of mother-to-child transmission of HIV. Eight vaccine trials, three trials on microbicides and one trial focused on mechanisms to maximise retention and adherence to treatment, have been supported.

The HIV/AIDS funding under the first EDCTP programme focused on the key prevention and treatment issues and challenges of research in sub-Saharan Africa. The EDCTP-commissioned bibliometric analysis reported that the normalised citation impact (NCI) of EDCTP-funded papers (2003-2011) was exceptionally high in the areas of HIV/AIDS (3.24) and HIV/TB co-infection (5.10) compared with global research benchmarks (1.14 and 1.35, respectively). A high citation index indicates that a publication has had a major impact on the field and possibly that the research was of high importance. This high citation index for EDCTP-funded research demonstrates the success of the funding strategy of the first programme to support research on key clinical challenges and policy-relevant questions in HIV/AIDS in sub-Saharan Africa. With the release in 2014 of several high profile publications, it is anticipated that EDCTP-funded research publications will retain and/or improve upon this high citation index in the period 2012-2016.

Prevention of mother-to-child transmission of HIV

Significant progress has been made in the prevention of mother-to-child transmission of HIV (PMTCT). In the first half of 2014, the number of pregnant women receiving antiretroviral medicines rose by 13%, compared to the first half of 2013, as the world progressed towards the targets of the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. The results of the Kesho Bora study, financed by several funders including EDCTP, supported the 2010 revised WHO guidelines 'Antiretroviral drugs for treating pregnant women and preventing HIV infections in infants'. Intensive efforts at international level to implement PMTCT and eliminate the mother-to-child transmission of HIV have resulted in a 40% decrease in the number of children newly infected with HIV in low- and middle-income countries to an estimated 240,000 in 2013.

However, it is still estimated that more than 200,000 children per year become infected as a result of breast milk transmission. The PROMISE-PEP trial aimed to prevent post-natal transmission of HIV through provision of a prophylaxis during the breastfeeding period (peri-exposure-prophylaxis: PEP). The trial, led by Professor Philippe Van de Perre (Montpellier University Hospital Centre (CHU), France), was carried out in Burkina Faso, South Africa, Uganda and Zambia to investigate the safety and efficacy of prolonged (50 weeks) peri-exposure prophylaxis in infants

born to HIV-infected mothers not eligible for highly active anti-retroviral therapy (HAART). Preliminary results of the trial showed a transmission rate of 1.1% at 12 months (the lowest ever reported) and a survival rate of 96% among infants who remained uninfected for a period of 50 weeks (highest ever reported). The trial, which completed in 2014, has provided its findings to the WHO expert panel reviewing the guidelines for the prevention of mother-to-child transmission of HIV.

HIV diagnosis and treatment in children

Expansion of diagnosis and provision of anti-retroviral therapy (ART) for children have been highlighted as key challenges by UNAIDS in the light of recent data indicating that less than one quarter of HIV-infected children are receiving treatment. EDCTP has been highly active in funding research to address this challenge.

EDCTP supported the development of paediatric formulations of ART through the CHAPAS-1 trial, which contributed to the data that led to the USA Food and Drug Authority (FDA) approval of the use of Triomune Baby/Junior for HIV-infected children. The CHAPAS-1 trial, led by Professor Chifumbe Chintu (University Teaching Hospital, Zambia) also provided data to support the WHO recommended weight-band dosing tables for ART. Following on from this, the CHAPAS-3 trial, led by Dr Veronica Mulenga (University Teaching Hospital, Zambia) has provided important data on optimal first-line anti-retroviral (ARV) regimens for treatment of HIV-infected children in Africa.

The findings were presented at the Seventh EDCTP Forum and showed that the three regimens tested were well tolerated and that there was no difference in the primary toxicity end-point. These important results confirm that ART given as WHO-recommended fixed-dose combinations is highly effective in children. The trial also included analyses of adherence/acceptability, cost-effectiveness and viral load suppression. The data on efavirenz have been shared with the USA FDA for preregistration of the new, scored 600mg efavirenz tablet and the CHAPAS-3 trial results will be shared with the WHO for prequalification of these fixed-dose combination drugs. The trial findings, which will be published in 2015, indicate that priority must be given to early diagnosis and treatment in order to expand treatment to all HIV-infected children.

Prof. Philippe Van de Perre

The issue of HIV-1 transmission through breastfeeding exists because in many places in sub-Saharan Africa, women are confronted with a cruel dilemma to provide their children with the best possible feeding. Breast feeding is best suited for infant growth but at the same time increases the risk of transmitting HIV-1. Apparently, these women have little choice since infant formula feeding is not safe in most of these countries and is associated with high morbidity and poor infant growth. In addition, formula feeding is not the social norm, thereby carrying a major risk of stigma.

Another issue of concern is that researchers from developed countries where postnatal transmission does not exist have been reluctant to give prophylactic antiretrovirals to children for prolonged period of time. Despite the many studies addressing HIV-1 transmission through breastfeeding, PROMISE-PEP is the first one that covers the whole duration of exposure to HIV with a prophylactic drug.

The WHO has recommended another option to reduce postnatal transmission and this involves systematically treating all pregnant women with antiretrovirals therapy (ART), irrespective of their CD4 count. However, we have now learnt that this strategy is not as effective as we thought it would be, for several reasons, including classical programmatic issues and more surprisingly, drug adherence problems. One year after initiation, almost half of the women were no longer on ART, leaving their children unprotected during breastfeeding. Finally, our group showed that HIV could be transmitted from infected breast cells (and not only the 'free' virus) which are not impacted by ART, thus contributing to residual transmission despite maternal ART.

The PROMISE-PEP studies investigated the extent to what infant prophylaxis given from birth until the end of breastfeeding (one year) could reduce HIV transmission. For this purpose, we compared two already known drugs for HIV care: lamivudine and lopinavir/ritonavir.

PROMISE-PEP team at CROI 2014 in Boston MA, United States.

"By reducing the HIV risk to a minimum, this strategy allowed the women to breastfeed safely, which is the best they can do for their children. We also encouraged and counselled women to exclusively adopt breastfeeding for the first six months, which further reduces morbidity, HIV risk, and may improve infant growth."

Prof. Philippe Van de Perre
PROMISE-PEP Project Coordinator

The concept of pre-exposure or post-exposure prophylaxis using ART has long been proven effective in adults. For example, ART is given for a short period of time (1-3 months) after accidental (through blood, for health care workers) or high-risk sexual exposure to HIV in adults. Several trials have also validated the hypothesis that ART taken before exposure could prevent sexual transmission of HIV. We adapted this strategy to postnatal transmission, where infants are almost continuously exposed to HIV through breastmilk. Nevertheless, the detailed understanding of how these drugs work when used as a prophylaxis is not fully understood.

In our studies, it was revealed that infant prophylaxis using ART for one year can achieve a very low rate of HIV-1 transmission through breastfeeding. This strategy proved safe, although we will continue to follow up these children to ensure that infant ART does not diminish their development in the long-term. However, the transmission rate in our study still existed, mainly due to drug adherence issue. There is still room for improvement to achieve zero transmission and no more children living with HIV in the future.

By reducing the HIV risk to a minimum, this strategy allowed the women to breastfeed safely, which is the best they can do for their children. We also encouraged and counselled women to exclusively adopt breastfeeding for the first six months, which further reduces morbidity, HIV risk, and may improve infant growth.

This study was carried out by a consortium of several university teams from Africa (Burkina Faso, South Africa, Uganda and Zambia) as well as from France and Norway. All these teams have been working together for a long time and one of the aims of this consortium was to build the African capacities to develop and implement this kind of research, which involves many disciplines including biology, medical care, data management, counselling.

The study was developed and implemented together within the consortium. We transferred to laboratories in Africa all required techniques to conduct the project. Now they are also used for routine practise (e.g. infant diagnosis, viral load) with international quality standards (including quality control scheme).

In addition, during the project, four African investigators and one European student completed their PhD (virology, clinical epidemiology) in European universities, Bergen and Montpellier, and six students also completed their MSc in Europe.

Although we have made much progress to tackle breastfeeding transmission of HIV1, we now have the tools to eliminate it. This will happen through two aspects: (a) addressing the programmatic challenges that are still very frequent in many African countries which include access to antenatal care, procurement of HIV tests and ART in care setting; (b) the need to revise the current strategy which leaves too many children with HIV infection. A one-size-fit-all strategy may not cover all the needs and requirements in the various settings and individual situations. Our findings will certainly contribute to the elimination of mother-to-child transmission of HIV through breastfeeding.

EDCTP had a pivotal role in the success of this study primarily through their great financial support. The organisation, through the Project Officer, was also very helpful and supportive to address the many issues that we came across during the course of such a large study.

PROMISE-PEP

Official title:
A randomised controlled trial comparing the efficacy of infant peri-exposure prophylaxis with Lopinavir/Ritonavir (LPV/r) versus Lamivudine to prevent HIV-1 transmission by breastfeeding.

Project Coordinator:
- Prof. Philippe Van de Perre, France (CHU, France)

Cofunders:
- EDCTP
- French National Agency for Research on AIDS and Viral Hepatitis (ANRS, France)
- The Research Council of Norway (Norway)
- Swedish International Development Cooperation Agency (Sida, Sweden).

Total budget: € 11,737,854
EDCTP budget: € 1,986,854

Second-line treatment

Anti-retroviral therapy is highly effective in preventing or reversing the decline in immune function in HIV-infected patients. However, increasing HIV resistance to ART is making it necessary to switch therapy to a second-line or even third-line treatment. Following the massive rollout of ART in Africa, large numbers of people are receiving first-line therapy and growing numbers are developing treatment failure and requiring second-line therapy. Given the high cost of second-line therapies, it is important that a strong evidence base guides treatment policy and optimises drug use in sub-Saharan Africa.

The EARNEST trial, led by Prof. Peter Mugyenyi (Joint Clinical Research Centre, Uganda) and Prof. Nick Paton (Medical Research Council, UK), is the largest documented study of second-line treatment conducted in sub-Saharan Africa. A total of 1,277 adults and adolescents with HIV infection and first-line treatment failure were randomised to one of four treatment arms and followed for 144 weeks.

The trial, which reported its findings in the *New England Journal of Medicine* in 2014, showed that combining a boosted protease inhibitor with raltegravir, a heat-stable integrase inhibitor, to create a second-line regimen with two completely new drug classes was not superior to nucleoside reverse transcriptase inhibitors (NRTIs). The raltegravir-containing regimen is significantly more expensive and therefore not suitable as a standard second-line regimen for large-scale use in low-income settings. Protease inhibitor monotherapy was shown to be inferior in terms of suppressing viral load. This trial provided gold standard evidence to support the WHO-recommended regimen of a boosted protease inhibitor (in this case, lopinavir). The trial results have been included in the 2014 revision of the International Antiviral Society-USA HIV treatment guidelines and have been made available to WHO.

Prof. Peter Mugyenyi

Following the massive rollout of antiretrovirals therapy (ART) in Africa, a large number of people are receiving first-line ART, and over the coming few years an increasing number will be developing treatment failure and requiring second-line therapy. There is an urgent need to develop the evidence base for second-line therapy in Africa and other low-income countries where there is extensive nucleoside analog reverse-transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) resistance at the time of failure and it is likely that the virological potency of the second-line regimen is mostly due to the boosted protease inhibitor (bPI). There is increasing evidence from randomised trials that lopinavir/ritonavir can achieve excellent results when used alone. In addition, the development of new drug classes has widened the possibilities for effective second-line therapy and increased the number of viable second-line treatment options that need to be evaluated.

The WHO 2013 guidelines for second-line therapy were based on poor to moderate quality evidence (no randomised controlled trial data). The 2015 guidelines will have very high quality evidence from a definitive trial that was conducted in a way that is directly relevant to the public health approach to ART delivery. The impact of these guidelines is that they enable the standardisation of clinical practice by informing healthcare workers of the best management approaches relevant to their settings. They also guide national programme policy and drug procurement decisions. The EARNEST trial aims to inform the WHO 2015 guidelines for second-line therapy.

The main objectives of the EARNEST trial were to determine whether a combination of lopinavir (Aluvia) with raltegravir was superior to the standard of care for second-line HIV therapy comprising of a combination of Aluvia with two recycled NRTIs, and to determine whether Aluvia monotherapy was non-inferior to the standard of care combination

"The findings showed that the WHO recommendations for second-line therapy were actually correct, as it provided the evidence to support the previously non-evidence-based policy."

Prof. Peter Mugyenyi
EARNEST trial Project Coordinator

During our studies, the standard-of-care combination did exceedingly well, with high levels of viral load suppression at 96 weeks, sustained out to 144 weeks. The raltegravir combination also did well, but it was not superior to the standard-of-care combination. This is reassuring. However the PI monotherapy option was inferior to standard of care in terms of viral load suppression and had more resistance.

The findings showed that the WHO recommendations for second-line therapy were actually correct, as the study provided the evidence to support the previously non-evidence-based policy. It also showed that there was no need to bring raltegravir forward to second-line therapy from its current position in third-line, and the trial showed that PI monotherapy should not be used in the public health approach, a question that had been discussed for the previous 5-10 years.
The network contained a mixture of experienced and new clinical trial sites, and there was significant transfer of knowledge from the experienced sites (as well as the trial coordinating centre) to build capacity at the less experienced sites. The trial also increased the awareness and confidence of the medical staff at the sites in recognising first line failure, and appropriately managing the switch to second-line therapy. Several members of the research team studied for MSc or PhD degrees around the trial. The trial strengthened networking amongst sites in 5 African countries.

The problem of HIV in Africa remains a formidable challenge, because the epidemic rages on and unacceptably high numbers are daily being infected. The objective of new roll out should be aimed at ending the epidemic. To achieve this, it requires treating HIV early (Test and Treat) as treatment is highly effective as prevention. This is over and above other established preventive initiatives. Further, treatment must use the best available first-line drugs (evidence based) closely monitored with VL as it is most effective in detecting emerging resistance. It also requires monitoring of resistance which enables early intervention to and determines timely switch to second line or third-line drugs. Besides helping to reduce widespread resistance, it also reduces costs as wasteful use of ineffective drugs will be minimised.

EDCTP funded the EARNEST trial. It also ensured that the project timelines were met and that a tight rein was kept on expenditure to complete the trial within budget.

Members of the EARNEST team at the Investigators' Meeting on 13-14 February 2014 in Kampala, Uganda

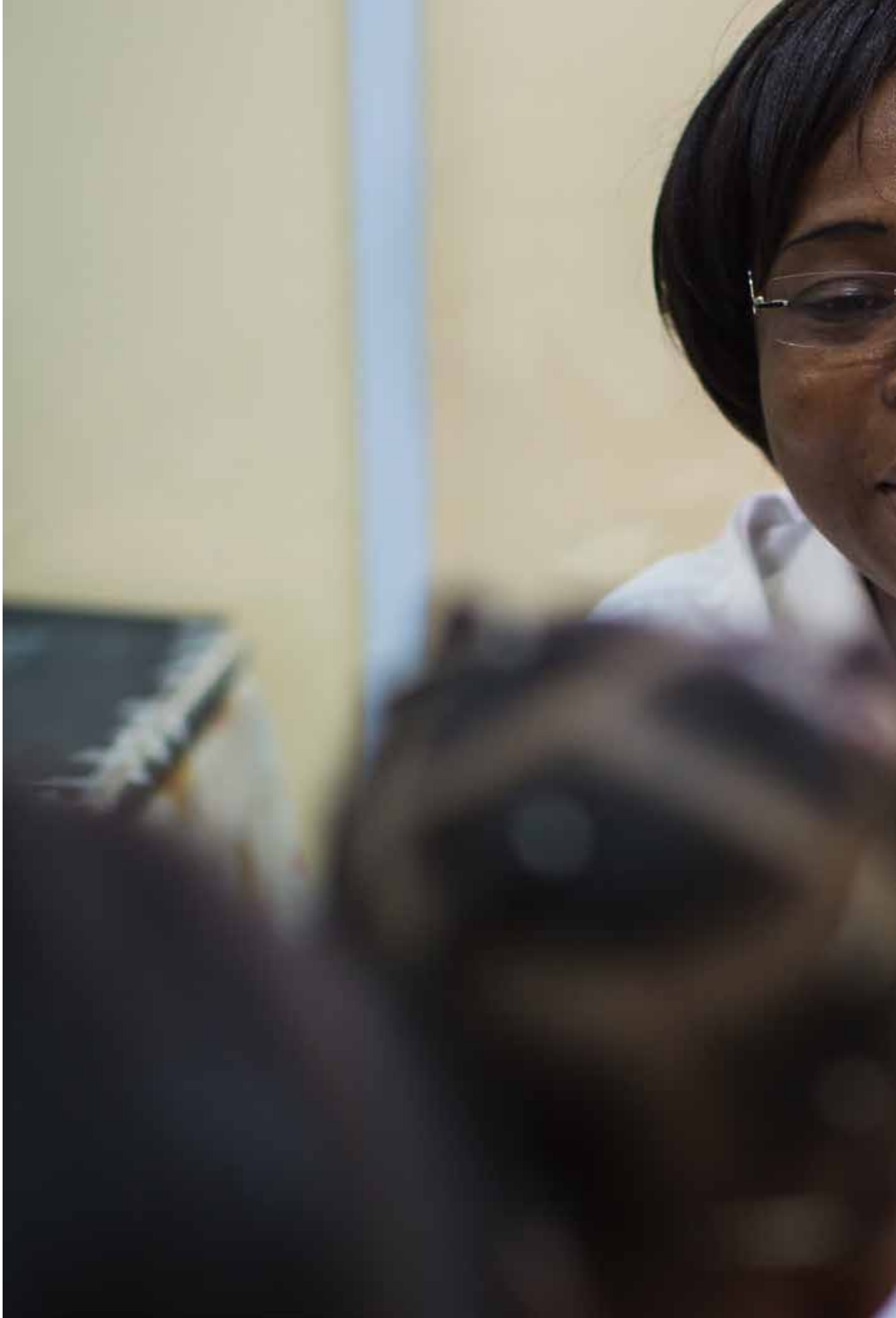
EARNEST trial

Official title:
The Europe - Africa Research Network for Evaluation of Second-Line Therapy: The EARNEST Trial

Project Coordinators:
- Prof. Peter Mugyenyi (Joint Clinical Research Centre, Uganda)
- Prof. Nick Paton (UK Medical Research)

Cofunders:
- EDCTP
- Carlos III Health Institute (Spain)
- Department for International Development (DfID, United Kingdom)
- Department of Foreign Affairs, Ireland
- Istituto Superiore di Sanità (Italy)
- Medical Research Council UK
- Merck & Co. Inc (United Kingdom)
- Prince Leopold Institute of Tropical Medicine (Belgium)
- Swedish International Development Cooperation Agency (Sweden)

Total budget: € 5,050,857
EDCTP budget: € 1,844,570

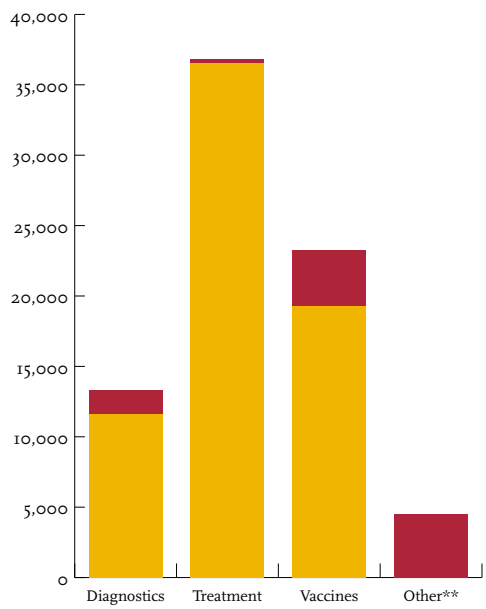


Tuberculosis

Tuberculosis (TB) remains an epidemic in much of the world, causing the deaths of nearly 1.5 million people in 2013, mostly in developing countries. Every year approximately 9 million people fall ill with TB. A third of them are not reached and consequently not treated. Unmistakably, tremendous progress has been made in recent years, and the world is on track to meet the Millennium Development Goal of reversing the spread of TB by 2015. But it is not enough. Drug-sensitive and drug-resistant TB constitute a global health security threat.

In May 2014, at the World Health Assembly, governments agreed on an ambitious new 20 year (2016-2035) strategy to end the global TB epidemic. The strategy sets out key challenges and targets, including early diagnosis, universal drug-susceptibility testing; treatment of all people with TB and management of co-morbidities, especially HIV-TB co-infection. The report calls for intensified research and innovation to focus on discovery, development and rapid uptake of new tools, interventions and strategies, as well as research to optimise implementation and impact. EDCTP's portfolio of tuberculosis projects covers many of these highlighted areas.

Tuberculosis funding of signed grants, 2003-2014 (€ '000)*



	Clinical trial	Non trial
Diagnostics	€ 11,583	€ 1,731
Treatment	€ 36,539	€ 273
Vaccines	€ 19,250	€ 4,005
Other**	-	€ 4,530
Total	€ 67,372	€ 10,539

* Total funding including studies on HIV/TB co-infection
** Including studies on immunology, epidemiology and cross-cutting issues

TB research supported by EDCTP

The EDCTP portfolio on TB reflects a diverse range of diagnostics studies as well as treatment and vaccine trials. TB research received the largest share of the funding in the project portfolio of EDCTP's first programme, with a total of € 70.68 million (33.3%) for 36 projects. Additionally, EDCTP invested € 7.23 million (3.4% of total EDCTP grant funding) to support 12 research projects on HIV/TB co-infection.

In its first programme, EDCTP's funding strategy for TB research has focused on the key issues and challenges in sub-Saharan Africa, recognising the impact of HIV/TB infection in this region. An EDCTP-commissioned bibliometric analysis has tracked the increasing prominence of this region in TB and HIV/TB research, showing that TB research output in sub-Saharan Africa increased by 81% between 2003 and 2011. EDCTP-funded TB and HIV/TB publications had an exceptionally high citation impact (NCI: 4.08) that was more than four times the world average. Of note, EDCTP-funded research papers on HIV/TB co-infections were cited more than five times the world average (5.1). With the release in 2014 of several major publications from EDCTP-funded trials, the high citation impact of EDCTP-funded research on TB is expected to continue.

TB diagnostics

EDCTP has made considerable investment in research into TB diagnostics, through a diverse portfolio of research studies from early stage testing of biomarkers, evaluation of new and improved diagnostics through to implementation of diagnostics in a real life setting.

A Senior Fellowship awarded to Professor Mark Nicol (University of Cape Town, South Africa) provided supporting data leading to the WHO endorsement of GeneXpert in December 2010. Following on from the WHO endorsement, a rapid roll-out of GeneXpert has occurred. The TB-NEAT consortium, supported by EDCTP and led by Prof. Keertan Dheda (University of Cape Town, South Africa), has measured the clinical effect of GeneXpert, which is an expensive intervention, by looking at its performance in well-managed primary-care health care facilities in four countries. The study, published in *The Lancet* in 2014, showed that GeneXpert can be administered accurately by a nurse in primary-care clinics, resulting in more patients starting same-day treatment, more culture-positive patients starting therapy, and a shorter time to treatment. However, the benefits did not translate into lower TB-related morbidity, partly because of high levels of empirical evidence-based treatment in smear-negative patients.

Diagnosis of TB in children is challenging because children tend to have lower levels of infectious bacteria, making it harder to detect by microscopy and to grow in culture, and because sputum induction in young children is difficult. The EDCTP-funded TB-CHILD consortium, led by Dr Fred Lwilla (Ifakara Health Research and Development Centre, Tanzania) and Dr Klaus Reither (Swiss Tropical and Public Health Institute, Switzerland), has explored the performance of several diagnostic tests in children.

Limited data exist on the performance of GeneXpert in diagnosing TB in children. The TB-CHILD consortium assessed the diagnostic accuracy of GeneXpert using culture-confirmed TB cases as the reference standard in a study of 451 children in Tanzania and Uganda. GeneXpert provided timely results with moderate sensitivity and excellent specificity, detecting 1.7 times more culture-confirmed cases than smear microscopy with a similar time to detection. However, low yields in children with highly probable and probable TB remain problematic, making the search for new sputum-independent diagnostics a priority.

The consortium also reported positive results from a study of a new sputum-independent assay, known as TAM-TB, in *The Lancet Infectious Diseases* in 2014. The TAM-TB assay is the first immunodiagnostic tool which can detect active tuberculosis disease in children with sensitivity similar to culture and with excellent specificity in a tuberculosis-endemic setting.

Dr Klaus Reither

TB in children contributes significantly to the burden of the disease in Africa. An accurate diagnosis in children in TB-endemic settings remains challenging for various reasons, but particularly because it is very difficult to collect sputum samples from younger children. In addition Mycobacterium tuberculosis *is often not detectable in paediatric specimen with low bacillary load, and host biomarkers are not yet in place to reliably identify active TB. Moreover, symptoms and radiological features are non-specific and overlap with those of other diseases, such as pneumonia, malnutrition or HIV-associated diseases.*

For these reasons, in Africa the diagnosis is routinely made on the basis of a combination of clinical features, contact history, chest radiography, and a tuberculin skin test, and often with scoring charts that have poor diagnostic accuracy. Consequently, it is essential to continue research to find better, preferably non-sputum-based diagnostic approaches.

Therefore, the TB CHILD project aimed to develop or evaluate a variety of new diagnostics for paediatric TB. Moreover, developing sustainable, collaborative research capacity for the diagnosis of childhood TB in parts of sub-Saharan Africa was embedded in the project.

We developed the T cell activation marker–TB (TAM-TB) assay, a blood test which measures specific immune defence markers within less than 24 hours. Specifically, the assay measures the CD27 expression of CD4 T cells producing interferon gamma in response to Mycobacterium tuberculosis *antigen stimulation using a standard intracellular cytokine staining procedure and polychromatic flow cytometry. In case of active TB, the CD4 T cells down-regulate the cell surface protein CD27, which allows for a differentiation between latent and active TB.*

We were able to demonstrate in a proof-of-concept study that the TAM-TB assay can detect active TB disease with high

"TAM-TB assay has the potential to advance the diagnosis of childhood TB on district level by delivering accurate results within one day."

Dr Klaus Reither
TB-CHILD Project Manager

sensitivity and specificity in children living in a TB-endemic setting. The TAM-TB sub-study was conducted by an international research team from the Department of Infectious Diseases and Tropical Medicine of the Ludwig-Maximilian-University of Munich (Germany), the Swiss Tropical and Public Health Institute (Switzerland), the NIMR-Mbeya Medical Research Centre and the Ifakara Health Institute (Tanzania).

In order to develop the current, still complex version of the TAM-TB assay into a diagnostic tool which can be used in communities in resource-poor settings, several further steps of development and simplification are planned. Ultimately, the TAM-TB assay should become compatible with flow cytometers that are currently in widespread use for measuring CD4 T cell counts in HIV/AIDS-affected countries. In this way, the TAM-TB assay has the potential to advance the diagnosis of childhood TB at district level by delivering accurate results within one day.

Capacity development was an essential part of the TB CHILD project. Initially, when the sites in Tanzania and Uganda began participation in the TB CHILD project, they had different levels of experience, expertise and TB research infrastructure. First we did a need assessment and team building. The TB CHILD sites and staff then received important support through short-term and postgraduate training programmes, networking activities and a research infrastructure upgrade. African and European investigators worked in a spirit of mutual learning and were able to successfully conduct Good Clinical Practices (GCP)-compliant trials at the three clinical sites. Through the TB CHILD project, these sites are now similarly skilled and equipped for further TB trials.

EDCTP provided this needed opportunity to conduct trials on diagnosis of paediatric TB in East Africa and the essential support for TB CHILD research studies, capacity building and a long-term perspective in the fight against TB.

Nevertheless, definitive TB diagnosis in children is still a challenge in Africa, as well as worldwide. Consequently, there is still an urgent need for (possibly sputum-independent) biomarkers for the diagnosis of active TB disease in symptomatic children. Potentially, TAM-TB is one such candidate assay, using CD27 as a marker, which needs to be further optimised, simplified and validated.

More generally, there is a need for more collaborative, international groups of scientists to define priorities, to address research gaps and to catalyze efforts towards harmoniation and collaboration in research on TB diagnostics for children.

Finally, better diagnostics might not be enough to improve the situation of the children who are suffering from TB or are at risk. In addition to better drugs and vaccines, we need to strengthen health systems (including the national TB programmes), reduce stigma, improve health education, develop better control strategies for HIV/AIDS, and fight against inequity and poverty. This is equally important to avoid an unnecessary TB disease burden among children.

TB CHILD

Official title:
Evaluation of new and emerging diagnostics for childhood TB in high-burden countries

Project Coordinators:
- Dr Fred Lwilla (Ifakara Health Research and Development Centre, Tanzania)
- Dr Klaus Reither (Swiss Tropical and Public Health Institute, Switzerland)

Cofunders:
- EDCTP
- Aispo-Nsambya Hospital (Uganda/Italy)
- Bundesministerium für Bildung und Forschung (BMBF, Germany)
- FIND (Switzerland)
- Fondazione Centro San Raffaele del Monte Tabor (Italy)
- Ministry of Foreign Affairs – Italian Directorate for Development Cooperation (Italy)
- LMU-Klinikum of the University of Munich (Germany)
- State Secretariat for Education and Research SER/Swiss National Science Foundation (Switzerland)
- Swiss Agency for Development and Cooperation (SDC, Switzerland)

Total budget: € 3,331,073
EDCTP budget: € 1,495,737

TB treatment

Control of drug-susceptible TB is reliant on a standard six-month treatment that has been in place for more than 30 years. EDCTP has supported several clinical trials aiming to shorten and simplify TB treatment as this could improve patient adherence, reduce toxicity and decrease treatment costs.

The EDCTP-funded Pan African Consortium for Evaluation of Antituberculosis Antibiotics (PanACEA) explores new drugs that have the potential to shorten TB treatment. The consortium was formed to conduct a series of cooperative clinical trials to evaluate three different drugs (Moxifloxacin, Rifampicin and SQ109) for the treatment of drug-sensitive tuberculosis to simplify and shorten the current regiments. The consortium, which comprises of four European universities and 12 African clinical trial centres, aimed to establish a sustainable framework for clinical trials of TB drugs.

One of EDCTP's most ambitious trials, REMoxTB, is one of the projects under the umbrella of PanACEA. This phase III global clinical trial of new TB drug regimens, cofunded by the TB Alliance, reported its results in the *New England Journal of Medicine* in 2014. EDCTP supported the trial sites in sub-Saharan Africa which contributed approximately 70% of the 2,000 patients enrolled in the trial. The trial aimed to shorten the treatment time for TB from six to four months by replacing one of the drugs in the standard six-month treatment regimen with moxifloxacin. The trial, led by Prof. Stephen H. Gillespie (St. Andrews University, Scotland), showed that the test regimen although demonstrating greater bactericidal activity at the start of treatment was inferior to the standard treatment. Patients on the test regimen were more likely to relapse than those on the standard six-month regimen.

The PanACEA consortium also conducted the MAMS-TB-01 study, a multi-arm multi-stage trial to identify regimens to include in a phase III trial for shorter treatment of TB. The MAMS design allows for several different treatment regimens to be evaluated against the standard regimen for TB in a single trial. During the course of the trial, interim analyses are conducted at planned intervals where poorly performing regimens can be dropped based on pre-specified rules outlined in the protocol. In this way, poorly performing regimens are dropped early in the trial and only those that perform better than pre-specified thresholds are continued for evaluation against the common control. In summary, this trial methodology enables an efficient evaluation of multiple experimental treatment arms within one study by eliminating inefficient treatment arms at an early stage. The study completed enrolment of 365 patients from 7 sites in Tanzania and South Africa in March 2014.

The EDCTP-funded RIFAQUIN trial, led by Dr Amina Jindani (INTERTB Consortium at St George's, University of London), tested two regimens in which moxifloxacin replaced isoniazid in an intensive phase that was followed by either two months of standard-dose rifapentine and moxifloxacin twice weekly or four months of high-dose rifapentine and moxifloxacin once weekly. The six-month regimen that included weekly administration of high-dose rifapentine and moxifloxacin was as effective as the control regimen. However, the four-month regimen was inferior to the control regimen. The once-weekly drug combination (which reduces the total number of tablets to be taken from 360 to 140) offers the potential to increase adherence, particularly in countries where clinics are severely under-resourced and may have difficulties supervising treatment and where patients may have to travel many miles to receive treatment. Increased adherence to treatment may help to counter the growing problem of drug resistance, which may occur when patients take their medication irregularly. The findings of the RIFAQUIN trial were published in the *New England Journal of Medicine* on 23 October 2014.


sunware
Q-line box

Prof. Martin Boeree

Prof. Michael Hoelscher

Prof. Stephen Gillespie

There is a large body of evidence of preclinical data, such as compelling data in mice and clinical trials in humans as far as phase II that points towards the potential to shorten TB treatment duration. However, until now there has been no successful phase III trial providing evidence that shorter treatments are sufficiently effective using a classical non-inferiority design. Recently, three phase III clinical trials with quinolones were published in the New England Journal of Medicine *which showed no non-inferiority for treatment of four months duration. Yet, the cure rates of the "inferior" arms were around 85%.*

There are many challenges in the search for a shorter regiment to treat TB. For example, the development of drugs in the past was often done independently, without testing for suitable companion compounds. This heightens the risk that a valuable potent drug will be lost through the emergence of drug resistance. In the past, drugs were also added to a regimen without knowing the correct dose as in the case of rifampicin. Additionally, current surrogate endpoints, such as 8 weeks culture conversion rates or hazard ratios have limited predictive value for the final relapse-free cure endpoint. This suggests that phase II studies should do a basic assessment of relapse before moving the candidate into the very expensive phase III trials. Furthermore, testing new regimens is very challenging and expensive. Innovative, more rapid methods are required that can be approved by regulators.

The PanACEA consortium has tried to address these issues. The main aim of PanACEA was to develop the capacity of African researchers and research sites to perform relevant clinical trials that would improve the outcome of TB treatment. Thus, we focused on the effective, efficient conduct of the selected clinical trials and on establishing a long-lasting framework to benefit future trials of TB drugs.

More specifically, the objectives of PanACEA were to develop new regimens for shortening and simplifying TB treatment from the current 6 months to 4 months. This was done through regulatory-quality EBA, phase II and III clinical trials. PanACEA initially started with three independent groups (REMox, HIGHRIF and SQ109) that shared a common capacity development approach. We quickly understood that additional value could be obtained by pooling our resources and expertise to create innovative research methods. We created a "lean and mean" management structure for a large collaboration with more than 15 centres to ensure that we could respond rapidly to the changing research environment. We developed the Multi-Arm Multi-Stage (MAMS) approach for TB clinical research which allowed us to explore the optimal dose of rifampicin and a novel drug. A scientific oversight group was put in place which was helpful in providing external input to critical decisions and validating the discussions of the research group.

As part of the PanACEA consortium, the REMoxTB trial recruited 1,931 patients (with more than 1,300 in Africa) in order to investigate the proposition that moxifloxacin containing regimens might be more bactericidal and thus allow for treatment shortening. However, the results of the trial showed that both moxifloxacin containing regimens were more bactericidal, but that the four month regimens were not non-inferior.

This seems to indicate that, even though patients on the regimens containing moxifloxacin were culture-negative significantly faster, a population of bacterial cells remained that caused a higher relapse rate. In the PanACEA HIGHRIF studies we were able to show that higher doses of rifampicin (3.5 times higher than the current dose) were more bactericidal. Careful mathematical modelling of the data from this trial indicated that this improvement may be attributed rifampicin killing a population of cells that are associated with relapse. The PanACEA MAMS TB 01 study has also investigated this higher dose of rifampicin and this has shown very exciting

"The trials that we performed and the focus on capacity development have created an African-European partnership that is successful, innovative and sustainable."

Prof. Martin Boeree,
PanACEA HIGHRIF Project Coordinator

improvements in the speed of bacterial elimination. Further trials will be needed to explore this intriguing result more thoroughly as will trials of new drugs targeted on dormant bacilli.

The trials we performed and the focus on capacity development have created an African-European partnership that is successful, innovative and sustainable. The regulatory clinical trials REMoxTB, HIGHRIF, SQ109 and MAMS studies were very successful in developing clinical research capacity across Africa. We now have a number of outstanding research sites and investigators who are valued by international researchers as collaborators. The EDCTP-funded PanBIOME project, which has grown out of the PanACEA consortium, will build infrastructure and research capability in molecular diagnostics and treatment monitoring in TB.

PanACEA

Official title:
Pan African Consortium for Evaluation of Antituberculosis Antibiotics (PanACEA)

Projects:
- REMox: Rapid Evaluation of Moxifloxacin in the treatment of sputum smear positive TB: REMoxTB
- HIGHRIF: Rapid evaluation of high-dose rifamipicin and other rifamycins in TB
- SQ-109: Evaluation of a novel TB drug (SQ109) to shorten and simplify TB treatment

Project Coordinators:
- Prof. Stephen Gillespie (University College London, UK)
- Prof. Martin Boeree (Radboud University Nijmegen, Netherlands)
- Prof. Michael Hoelscher (Ludwig-Maximilians Universität München, Germany)

Cofunders:
- EDCTP
- Bayer (Germany)
- Bill & Melinda Gates Foundation (USA)
- Federal Ministry of Education and Research (BMBF, Germany)
- Global TB Alliance (USA)
- Institute for Medical Bioinformatics (Germany)
- Klinikum der Universität München (Germany)
- Medical Research Council (UK)
- Medical Research Council South Africa (South Africa)
- Netherlands Organisation for Scientific Research (NWO, Netherlands)
- Prince Leopold Institute of Tropical Medicine (Belgium)
- Radboud University Nijmegen (Netherlands)
- Sanofi-Aventis (France)
- Sequella (USA)
- Swiss Tropical and Public Health Institute (Switzerland).

Total budget: € 14,121,728
EDCTP budget: € 6,945,088

TB vaccines

Two of the five EDCTP-funded TB vaccine trials have reported their findings in 2014. The phase II trial (Aeras 402/Crucell Ad35) was carried out in Kenya, Mozambique and South Africa. Although the safety profile of the vaccine was excellent, the immunogenicity results were disappointing. The vaccine will not proceed further in the development pipeline, although studies are currently underway (funded by Aeras, Crucell and Oxford University) to test whether the immune responses can be boosted by giving a dose of the MVA85A vaccine candidate.

The EDCTP-funded phase II trial of H1/IC31® in HIV-infected adults (CD4+ lymphocyte counts > 350 cells/mm3) in South Africa and Tanzania reported that the vaccine was well tolerated and safe. It induced a specific and durable Th1 immune response. This vaccine will be developed further by adding a latency-associated antigen added to the H1/IC31® backbone in order to boost the immunogenicity.

The EDCTP-funded trials of the MVA85A vaccine and the THYB-04 vaccine were completed in 2014. The results are expected to be published in 2015.

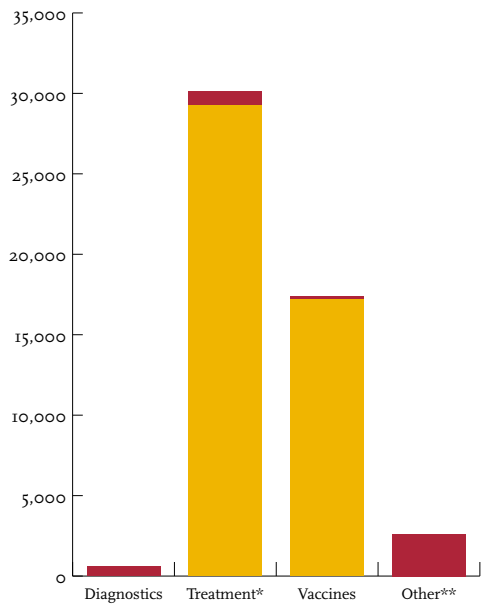

BROKEN GLASS

Malaria

According to the WHO World Malaria Report 2014, 198 million cases of malaria occurred globally in 2013 and the disease led to 584,000 deaths. The burden is heaviest in sub-Saharan Africa, where an estimated 90% of all malaria deaths occur. Children younger than five years old account for 78% of all malaria deaths.

In its first programme, EDCTP funding strategy focused on clinical studies of high relevance to sub-Saharan Africa, in particular, research on malaria treatment for high-risk populations including children and pregnant mothers, as well as HIV-infected individuals, and the development and testing of malaria vaccine and drugs.

Malaria funding: signed grants 2003-2014 (€ '000)



	Clinical trial	Non trial
Diagnostics	-	€ 595
Treatment*	€ 29,270	€ 857
Vaccines	€ 17,166	€ 191
Other**	-	€ 2,613
Total	€ 46,436	€ 4,256

* Including funding to support studies on malaria in pregnancy
** Including studies on immunology, epidemiology, parasitology and cross-cutting issues

Malaria research supported by EDCTP

In the EDCTP portfolio on malaria research, there are a total of 22 antimalarial drug trials, including prevention/chemoprophylaxis and treatment trials. In addition, EDCTP has supported 12 clinical trials for malaria vaccines in the first programme. Since 2003, malaria research has received € 50.69 million of funding (23.9% of total EDCTP grant funding) through a total of 42 grants.

EDCTP's funding strategy for malaria has focused on important clinical issues of high relevance to sub-Saharan Africa, in particular, research on malaria treatment in special populations. Such studies are highly challenging to conduct but can produce valuable evidence to guide treatment policy. A bibliometrics analysis commissioned by EDCTP showed that Europe accounted for 43.4% of the world output for malaria research papers and sub-Saharan Africa 21%. The NCI (normalised citation impact) of EDCTP-funded malaria papers was 1.70, which was slightly higher than the benchmark for global research in malaria (NCI: 1.24). Five papers resulting from EDCTP funding were noted as being very highly cited (NCI ≥ 8 or ≥4 and ≤ 8) during 2003-2011. Several of the malaria studies supported by EDCTP are likely to influence national or international policy.

Malaria treatment

Some of the antimalarial drug and treatment trials are phase IV post-marketing studies evaluating the use of antimalarials in real-life settings in low-income countries. Importantly, many other studies are phase IIIb clinical trials focusing on special populations such as pregnant women, children and HIV-infected individuals.

Trials evaluating optimisation of antimalarials in special populations for potential label extensions are very labour-intensive requiring extensive pharmacological analysis and a highly cautious approach in order to ensure patient safety. These studies are essential to produce evidence that will inform and guide future malaria prevention and treatment policies.

The WANECAM consortium led by Professor Abdoulaye Djimde (Malaria Research & Training Centre, Malawi) is conducting a phase IIIb/IV clinical trial assessing the safety and efficacy of repeated administration of four ACTs (Pyramax® (artesunate-pyronarine), Eurartesim™ (dihydroartemisinin-piperaquine), Coartem or Coartem-D (artemether-lumefantrine) and Coarsucam(artesunate-amodiaquine) over a two-year period in children and adults with uncomplicated malaria. The current approved label of Pyramax® limits its administration to once only, which is not useful for Africa where high risk groups, especially children, experience several episodes of malaria per season. Data from the trial has supported the submission of the Pyramax® film coated tablets variation for its indication being extended to repeated courses of treatment (submitted to the European Medicines Agency (EMA) in March 2014) and the Pyramax® granules for oral suspension line for extension of application to paediatric formulation (submitted to EMA in October 2014). The first results from the trial were submitted for publication at the end of 2014.

Prof. Abdoulaye Djimde

"We are particularly proud of our achievements in Guinea Conakry, which went from a site with no working microscope and only one trained investigator, to its current state with 25 trained investigators and a functional molecular biology laboratory. We have now recruited and are following up over 800 patients in the WANETAM trials."

Prof. Abdoulaye Djimde,
WANECAM Project Coordinator

There are numerous challenges in conducting clinical trials in West Africa in particular, and Africa in general. These include a clear understanding and buy-in from the communities where the trials are conducted; adequately trained personnel capable of conducting good clinical practice (GCP)-compliant trials; the right infrastructure (facilities, equipment, reliable electricity, internet connectivity) and an adequate supply chain; an appropriate ethical and regulatory environment with trained ethicists and regulatory affairs officers; and capable finance management and administrative support.

The EDCTP Senior Fellowship helped me to build a core research team trained in running ICH-GCP-compliant clinical trials. Members of my team are currently serving as clinical coordinators and field team leaders for the WANECAM trials. The outcome of the trials we conducted as part of my Senior Fellowship made us better known in this field of research and increased our chances of being funded for this project. The trial design used during my Senior Fellowship actually formed the back-bone of the WANECAM trials.

The overall objective of this project is to develop a sub-regional consortium of research sites from Burkina Faso, Guinea and Mali, with state-of-the-art clinical trial sites, laboratories, research teams and well characterised populations ready to undertake phases I-IV development of new drugs.

Our trials are still ongoing and will be completed in December 2015. Our results are likely to bring two new ACTs to use in sub-Saharan Africa.

Through this project, we improved the research landscape, equipment and know-how in all aspects of a complex clinical trial in all participating sites. We are particularly proud of our achievements in Guinea Conakry, which went from a site with no working microscope and only one trained investigator, to its current state with 25 trained investigators and a functional molecular biology laboratory. We have now recruited and are following up over 800 patients in the WANETAM trials.

EDCTP contributed to the trials in providing the necessary financial resources as well as valuable technical assistance in project management, financial management and overall coaching throughout the project.

The expansion of the second EDCTP programme to include early phases of clinical development is a very welcome development. The current efforts in developing capacity need to be sustained as the need for new drugs remains a major challenge. Indeed drugs remain one of the main pillars of the overall agenda for malaria elimination and ultimate eradication.

The WANECAM team at a site visit in Niankoloko, Burkina Faso

WANECAM

Official title:
An integrated approach to clinical trials, capacity building and networking in West Africa

Project Coordinator:

- Prof. Abdoulaye Djimde (Malaria Research & Training Centre, Mali)

Cofunders:

- Centre national de formation et de recherche en santé rurale (CNFRSR, Republic of Guinea)
- Centre national de recherche et de formation sur le paludisme (CNRFP, Burkina Faso)
- EDCTP
- Federal Ministry of Education and Research (BMBF, Germany)
- Institut de recherche en sciences de la santé (IRSS, Burkina Faso)
- Malaria Research & Training Centre (Mali)
- Medical Research Council (MRC, UK)
- Medicines for Malaria Venture (MMV, Switzerland)
- Swedish International Development Cooperation Agency (SIDA, Sweden)
- University Claude Bernard Lyon (France).

Total budget: € 9,283,169
EDCTP budget: € 2,824,118

Prevention and treatment of malaria in pregnancy

Pregnant women are a high-risk group for malaria infection and require safe and effective antimalarial treatment. Infection with malaria during pregnancy can cause severe maternal anaemia, stillbirths, and pre-term and low-birthweight babies, and is responsible for the deaths of many African women and their babies. However, because pregnant women are systematically excluded from clinical trials, there is insufficient information on the safety and efficacy of antimalarials in pregnancy. Finding new drugs to treat and/or prevent malaria infection in pregnancy was identified as a priority by EDCTP, leading to a 2007 call for proposals.

Three grants were funded under this call, all of which reached their official end date in 2014. Five clinical trials were supported which have completed recruitment and follow-up for the primary outcome, although secondary end-points and data analysis particularly in relation to the birth cohort are ongoing. These trials, which together recruited more than 15,000 African women, following them through pregnancy and studying the outcomes of children born, have provided an extensive data resource on malaria in pregnancy. The individual trials are summarised below.

The PREGACT trial, led by Professor Umberto D'Alessandro (previously Institute of Tropical Medicine, Belgium; currently MRC The Gambia Unit), recruited 3,428 pregnant women with confirmed malaria infection in four countries (Burkina Faso, Ghana, Malawi and Zambia) in order to test the safety and efficacy of artemisinin-based combination therapies (dihydroartemisinin-piperaquine, mefloquine-artesunate, amodiaquine-artesunate and artemether-lumefantrine) when administered to pregnant women with *P. falciparum* infection during the second and the third trimester. The grant was completed in 2014. The findings of the trial will be published in 2015. The results will feed directly into the WHO malaria treatment guidelines, in particular, regarding the performance of dihydroartemisinin-piperaquine for which no recommendation could be made in the current malaria treatment guidelines due to lack of data. Follow-up of the children born to the pregnant women in the trial is ongoing, as is the laboratory analysis of the pharmacokinetic data and placental infection.

The current WHO policy recommends intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) in pregnancy. However, this policy is at risk due to increasing parasite resistance to SP. These problems prompted the IPT-SP study, coordinated by Professor Feiko ter Kuile (Liverpool School of Tropical Medicine, UK). The study investigates the declining IPTp effectiveness and studies alternative approaches to IPTp-SP. The two options considered are replacing SP with other drugs for IPTp, and alternative strategies to replace IPTp.

The ISTp-A trial recruited 5,354 pregnant women across Burkina Faso, Ghana, Mali and The Gambia. Women were randomised to receive either IPTp-SP which is the current policy or scheduled intermittent screening and treatment in pregnancy (ISTp). The trial demonstrated that ISTp was non-inferior to IPTp-SP in preventing low birth weight and anaemia. Additionally, there was no difference in the proportion of deliveries that had an adverse outcome between the two groups. Furthermore, the study showed that use of the rapid diagnostic tests for malaria led to women who received ISTp being diagnosed with episodes of malaria between routine antenatal clinic visits more frequently than women who received IPTp-SP (192 vs 107 episodes). These results indicate that intermittent screening and treatment could be implemented at antenatal clinics as an alternative to IPTp. Data from the trial about the cost-effectiveness of the two methods are currently under analysis. The trial also demonstrated that despite growing concerns about the impact of SP resistance in East and Southern Africa, SP remains effective at clearing existing infections and improving haemoglobin concentration when provided as IPTp to asymptomatic pregnant women in Mali and Burkina-Faso.

The ISTp-B trial conducted in Malawi comparing ISTp with IPTp-SP showed that the effectiveness of IPTp is compromised in areas where the PfDHPS A581G mutation is present in the parasite populations. The results of this trial and the data on the relationship between SP resistance and SP-IPTp effectiveness were presented at the WHO Evidence Review Group on Malaria in Pregnancy.

Given the rising resistance to sulphadoxine-pyrimethamine (SP), a consortium led by Professor Clara Menéndez

(Hospital Clinic of Barcelona, Spain) conducted two trials to look at the potential for using mefloquine (MQ) as an alternative to SP. The first trial compared the safety, tolerability and efficacy of MQ to SP as IPTp for the prevention of malaria effects on the mother and her infant (HIV-uninfected women) in a trial of 4,749 pregnant women in Benin, Gabon, Mozambique, and Tanzania. The trial compared two-dose MQ or SP for IPTp and MQ tolerability of two different regimens. The results indicated that there was no difference in low birth weight prevalence (primary study outcome), as well as no differences in the prevalence of placental infection and adverse pregnancy outcomes between groups. Women receiving MQ had reduced risk of parasitaemia and anaemia at delivery and reduced incidence of clinical malaria. Despite these positive results, tolerability was poorer in the two MQ groups compared to SP. The most frequently reported related adverse events were dizziness and vomiting, with similar proportions in the full and split MQ arms. The findings do not support the use of MQ instead of SP for IPTp.

A second trial evaluated the safety and efficacy of MQ as IPTp for malaria in HIV-infected pregnant women receiving cotrimoxazole prophylaxis (CTXp) and long-lasting insecticide treated nets (LLITNs). A total of 1,071 HIV-infected women from Kenya, Mozambique, and Tanzania were randomised to receive either three doses of IPTp-MQ (15 mg/kg) or placebo given at least one month apart; all received cotrimoxazole preventive therapy and a bed net. The IPTp-MQ arm was associated with reduced rates of maternal parasitemia, placental malaria, and reduced incidence of non-obstetric hospital admissions. There were no differences in the prevalence of adverse pregnancy outcomes between groups. Despite these positive findings, drug tolerability was poorer in the MQ group (dizziness and vomiting). Unexpectedly, HIV viral load at delivery was higher in the MQ group compared to the control group ($p = 0.048$) and the frequency of perinatal mother-to-child transmission of HIV was increased in women who received MQ. The trial results, published in the *PLOS Medicine* on 23 September 2014, confirmed that MQ was not well tolerated and therefore this limits its potential for IPTp.

The findings from these five clinical trials are for consideration at a meeting of WHO's Evidence Review Group on Malaria in Pregnancy to be held in early 2015.

Malaria vaccines

EDCTP is very active in the field of malaria vaccines with 12 clinical trials in the portfolio of the first programme. Among these trials is an open-label randomised controlled human malaria infection (CHMI) pilot study using aseptic, cryopreserved *P. falciparum* sporozoites (PfSPZ Challenge) to evaluate safety, infectivity and parasite growth dynamics was carried out in Kenyan adults with low to moderate prior exposure to *P. falciparum*. All trial participants developed blood-stage infection, although one remained asymptomatic and blood-film negative until day 21 post-injection. This participant had a reduced parasite multiplication rate which was correlated with the immune response to parasite schizonts. The study investigators, led by Bernhards Ogutu (Kenya Medical Research Institute (KEMRI), Kenya), concluded that PfSPZ challenge is safe and infectious in malaria-endemic populations and could be used to assess the efficacy of malaria vaccines and drugs in African populations. This was the first CHMI study undertaken in Kenya. CHMI is a potential model for assessing the efficacy of malaria vaccines and drugs in African populations, however, the extensive exclusion criteria for such studies mean that it is necessary to screen large numbers of volunteers in order to identify a sufficient number of healthy, eligible adults.

The Malaria Vectored Vaccine Consortium (MVVC), led by Odile Leroy (European Vaccine Initiative (EVI), Germany), published eight papers in 2014, relating to clinical trials that are supported under their first EDCTP grant (MVVC1). Several trials are continuing under the MVVC2 grant, including studies of a promising vaccine candidate R21 adjuvanted with a licensed clinical grade adjuvant. R21 is a biosimilar of the GlaxoSmithKline (GSK) RTS,S vaccine.

Prof. Umberto D'Alessandro

"The PREGACT trial provides the evidence base for the recommendations of ACT for pregnant women infected with malaria."

Prof. Umberto D'Alessandro, PREGACT Project Coordinator

Although malaria is the most important human parasitic disease, few studies on antimalarial drugs have been carried out in pregnant women. Pregnant women are a high-risk group requiring effective antimalarials but they are systematically excluded from clinical trials for fear of teratogenicity and embryotoxicity. This has complicated the development of evidence-based recommendations for the prevention and treatment of malaria during pregnancy.

In addition, pregnancy is associated with physiological changes such as increased volume of distribution, reduced gut motility, increased renal blood flow, hormonal changes, and increased protein binding that may alter drug disposition and metabolism. It is therefore important to recognise the changes in pharmacokinetic parameters that may occur in pregnancy as incorrect dosing may result in maternal and foetal toxic effects, therapeutic drug failures resulting in poor pregnancy outcomes or maternal death.

The PREGACT project aimed to identify artemisinin-based combination treatments (ACT) that can be safely and efficaciously used to treat women with malaria in their second and third trimester of pregnancy. More specifically, the research objectives were to determine the safety and efficacy of four ACTs (dihydroartemisinin-piperaquine, mefloquine-artesunate, amodiaquine-artesunate and artemether-lumefantrine) when administered to pregnant women with P. falciparum *infection during the second and the third trimester. This head-to-head comparison of the four treatments aimed at identifying at least two valid first-line and one second-line (rescue) treatments. The PREGACT project also aimed to collect explanatory variables, i.e. drug pharmacokinetics and* in vitro *parasite drug sensitivity, for treatment failure (PCR-corrected) and for recurrent infections.*

In order to evaluate the safety and efficacy of the ACTs, treatment was directly observed to ensure that women had actually taken the drugs. Following this, the women were actively followed for 9 weeks (i.e. till day 63 post-treatment). Women were also visited after delivery and they were examined together with their newborn. The infant was visited again at his/her first birthday.

The project found that all four ACTs were safe and efficacious, though with some difference between them. The PREGACT trial provides the evidence base for the recommendations of ACT for pregnant women infected with malaria. But more needs to be done. Though ACTs are excellent options for treating malaria in pregnant women, they can be used only during the second and third trimester of pregnancy. There is the need to continue developing antimalarial treatments that can be used during pregnancy.

PREGACT has been an excellent opportunity to build the research capacity of the African institutions involved. The project comprised the training of three MSc and five PhD students as well as a post-doctoral fellowship. Moreover, the capabilities of conducting clinical trials in each of the African institutions involved have been upgraded and improved. For example, a research building was renovated in Malawi, laboratories were equipped in other sites, and research staff went through GCP and data management training. EDCTP, together with other donors such as the Bill & Melinda Gates Foundation, has been essential to the successful completion of the trial.

PREGACT

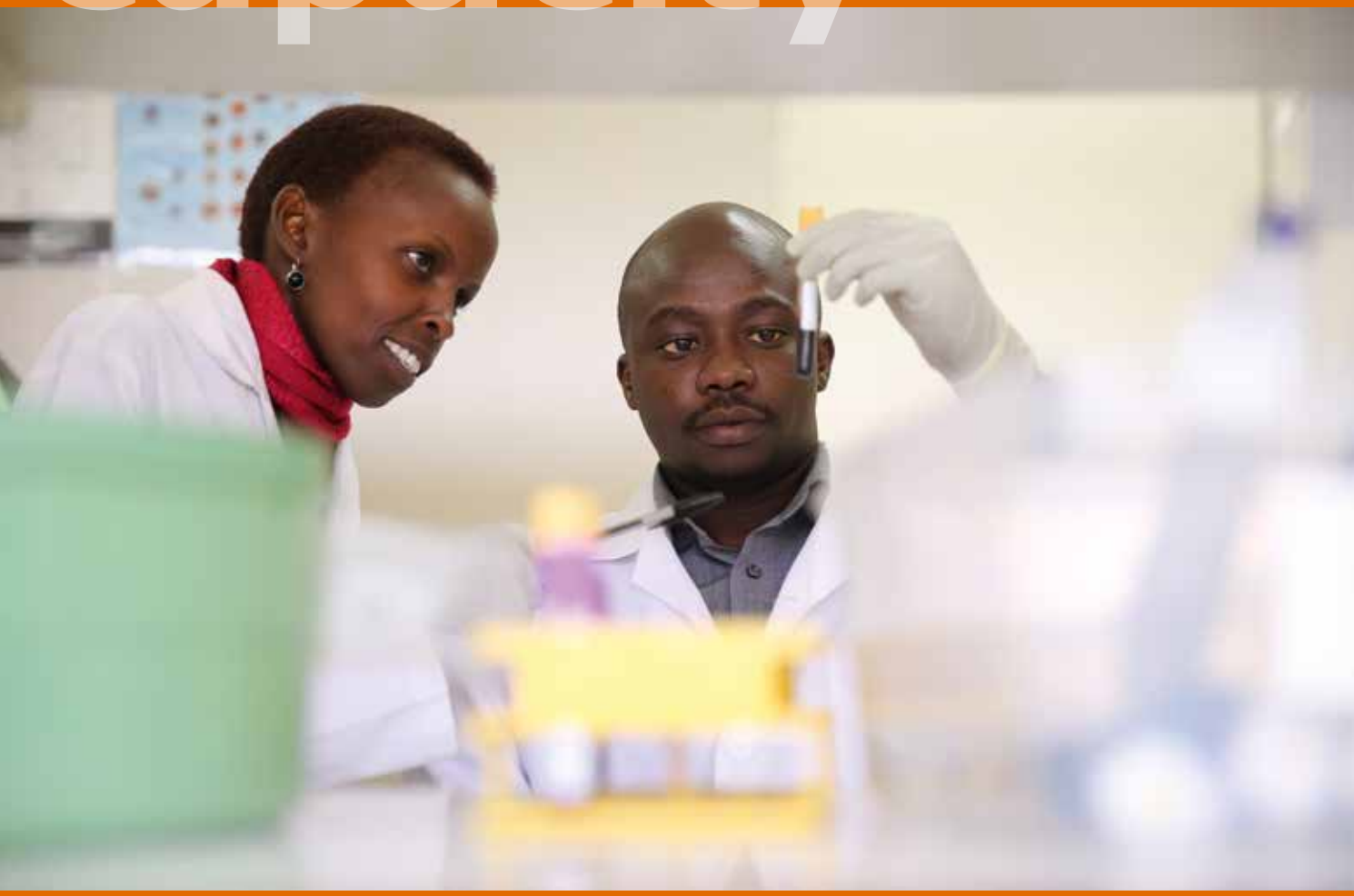
Official title:
Safe and efficacious artemisinin-based combination treatments for African pregnant women with malaria

Project Coordinator:
- Prof. Umberto D'Alessandro (MRC The Gambia Unit)

Cofunders:
- Austrian Federal Ministry of Science (Austria)
- Bill & Melinda Gates Foundation (USA)
- EDCTP
- Liverpool School of Tropical Medicine (UK)
- Medical Research Council (MRC, UK)
- Netherlands Organisation for Scientific Research (NWO, The Netherlands)
- Prince Leopold Institute of Tropical Medicine (Belgium)

Total budget: € 6,529,609
EDCTP budget: € 2,988,993

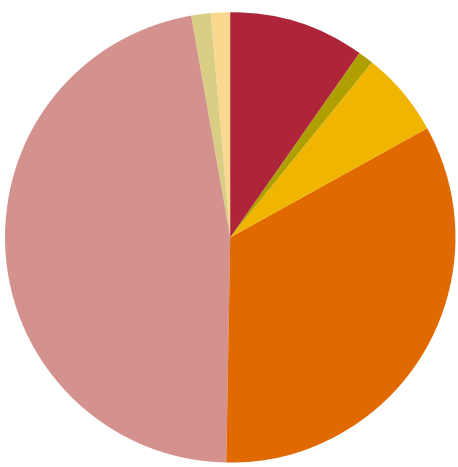
Research capacity



EDCTP supports sustainable capacity for conducting clinical trials by: supporting the training, attracting and retaining of scientific leadership in Africa; improving and upgrading research infrastructure; and strengthening the ethical, regulatory and legal framework for conducting trials. This chapter summarises the progress made in strengthening capacity through EDCTP's fellowship schemes, ethics grants, and postgraduate training integrated with EDCTP grants.

EDCTP adopted a programmatic approach to capacity development. Its capacity development activities, such as training and infrastructure upgrades of clinical research centres as well as networking activities, are integrated in research projects. This approach will be continued under EDCTP2. Moreover, EDCTP2 will support three fellowship schemes: Senior Fellowships, Career Development Fellowships and Clinical Research and Development Fellowships in joint collaboration with WHO-TDR. By the end of 2014, EDCTP had supported a total of 516 African researchers at various career stages.

Number of trainees funded by EDCTP (2003-2014)



Career stage	Number of trainees
Senior Fellows	51
Career Development Fellows	5
Postdoctoral researchers on EDCTP grants	32
PhD students	172
Master's students	242
Medical Diploma students	7
Bachelor's students	7
Total	**516**

Senior Fellowship programme

The Senior Fellowship grant scheme supports the development of African mid-career scientists into leading investigators with established research teams, helping them to become more competitive internationally. This grant scheme has supported the re-integration of scientists into African institutions. Since the inception of this grant scheme in 2004, 51 Senior Fellows (40 male, 11 female) have been funded from 10 calls for proposals. Of these, five fellows (approximately 10%) have used this grant scheme for re-entry into their host countries. Sixteen (16) fellows are conducting clinical trials as part of their fellowships, with the remainder focused on clinical and/or epidemiological research. The majority of fellowships have closed, with 12 grants active at the end of 2014. Many of the fellows have been successful in attracting additional, large-scale funding from other agencies by the end of their EDCTP fellowship.

Master's Fellowships

The call for proposals for Master's Fellowships in Epidemiology and Medical Statistics aimed to build research capacity in sub-Saharan Africa by supporting the training and career development of junior researchers in the field of epidemiology and medical statistics.

Launched in 2013, the scheme provided funds for the fellow to undertake a taught master's course in epidemiology or medical statistics at an internationally recognised centre of excellence. It also enabled the fellow to conduct a field study of 6-12 months duration at an institution in sub-Saharan Africa to build practical skills. The call for proposals was funded by Sweden and the United Kingdom (EDCTP Participating States). A total of 52 eligible applications were received. Of these, eight awards were recommended for funding in May 2014.

Prof. Photini Kiepiela

It is often difficult to provide training opportunities for staff involved in clinical trials, particularly in Africa. When many clinical trials are conducted, time is difficult to find. Web-based technology promises the convenience and flexibility of learning anywhere, anytime. These qualities of online learning are extremely attractive for busy clinicians who are geographically dispersed across cities and countries.

The overall objective of the study was two-fold. First, we wanted to create, deliver, provide and evaluate training programmes to medical and psycho-social staff. The programmes would blend face-to-face training as well as online distance learning in basic principles and methods of immunology, HIV and TB pathogenesis and vaccinology, research protocol development and implementation, and laboratory methodology. In future, African students, clinical investigators, researchers and laboratory staff would be able to use this facility to develop new content and activities to address specific needs in their settings.

The training programmes were developed through the Medical Research Council of South Africa HIV Prevention Research Unit (HPRU), in partnership with the Health Sciences eTraining Foundation (HSeT). HSeT set up a portal as a facility for e-learning teaching programmes and activities. Prior to each workshop, HSeT created a workshop-specific e-learning portal (http://hdi.bio-med.ch) which housed curricula developed collaboratively by the HSeT team and workshop faculty. We created self-directed, on-line curricula and developed tools and web content for training including interactive pre-workshop activities, protocol based learning, quiz, and pre-workshop modules.

The blended-learning approach allowed scholars to adequately prepare for the face-to-face workshop with online activities and reading assignments. Overall, scholars found the e-learning workshops rewarding and worthwhile due to the depth and detail of the material. The project

"The three day face-to-face workshop provided personalised lecture material from TB experts and HIV researchers and was recognised as a rare and valuable opportunity for trainees."

Prof. Photini Kiepiela,
EDCTP Senior Fellow

successfully organised four workshops on: Statistical Methods in HIV Vaccine Trial Design and Evaluation; Vaccine Strategies against TB; the Mucosal Immunity Workshop; and a Mucosal Immunity HIV/HPV Workshop.

A total of 74 post-graduate students were trained. Networking took place with HSeT and international collaborators, namely the OCTAVE Project (Online Collaborative Training for AIDS Vaccine Evaluation) the HIV Vaccine Trials Network (HVTN) and the Statistical Centre for HIV/AIDS Research & Prevention (SCHARP) to provide the statistical workshop. Collaboration with experts from the University of Cape Town was sought to be able to provide the other workshops.

Secondly, the project aimed to describe the human leukocyte antigen (HLA) and/or killer immunoglobulin receptors (KIRs) gene combinations in HIV-infected and uninfected women, as well as their impact on resistance or susceptibility to HIV-1 infection. Part of the innate immune system, natural killer (NK) cells express either inhibitory or activating receptors; the balance between these receptors affects the function of the individual cell clone. The majority of receptors include KIRs that bind to HLA and HLA like molecules. Little is known about KIR and HLA allele frequencies in South Africa where subtype C is prevalent and their impact on HIV-1 disease acquisition or progression. It was important to study the role of host HLA and KIR genotype as HLA class I contributes to both the innate and adaptive immune responses. This type of studies has not been conducted extensively in African populations. Hence this study is essential in understanding host susceptibility and immune response in African populations with a high level of exposure to HIV-1 clade C infection.

The KIR: HLA genotyping project extracted 557 DNA samples from stored dried blood spot specimens obtained from exposed seronegative individuals and in those who subsequently became HIV-1 infected (i.e. seroconverters recruited from two microbicide trials). This was possible because women (aged 18-40 years with a 24-month follow-up period) had signed an informed consent form for storage and future testing of their dried blood spot samples.

The main finding was that individuals with an inhibitory: activating KIR gene ratio of ≤1.5 had a 34% reduced risk of acquiring HIV-1 infection compared to those with inhibitory: activating KIR gene ratio of ≥1.5. There was a higher frequency of 2DS2+C1 gene combination in HIV-1 infected individuals compared to HIV-1 exposed seronegative (59%vs48%) and those individuals harbouring this KIR: HLA ligand combination were 1.5 times more likely to acquire HIV-1 infection. Certain KIR: HLA ligand associations (2DS2+C1) are significantly linked with susceptibility to HIV-1 infection.

A post-graduate student, Ms. Siphelele Zulu (South Africa) undertook the KIR: HLA genotyping at the National Institute of Communicable Diseases. She will submit her Master's thesis entitled "The evaluation of KIR: HLA genes in acquisition or resistance to clade C HIV-1 infection in women in KwaZulu-Natal, Durban, South Africa" to the University of KwaZulu-Natal post-graduate committee. Additionally, a manuscript is prepared for submission to a peer-reviewed journal.

Photini Kiepiela

Official title:
Training in mucosal immunity and the evaluation of KIR:HLA genes in HIV-1 clade C infection: key components to HIV vaccine design

Project Coordinator:
- Prof. Photini Kiepiela (Medical Research Council, HIV Prevention Research Unit, South Africa)

Total budget: € 222,277
EDCTP budget: € 196,775

Dr Collen Masimirembwa

"Cost effectiveness analysis (CEA) in African Americans indicated that integrating the CYP2B6*6 genotyping for this population would result in savings of over 20 million USD a year in the USA. Projecting this model to sub-Saharan Africa indicates the possibility of enormous savings for public healthcare systems."

Dr Collen Masimirembwa,
EDCTP Senior Fellow

The main safety concerns in the use of anti-retroviral drugs in Africa are that they are now the leading cause of adverse drug reactions (ADRs). These are associated with poor quality of life, reduced economic productivity, stigma due to some of their disfiguring effects, costs to the healthcare system in treating them and risk of poor treatment compliance that could promote the emergence of drug resistance HIV. Despite the enormous cost implications at individual and public health levels, little is being done to understand and reduce the burden of adverse drug effects in the use of anti-retroviral drugs in Africa. With over 7 million people in Africa on anti-retroviral treatment (ART) and 30-80% experiencing at least one severe ADR, the economic and social burden of ART-associated ADRs is a public health challenge of enormous proportions.

In response to this issue, the main objective of our project was to validate, in a clinical setting in Zimbabwe, a genetic biomarker for drug safety and explore its predictive power to guide dose adjustments of the anti-retroviral drug, efavirenz. The genetic biomarker being a DNA sequence variation in the gene that codes for the liver enzyme, CYP2B6, responsible for the metabolism and elimination of efavirenz from the body. Patients who carry this genetic variant have reduced enzyme activity hence reduced capacity to eliminate efavirenz from the body and end up with high and toxic levels of the drug when given the standard dose of 600 mg/day.

*There were four main findings from this project. The first result was the demonstration that the low activity CYP2B6*6 genetic variant occurred at high frequency in populations of African origin (34-50%) compared to Caucasian and Asian populations (16-20%). It also demonstrated that CYP2B6*6 is a predictive biomarker of high efavirenz concentrations and susceptibility to central nervous system (CNS) side effects. Additionally, the project found the derivation of a CYP2B6*6 genetic test-based dosing algorithm that can be used to tailor make the dose of efavirenz given for safe and efficacious outcome. The final main finding was the setting up of validated analytical methods for the determination of efavirenz concentration and genetic tests for determining the CYP2B6 genotype in patients on efavirenz based ART.*

*The clinical relevance of these findings are that testing of patients for the CYP2B6*6 genetic variant can guide doctors in either explaining the CNS ADRs their patients might be experiencing or predicting those who will be at greater risk for such ADRs if treated with an efavirenz-based ART regimen. This will help with patient management and decisions on whether to put patients on alternative ART regimens or adjusting the dose of the drug. The finding will further enable doctors to adjust doses of efavirenz in patients of CYP2B6*6 genetic status where we have shown that patients carrying CYP2B6*6 variants require only 200 mg/day compared to the standard dose of 600 mg/day and still achieve safe and efficacious drug levels. The dosing algorithm further showed that patients carrying one or no CYP2B6*6 genetic variant would require 400 mg/day instead of the standard 600 mg/day.*

*Our predictions have been supported by many clinical case studies in Japan, Europe, and South Africa and major clinical trials. Our demonstration that the CYP2B6*6 variant is found at high frequency across the sub-Saharan African populations (the Ibo, Hausa & Yoruba of Nigeria, the Kikuyu, Luo and Masaai of Kenya, the Shona, Ndebele & San of Zimbabwe and the Venda of South Africa) implies the clinical applicability of findings in the Zimbabwean population to most African populations. The findings therefore show that this genetic test could be more important for African populations than Caucasian and Asian populations. Clinical findings in African Americans, Tanzanians, Ethiopians and Ugandans have confirmed our findings.*

This work has resulted in five original research publications and contributed to our invitation to write two reviews in international peer reviewed journals with good impact factors and a book chapter in the field of pharmacogenetics. The project also resulted in the training of a PhD student in the pharmacogenetics of efavirenz.

The relevance and medical impact of findings from our project work are that the use of the current standard dose of 600 mg/day efavirenz is not appropriate in African populations. WHO initiates a new era in HIV/AIDS prevention and treatment that will see over

The team members: (front row) Georginah Nyabadza (Research Nurse & Study Coordinator), Dr Roslyn Thelingwani (Bioanalytical Chemist), Dr Collen Masimirembwa (Project Leader); (back row) Prof. Charles Nhachi (Clinical Pharmacologist), Dr Gerard Kadzirange (HIV/AIDS Specialist Physician), Dr Prosper Chonzi, (Clinical Epidemiologist & Public Health Specialist)

15 million people on ART. This ART roll-out is based on an efavirenz-based fixed dose combination. In Zimbabwe, of the 700,000 people on ART, more than 50% are on efavirenz-based ART.

*Efavirenz is however associated with neuropsychiatric adverse effects (AE), which, if not monitored and addressed might compromise the effectiveness of the drug and risk the development of resistance due to poor compliance. The pharmacogenetics-guided dose adjustments we have proposed will increase drug tolerability and thus increase compliance. It will also reduce costs of treatment associated with managing ADRS or changing patients to more expensive second-line protease inhibitor-based ART. Further cost reduction will be associated with the cost of goods as 20% of the patients in Africa are homozygous for the CYP2B6*6 variant and would only require 200 mg/day efavirenz.*
*Cost effectiveness analysis (CEA) in African Americans indicated that integrating the CYP2B6*6 genotyping for this population would result in savings of over 20 million USD a ear in the USA. Projecting this model to sub-Saharan Africa indicates the possibility enormous savings for public healthcare systems.*

*The financial support from EDCTP through this Senior Fellowship was central to the execution of this project. The grant enabled us to initiate the HIV/AIDS cohort through which we evaluated the utility of CYP2B6*6 as a biomarker for efavirenz exposure and risk for CNS side effects and the derivation of predictive pharmacogenetics guided dosing algorithm in the use of the drug. The financial support also enabled us to validate the CYP2B6 genotyping method and efavirenz drug concentration determination for clinical use. The EDCTP funding supported the establishment of a Clinical Trial Sciences Working Group at the African Institute of Biomedical Science and Technology (AiBST) which supported the conduct of the clinical study and is the backbone of current and future clinical studies at our institute. Through the EDCTP grant, Milcah Dhoro managed to complete her PhD studies on the pharmacogenetics of efavirenz.*

The EDCTP funding was also important towards procurement of some laboratory equipment used in the conduct of this work and is now available for future work at our institute. The support therefore, resulted in both individual and institutional capacity and capability strengthening at AiBST and collaborating institutes such as the University of Zimbabwe and Wilkins Hospital in clinical pharmacogenetics research.

*Through this project, we have reached a stage where EDCTP-funded studies from our laboratory and other groups have generated a strong case for the need to integrate CYP2B6*6 testing in the safe and efficacious use of efavirenz-based ART. Given the enormous costs associated with large scale ART roll-out to public health programs, the introduction of this genetic test needs to be evaluated for cost-effectiveness. We have therefore developed a proposal which is under review to conduct the CEA of integrating CYP2B6*6 genetic test-guided use of efavirenz in public healthcare sector settings.*

*We have started already offering efavirenz therapeutic drug monitoring (TDM) and CYP2B6*6 genotyping services to the Harare City Health hospitals. This involves the participation of 12 doctors working within Harare City Health who attend to the HIV/AIDS patients on ART. When they identify patients on efavirenz who are experiencing severe CNS adverse effects, samples are submitted to AiBST where the concentration of efavirenz and the CYP2B6*6 genotype are determined. The doctors then use the pharmacogenetic test report to make a decision whether or not to switch the patient to another regimen. As the medical doctors will gain confidence in the pharmacogenetic diagnostic test with respect to its value for patient management, we plan to move to the next step of using the genetic test to modify the dose of efavirenz in order to keep more patients on the affordable first-line therapy.*

Collen Masimirembwa

Official title:
A prospective study to evaluate a pharmacogenetic-guided dosing algorithm based on patient CYP2B6 genotype compared to the empirical standard dose in the safe and efficacious use of efavirenz in HIV/AIDS patients in Zimbabwe.

Project Coordinator:

- Dr Collen Masimirembwa (African Institute of Biomedical Science and Technology, Zimbabwe)

Total budget: € 196,645

EDCTP budget: € 196,645

Health Research Ethics

The ethics grants scheme started in 2005 and has continued as a flagship programme of EDCTP. There have been ten calls for proposals under the EDCTP ethics programme until 2011. A total of 75 grants have been awarded in 23 sub-Saharan countries, with funding of just over € 4 million.

The aim of the grant scheme is to strengthen the ethics review framework of sub-Saharan institutions and countries. The grants are awarded to develop the appropriate human resource and infrastructure required to establish functional, competent, independent and sustainable ethics review boards in Africa. Effective ethics review of health research, including clinical trials, is essential for the development of medical interventions and technologies in and for Africa.

Through this scheme, EDCTP has funded establishment and strengthening of ethics review framework for health research in countries that initially had no or limited ethics capacity such as Benin, Democratic Republic of Congo, Gabon, Guinea, Liberia, Mozambique, Rwanda and Togo.

Prof. Mariana Kruger

Over the last half-century many human rights abuses have occurred in the name of health research. In Africa and in other low- and middle-income countries where there is a high burden of disease, populations from which research participants are recruited, are often regarded as vulnerable. This means that either at an individual or at a community level such persons may not be able to adequately protect their own needs and interests. The purpose of a research ethics committee (REC) is thus to ensure that the needs, rights, interest and dignity of human research participants is adequately protected during the entire research process, and that both the benefits and burdens of research are justly distributed.

There have been many capacity development programmes in Africa, over the last decade aimed specifically at training research ethics committee members so that they can adequately fulfil their mandate. Many of these have been funded by the EDCTP. The goal of this project was to bring African scholars together, to write a book that would specifically consider research ethics from an African perspective and highlight some of the ethical challenges encountered when doing research in Africa.

Up until now there has not been a written and published resource for research ethics committees that was readily accessible and could be used by RECs throughout Africa as a common resource. The book **Research Ethics in Africa: A Resource for Research Ethics Committees**, *produced through this project has five parts. Part I introduces the book, provides a history of research ethics in Africa and discusses the MARC project (the Mapping of Research ethics committees throughout Africa). Part II 'The Research Ethics Committee' comprises five chapters and covers the operation of an REC including running a meeting, developing standard operating procedures etc. Part III covers many specific topics such as traditional medicine research, public*

"The book Research Ethics in Africa: A Resource for Research Ethics Committees, produced through this project, is the first book dedicated to research ethics from an African perspective."

Prof. Mariana Kruger,
SAREN-Ethics Project Coordinator

Dr Lynn Horn and Prof. Mariana Kruger hold a copy of the book

health research, vulnerable participants, risk benefit assessment and many others. Part IV is a section with valuable resources such as a chapter on educational resources, and Part V contains some useful templates. Archbishop Desmond Tutu, an international figure in the context of human rights, agreed to write a short forward. It is available as a free E-book 'App' at https://africansunmedia.snapplify.com.

The project leaders selected contributors who had participated in REC training programmes in the past, or that were actively involved in RECs. The starting point of the project was a two-day workshop where 18 potential authors got together to brain-storm and discuss the specific challenges that they faced as REC members, reviewing and approving health research projects that were to be implemented in Africa. Each workshop participant gave a presentation to the group. These presentations were followed up with breakaway discussion sessions. The workshop ended with decisions regarding the proposed content and chapters as well as authors for each chapter. As two authors dropped out, two new authors were co-opted to fill specific knowledge gaps. Sun Media was identified as a suitable academic publisher and after many drafts the book was finally published in July 2014.

EDCTP provided all the funding for the initial workshop that was held in South Africa in August 2012. EDCTP also provided the funding for language editing and the entire publication process. It covered also the printing of 275 hard copies that were distributed to RECs in Africa and South Africa as well as to those involved in research training programmes. The team believes translation of the book into French and Portuguese would be very useful.

The SAREN team

SAREN-Ethics

Official title:
Network of Southern Africa Research Ethics Committee (REC) Chairpersons and development of a review textbook for African REC members (SAREN – South African Research Ethics Network)

Project Coordinator:

- Prof. Mariana Kruger (Stellenbosch University, South Africa)

Total budget: € 40,718

EDCTP budget: € 40,718

PACTR: clinical trial registry

In preparation for the second EDCTP programme, EDCTP provided more financial support to develop the Pan African Clinical Trials Registry (PACTR). It is the only WHO-endorsed primary registry in Africa and trial registration in the PACTR portal (www.pactr.org) meets the requirements of the International Committee of Medical Journal Editors (ICMJE) and feeds information to the WHO International Clinical Trials Registry Platform (ICTRP). The PACTR registry facilitates understanding of regional research patterns, enables the identification of research gaps for future studies, and facilitates the investigation of the scope, quality and funding patterns of African trials. There was exponential growth in clinical trials registration with PACTR during 2014 with 388 clinical trials registered by end of the year.

Developing ethics and regulatory capacity

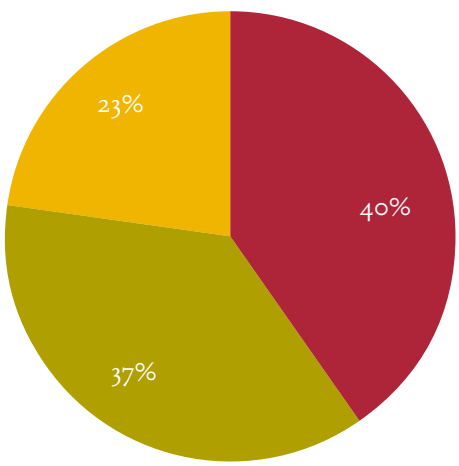
A comprehensive evaluation of the EDCTP grants programme for strengthening research ethics review in sub-Saharan Africa was commissioned as part of the EDCTP-Plus project. The evaluation of all 75 EDCTP-funded ethics projects focused on the three funding areas: the mapping of ethics review and clinical trial regulatory capacity in sub-Saharan Africa; establishing or strengthening of National Ethics Committees (NECs) and Institutional Review Boards (IRBs); and training (including the development of online training programmes) for research ethics review. The programme was recognised to have made a significant contribution in developing ethics capacity in sub-Saharan Africa through the establishing/strengthening of IRBs and NECs, training ethics committee members and ensuring that the boards and committees are independent. However, the assessment also concluded that there is still a lot to be done in terms of developing capacity for research ethics in Africa. These assessments, together with the discussion points and recommendations from the EDCTP stakeholder meeting on health research ethics have been taken into consideration in the planning of EDCTP2 activities to support ethics capacities.

Connecting research

EDCTP has shown that improved coordination of European research as well as collaboration with and among African researchers is of great benefit to all partners and reinforces the impact of the European contribution. Moreover, the programme is one of the few international initiatives to develop a partnership with African scientists by creating opportunities for ownership and leadership by those working on the ground in disease-endemic countries. Through its projects and collaborative approach, EDCTP supports African researchers to establish their own networks. African researchers lead over 72% of all EDCTP-funded activities.

In addition to bringing together European national research programmes and their African partners, EDCTP has maintained and developed links with third parties, including product development partnerships, multinational pharmaceutical companies, philanthropic organisations, and like-minded organisations contributing to the development of new clinical tools against HIV/AIDS, tuberculosis, malaria.

Funding contribution (expenditures and future commitment) to EDCTP projects:



European Commission*	€ 154,145,534
EDCTP Participating States	€ 139,653,826
Third parties**	€ 87,214,886
Total	**€ 381,014,246**

* Including a € 2,08 million contribution from an FP7 grant linked to an EDCTP grant

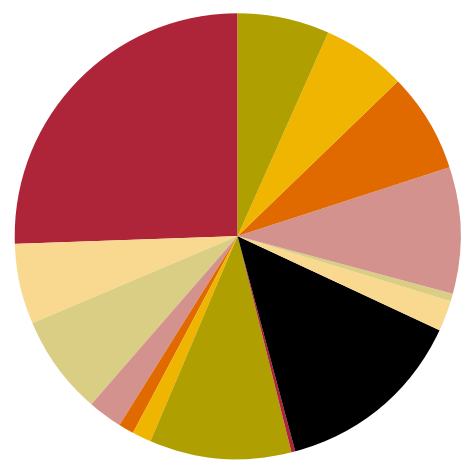
** Including a € 14,51 million contribution from African countries

Integrating European research

By end of 2014, the current European Participating States had collaborated (two or more countries involved) in 97 EDCTP-funded projects in sub-Saharan Africa. A total of 347 researchers based in Europe participated as collaborators in a total of 121 EDCTP projects. The projects without European investigators are capacity building grants that target African researchers, i.e. ethics grants, Senior Fellowships and studentships.

The signed grant value of all 254 EDCTP projects is € 211.98 million, comprising € 152.07 million EU funding and € 59.91 million cofunding disbursed by EDCTP of which € 51.66 million came from EDCTP Participating States and € 8.25 million from third-party organisations. The strong commitment to partnership is reflected in the 74% (€ 157 million) of EDCTP funding invested into activities implemented by African research institutions. The total value of all projects, also taking into consideration the cofunding that is contributed directly (i.e. not via EDCTP) to the projects, is € 381.01 million. This represents a substantial investment in research and capacity to tackle the three main poverty-related infectious diseases.

EDCTP Participating States total cofunding for research within the scope of the EDCTP programme, including cofounding of EDCTP projects, 2003-2014 (€ '000)



Austria	€ 1,572
Belgium	€ 55,003
Denmark	€ 53,636
France	€ 60,865
Germany	€ 77,938
Greece	€ 3,455
Ireland	€ 19,983
Italy	€ 115,891
Luxembourg	€ 2,289
Netherlands	€ 87,804
Norway	€ 11,424
Portugal	€ 9,549
Spain	€ 20,777
Sweden	€ 60,791
Switzerland	€ 50,450
United Kingdom	€ 215,282
Total	**€ 846,709**

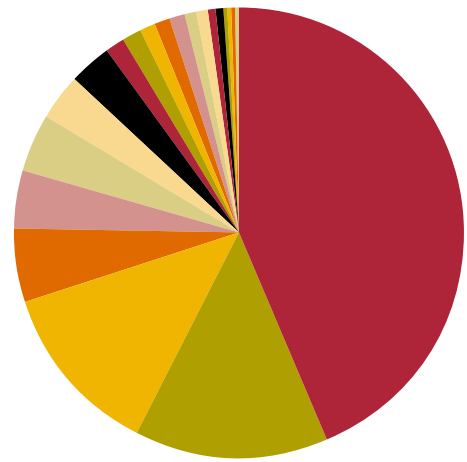
African research

EDCTP fosters African participation and leadership in the programme through African commitment and co-ownership both at the political and scientific level. EDCTP proactively engages with researchers, research managers, heads of institutions and senior government officials during EDCTP site visits in Africa and actively participates in various African forums.

The establishment in 2014 of the EDCTP Association, the implementing structure for EDCTP2, has resulted in the admission of African members of the Association. As of 31 December 2014, Cameroon, Congo, The Gambia, Ghana, Mozambique, Niger, Senegal, South Africa, Tanzania, Uganda and Zambia had joined the Association. Burkina Faso, Mali, and Gabon had expressed their intention to join. The EDCTP Association provides a mechanism to achieve a stronger, equal Europe-African partnership, with potential for greater integration of scientific and financial activities in EDCTP2. As part of their membership responsibilities, these countries have pledged to honour the annual membership contribution of at least € 200,000 (cash or in-kind) to support EDCTP2 activities. These commitments will contribute to achieving the target of raising € 30 million in cofunding from developing countries.

By end of 2014, African cofunding of EDCTP-funded projects was a total of €14.51 million, largely in-kind. South Africa, Tanzania and Uganda are the top three African countries in terms of cofunding contributions to EDCTP projects. This also reflects their high involvement in EDCTP projects as major recipients of EDCTP funding in Africa.

African cofunding contribution to EDCTP grants by country, 2003-2014 (€ '000)



South Africa	€ 6,333
Tanzania	€ 2,045
Uganda	€ 1,807
Zimbabwe	€ 763
Gambia	€ 608
Zambia	€ 593
Kenya	€ 507
Ethiopia	€ 412
Burkina Faso	€ 207
Gabon	€ 202
Mali	€ 181
Senegal	€ 154
Republic of the Congo	€ 150
Malawi	€ 145
Rwanda	€ 103
Guinea Conakry	€ 90
Benin	€ 77
Nigeria	€ 43
Mozambique	€ 41
Cameroon	€ 30
Ivory Coast	€ 16
Ghana	€ 5
Total	**€ 14,512**

Regional Networks of Excellence

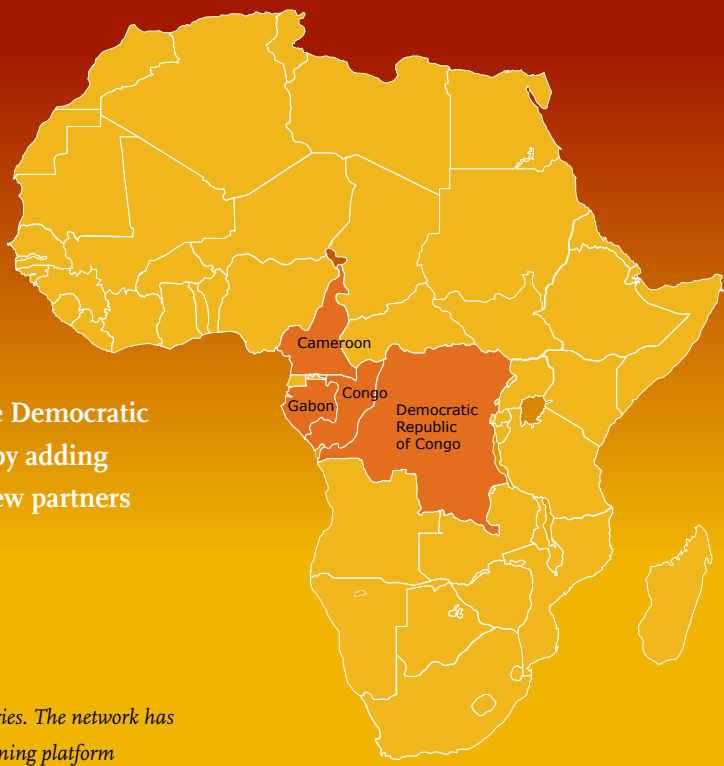
The EDCTP-funded Networks of Excellence facilitate regional collaboration by uniting diverse institutions that contribute their individual strengths in skills-based competencies and share infrastructures for conducting clinical trials. They provide a better environment for research and offer career opportunities in clinical research.

EDCTP funded the establishment of four regional Networks of Excellence for conducting clinical trials (NoE):

- The Central African Network for Tuberculosis, HIV/AIDS and Malaria (CANTAM; established 2008 www.cantam.org)
- The East African Consortium for Clinical Research (EACCR; established 2009 www.eaccr.org)
- The Trials of Excellence for Southern Africa (TESA; established 2009 www.tesafrica.org)
- The West African Network for TB, AIDS and malaria (WANETAM; established 2009 www.wanetam.org).

The grants for the NoEs ended in December 2014. In parallel to these grants, EDCTP provided additional funding to the networks through the EDCTP-Plus project to support activities such as: the development of laboratories in preparation for future international accreditation; information and computer technology infrastructure upgrade for improving communication within and across the networks; short-term training activities, tailored to the needs of each network; and financial management training, coordinated by the EDCTP Secretariat, as a mandatory activity for each network.

Prof. Francine Ntoumi



"In 2014, we expanded the network to include the Democratic Republic of Congo. We plan to expand it further by adding more institutions from Gabon and Congo, and new partners in France and United Kingdom."

Prof. Francine Ntoumi,
CANTAM Project Coordinator

The Central African Network on TB, HIV/AIDS and malaria (CANTAM) was established in 2009 as the first network of excellence in sub-Saharan Africa supported by EDCTP. In partnership with European countries, CANTAM aimed to build and develop health research capacities in our respective institutions and countries for the conduct of clinical trials on HIV/AIDS, malaria and tuberculosis in compliance with the international Good Clinical Practice (GCP) standards.

The main challenges we face in improving capacity to conduct research in the region are: to combine the different research cultures in the region; to ensure complete and enduring support from the national disease control authorities; and to increase the research budget allocated by the government.

We have built the infrastructure for two new facilities, the TB laboratory at the University of Yaounde, in Cameroon for the activities in microbiology, as well as the laboratory at the Marien Ngouabi University in Brazzaville, Congo. Both laboratories are fully equipped and have trained staff. They have also delivered publications based on the work conducted within these laboratories. The network has also established a training platform regionally in collaboration with UNICEF, WHO, WHO/AFRO, OCEAC. Furthermore, CANTAM was able to raise local funding support from the oil company TOTAL, to support malaria research activities. Many research activities in the region have been published in scientific journals. These studies acknowledge the support from CANTAM and show that the research conducted in Central Africa now receives increasing visibility.

EDCTP provided the initial funding in 2009 and has helped to show that research activities could be conducted also in Brazzaville, supporting the set-up of the first molecular biology laboratory of the single university of the country. Site visits under the leadership of the EDCTP High Representative contributed to give value to the network and has increased interest of national authorities in EDCTP, the Network of Excellence and its activities in the region.

CANTAM

Official title:
Central Africa Network on Tuberculosis, HIV/AIDS and Malaria for the conduct of clinical trials (CANTAM)

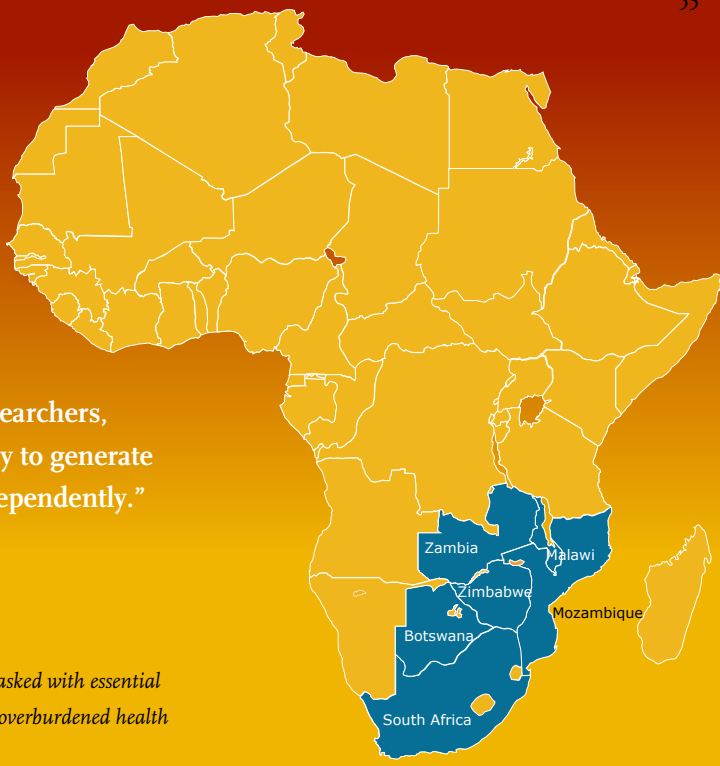
Project Coordinator:

- Francine Ntoumi (Congolese Foundation for Medical Research, Congo)

Total budget: € 3,147,644

EDCTP budget: € 2,467,644

Prof. Gerhard Walzl



"We need to continue developing more young researchers, who will be able to lead research teams with ability to generate high-quality research that will attract funding independently."

Prof. Gerhard Walzl,
TESA Project Coordinator

The TESA network was established to prepare Southern African research sites for clinical trials, including diagnostic, therapeutic and vaccines trials in the fields of HIV, malaria and TB infection.

One of the biggest challenges for African sites is the lack of reliable research funding mechanisms to support and to sustain the expertise and infrastructure that have been established during a particular trial. Institutions are not able to provide substantial financial support to research groups and local governments generally do not have adequate research funding programmes in place. Research groups and research institutions therefore have to rely on large international funding programmes that are extremely competitive and that are project specific. In Africa we clearly have access to far fewer funding opportunities than our counterparts in the developed world.

A lot of human resource capacity development is therefore lost when funding cycles end and staff training has to start afresh when new funding becomes available. Although this is to some extent a challenge facing researchers across the globe, it is more extreme in Africa. There are also insufficient numbers of health care professionals available in Africa to participate in research as they are generally tasked with essential clinical services in an overburdened health care system.

Networking provides sites with the opportunity to learn from each other and to exchange ideas and strengths. It provides opportunities for joint funding applications and to set up collaborative projects. In the TESA network, several workshops held to improve research skills have doubled as important networking events. We have also had an exchange programme where visits to more experienced partner laboratories were conducted to improve skill sets.

Several of the participating institutions have attained ISO15189 accreditation for their laboratories and are therefore now able to participate in clinical trials. This was only possible through the networking activities as experiences and procedures were exchanged between partners to accelerate the development of acceptable standards of the required procedures. Partners are now also more aware of each other's strengths and challenges, which will help in setting up future collaborative projects.

The funding provided by the EDCTP was essential support and carried the activities of the TESA network. We were able to train more than 500 staff members through different workshops and courses and TESA supported information sessions. The network has also seen a number of EDCTP-supported students complete their degrees as well as Senior Fellows completing their residency. Significant infrastructure upgrades were made possible by EDCTP funding.

We need to continue developing more young researchers, who will be able to lead research teams with ability to generate high-quality research that will attract funding independently.

TESA

Official title:
Trials of Excellence for Southern Africa (TESA)

Project Coordinator:

- Gerhard Walzl (Stellenbosch University, Immunology Research Group, South Africa)

Cofunders:

- Medical Research Council South Africa (MRC, South Africa)
- Leiden University (Netherlands).

Total budget: € 2,767,981

EDCTP budget: € 2,464,737

Prof. Pontiano Kaleebu

EACCR was established in May 2009 to contribute to relevant human and infrastructure capacity development to conduct high-quality clinical research. This included enabling less developed sites to improve their capacity to participate in multicentre clinical trials through mentorship and collaboration. The network aimed to improve and share clinical, laboratory, data management, project management and regulatory skills within the network and with other partners. Moreover, it also aimed to promote advocacy for regionally-owned research and health agenda; research use in policy and programming and resource mobilization.

There are many big challenges among which: inadequate funding including limited government research in the region; inadequate research infrastructure and limited critical mass of researchers as well as administrators; fragmentation and duplication of effort partly due to poor coordination; and poor use of research evidence in policy formulation and programming.

In order to address the challenges mentioned above there is a need to create partnerships, south-south and north-south. EACCR developed a well laid out plan with each partner identifying strengths and agreeing on responsibilities. Governance and implementation structures were put in place. We ensured there was a balance in all our activities to maximise regional impact. Efforts were made to share information including funding opportunities and to apply for joint funding.

We have created partnerships whereby institutions and scientists work together and know each other better beyond their disease expertise. The Network has established an active reciprocal monitoring scheme of 22 regional monitors in place, that assist researchers and sites to monitor studies in a more friendly and affordable approach. These have been involved in over ten clinical studies in the region.

"EDCTP facilitated south-south collaboration among 35 diverse regional institutions forming a functional network, drawing on their distinctive strength and harnessing synergy and complementarity."

Prof. Pontiano Kaleebu,
EACCR Project Coordinator

A total of 144 scientists were reached through short-term courses in GCLP, GCP, TB laboratory techniques, epidemiology, immunology, clinical monitoring and trial conduct, research and grant management. The Network supported 4 PhDs, 26 master's degree and 10 networking events. One of its EDCTP Senior Fellows was successfully awarded an MRC-UK African Research Leaders' grant of up to 5 years in mental health and capacity-building. Ten CANTAM sister network scientists have also been trained in workshops offered by EACCR.

Infrastructural upgrades have been made especially in the sister institutions that have less capacity in the conduct of clinical trials. The network's scientists have submitted a number of joint applications for funding, and this has strengthened the partnerships. About € 1.4 million in additional funds have been leveraged from other sources, such as Global Health Trials, The World Wide Antimalarial Resistance Network (WWARN), Wellcome Trust and the International Association of National Public Health Institutes.

EACCR is a partner in the Global Health Trials Network and there have been networking efforts with other consortia and potential partners. These include The African Network for Drugs and Diagnostics innovation (ANDi), TB Vaccine Trials in Europe and Africa (TB-TEA) and the Statens Serum Institute (SSI). EACCR has been an important advocacy tool that has contributed to Uganda and Tanzania becoming members of the EDCTP Association. Finally, the Network has actively participated in the East African Community Health and Science annual conferences.

EDCTP's support has been essential in several areas. It facilitated south-south collaboration among 35 diverse regional institutions forming a functional network, drawing on their distinctive strength and harnessing synergy and complementarity. EDCTP continued to support and provide a supervisory role including evaluation of technical and financial reports. EDCTP linked the network to other funders and partners and has contributed to the visibility and advocacy efforts of the network. In some of the funding opportunities, EDCTP has encouraged applicants to link their activities with the existing activities of the Networks of Excellence, including EACCR. Furthermore, EDCTP has raised the network profile in the East African Community including playing a key role on the East African Health and Scientific conferences.

EACCR

Official title:
East African Consortium for Clinical Research (EACCR)

Project Coordinator:

- Pontiano Kaleebu (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda)

Total budget: € 3,989,757

EDCTP budget: € 2,460,518

Prof. Souleymane Mboup

There are many challenges in improving capacity to conduct research in the region. It is necessary to attract more research funds on a longer term basis in order to support high quality research. It is also important to diversify funding sources in order to sustain activities within the network, and to give an opportunity to young scientists trained under the first EDCTP programme to be autonomous in grant writing and expertise to conduct clinical trials. Use of state-of-the-art tools to meet quality standards for the conduct of collaborative research projects is also needed. Moreover, attaining a legal status for WANETAM may facilitate efforts to guarantee its sustainability.

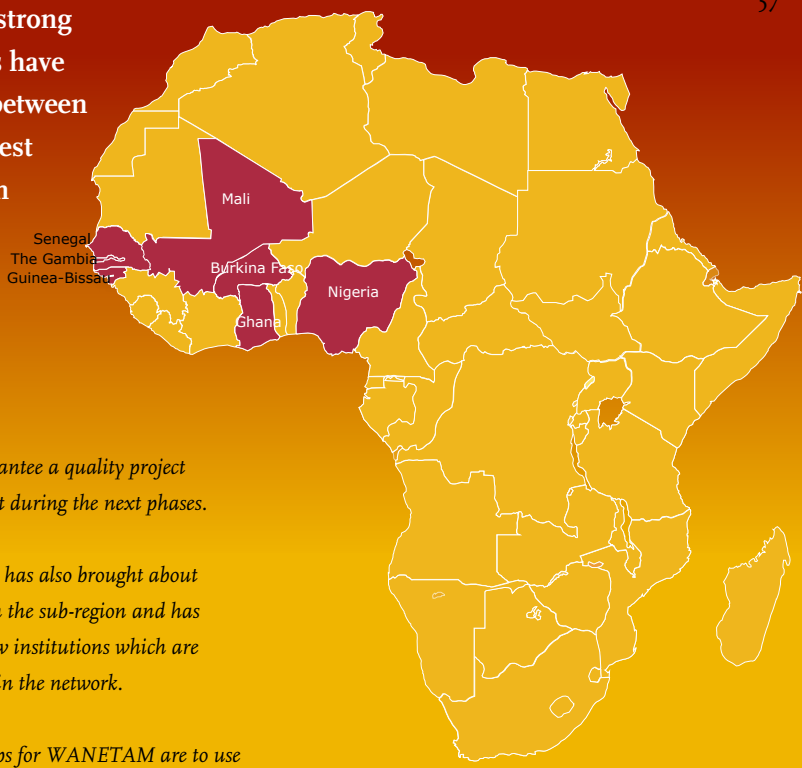
In the specific case of WANETAM, working in collaboration has given the opportunity to established institutions to share their expertise with the less established ones. Many joint training courses have been organised which have been monitored by facilitators within the network to achieve the sharing of expertise. WANETAM has also given the opportunity to different institutions within the network to conduct clinical trials and exploit data jointly. In the long run this collaboration will pave a way for the creation of a think-tank to address common issues such as outbreaks of emerging diseases, and to find pragmatic responses.

So far, WANETAM has developed strong south-south collaborations. Activities have enabled strong linkages and partnerships between established and sister institutions in the West African sub-region in spite of differences in official languages (French, English and Portuguese).

The network has trained a commendable number of skilful scientific personnel and built competencies in various facets of research and clinical trials including scientific support

"WANETAM has fostered development of strong south-south collaborations and its activities have enabled strong linkages and partnerships between established and sister institutions in the West African sub-region in spite of differences in official languages."

Prof. Souleymane Mboup,
WANETAM Project Coordinator



such as organised data management systems, clinical trial units and laboratory management. WANETAM has also supported the training of 298 researchers (including short-term training, PhDs and Master's).

We developed institutions infrastructure and well organised and established specific population cohort for research. Laboratories are equipped with state-of–the-art diagnostic tools coupled with complementary GCLP practice. Some laboratories within the network are seeking the attainment of GCLP accreditation.

Strong epidemiology competence is being developed following WANETAM-supported baseline surveillance and demographic surveys (e.g. protocols for molecular surveillance of malaria and monitoring of the efficacy of artemether-lumefantrine treatment, establishment of normal values of haematological and biochemical parameters in Africans that can be used in malaria management, survey of multi-drug resistant TB from new and re-treatment cases from all WANETAM sites).

WANETAM has built a critical mass of scientists to be able to address multi-site and multi-disciplinary clinical trials, phase Ib, phase II, phase III and phase IV pharmacovigilance studies. Skilful Project Managers have been trained and are capable of using new project management tools to guarantee a quality project management during the next phases.

The network has also brought about awareness in the sub-region and has attracted new institutions which are seeking to join the network.

The next steps for WANETAM are to use acquired skills and capacities to improve collaborative research; extend research scope by adding new diseases (NTDs); extend collaboration to new partners from renowned northern and southern institutions; undertake actions to involve governments and sub-regional institutions; extend funding opportunities to support activities within the network; and make use of the opportunity offered by the Global Health Network to implement the e-learning system.

The WANETAM Network of Excellence was funded by EDCTP, who also provided the network with technical assistance through training courses in Financial and Project Management in addition to the regular staff support.

WANETAM

Official title:
Capacity building to prepare West African sites for clinical trials on HIV, TB and malaria (WANETAM)

Project Coordinator:
- Souleymane Mboup (University Cheikh Anta Diop de Dakar (UCAD), Senegal)

Cofunders:
- The Netherlands-African Partnership for Capacity Development and Clinical Interventions against Poverty-related Diseases (NACCAP, Netherlands)
- Medical Research Council (MRC, UK)
- Medical Research Council Laboratories (The Gambia).

Total budget: € 4,146,420
EDCTP budget: € 2,499,920

Seventh EDCTP Forum

The Seventh EDCTP Forum was held in Berlin, Germany, on 30 June–2 July 2014. The Forum was officially opened by Dr Renate Loskill from Germany's Federal Ministry for Education and Research. It was attended by 358 participants from 25 African countries and 18 other countries around the world. The participants included scientific and health care communities, policymakers, regulators, product development partners, research and health funding organisations and foundations, private sector alliances, government representatives and non-governmental organisations.

The theme of the Forum was "The Partnership journey: New horizon for better health", a theme which describes both the core value underlying EDCTP strategy – partnership – and the journey EDCTP has travelled from its inception in 2003 to the present, leading, in December 2014 to the launch of EDCTP2.

The scientific presentations dealt with research in the three main PRDs (HIV, tuberculosis and malaria) as well as their interaction with NIDs. For each of the main PRDs, NIDs and health services optimisation research, a keynote address was given, outlining recent advances in the research area. There were two main themes underlying all the scientific presentations: clinical trial findings and their implications for implementation; and strengthening of capacity of sub-Saharan African researchers and institutions. Presentations were also made on cross-cutting topics including capacity development, networking and co-infections.

Overall, a total of 119 oral presentations were made, comprising 32 on HIV, 28 on TB, 30 on malaria and 29 on cross-cutting issues. The majority of the presentations were by researchers involved in EDCTP-funded projects.

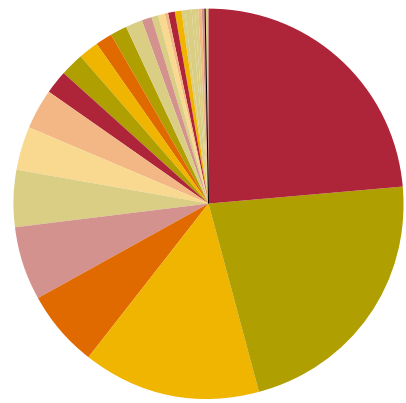
Dr Renate Loskill at the Seventh EDCTP Forum's opening address

International and third-party collaboration

In its first programme, EDCTP collaborated with several international organisations and third parties. EDCTP2 will work towards closer collaboration with industry, like-minded organisations, as well as funders of global health research and development cooperation agencies.

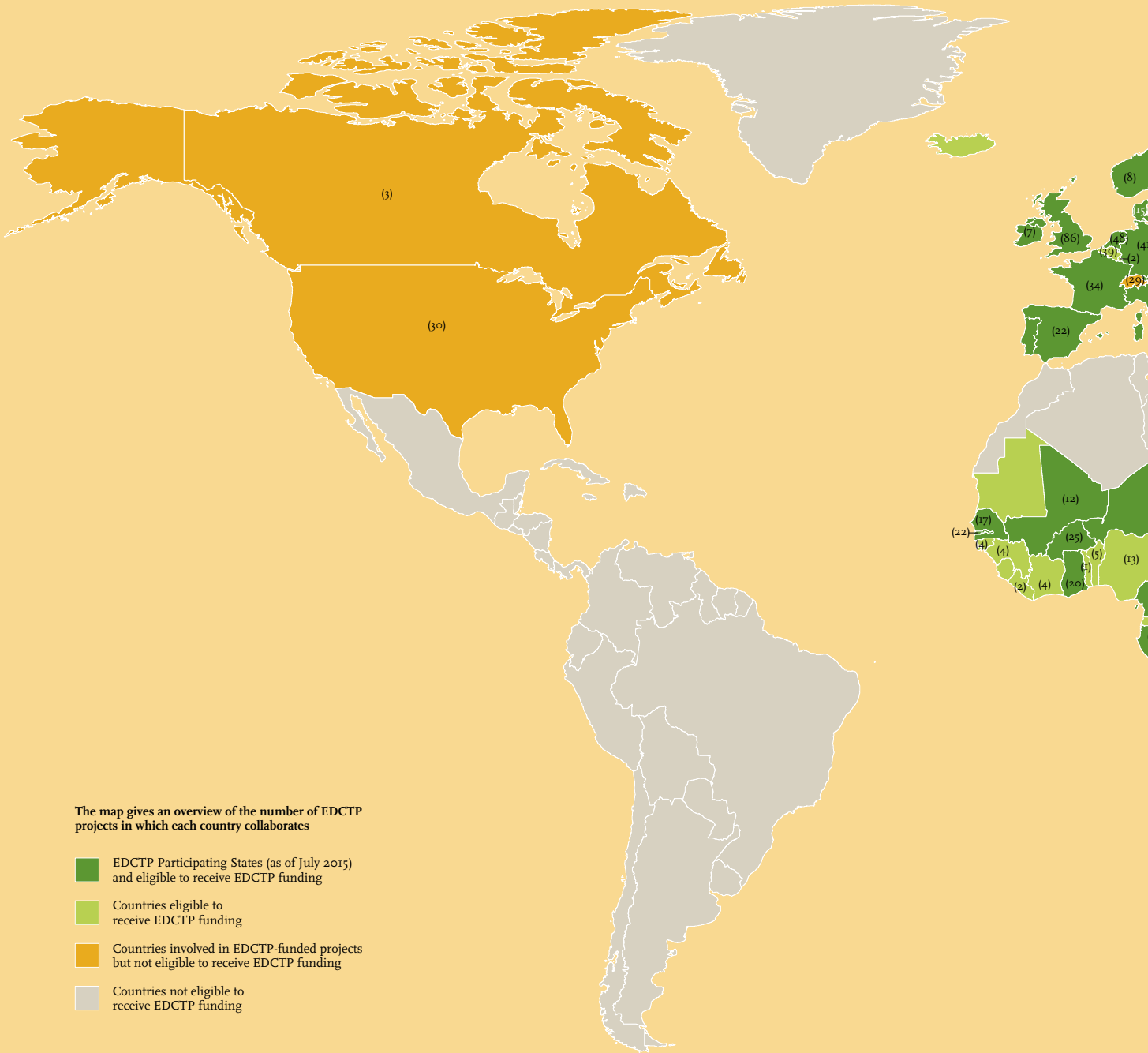
By end of 2014, EDCTP has leveraged a total of € 72.7 million of third-party cofunding for its projects. The majority of the third-party cofunding comprises in-kind contributions (€ 40.11 million; 55.2%), followed by cash contributions direct to project (€ 24.35 million; 33.5%) that are not administered by EDCTP, and € 8.24 million (11.33%) direct cash contributions via EDCTP. Cofunding contributions to the first EDCTP programme are mainly via collaborations on individual projects, with the exception of the EDCTP and Bill & Melinda Gates Foundation programmatic collaboration on the joint call for the support of clinical trials, capacity building and networking in HIV/AIDS vaccines. Cofunding from the private, for-profit sector such as pharmaceutical companies occurs primarily on EDCTP grants that support clinical trials, usually through provision of medical products for the trials. The financial contributions of pharmaceutical companies are likely to be underestimated as it can be difficult to assign a monetary value to the contributions involving provision of study drugs. Nevertheless, EDCTP and EDCTP-funded researchers have interacted with a wide range of organisations (for-profit and not-for-profit) over the years.

Third-party funding to EDCTP grants for all types of contributions 2003-2014 (€ '000)



Global TB Alliance	€ 16,948
Bill & Melinda Gates Foundation (BMGF)	€ 16,030
Aeras Global TB Vaccine Foundation	€ 10,633
Medicines for Malaria Venture (MMV)	€ 4,513
Sequella Incorporated	€ 4,376
European Vaccine Initiative (EVI, previously EMVI)	€ 3,923
Wellcome Trust	€ 2,479
Foundation for Innovative New Diagnostics (FIND)	€ 2,375
International Partnership for Microbicides (IPM)	€ 1,477
World Health Organization	€ 1,331
Bayer AG	€ 1,309
International AIDS Vaccine Initiative (IAVI)	€ 1,290
FHI360	€ 1,028
Foundation for the National Institutes of Health (FNIH)	€ 641
Sanofi Aventis	€ 376
Sanaria Inc.	€ 369
US National Institutes of Health (for the CHAMPS study)	€ 356
Chiracon GmbH	€ 355
Cipla Ltd.	€ 350
National Institute of Allergy and Infectious Diseases (NIAID)	€ 308
Delft Imaging Systems	€ 300
Vecura Company	€ 200
GlaxoSmithKline	€ 189
Walter Reed Army Institute of Research (WRAIR)	€ 178
International Association of National Public Health Institutes (IANPHI)	€ 178
Heidelberg Pharma GmbH	€ 165
Other	€ 1,027
Total	**€ 72,704**

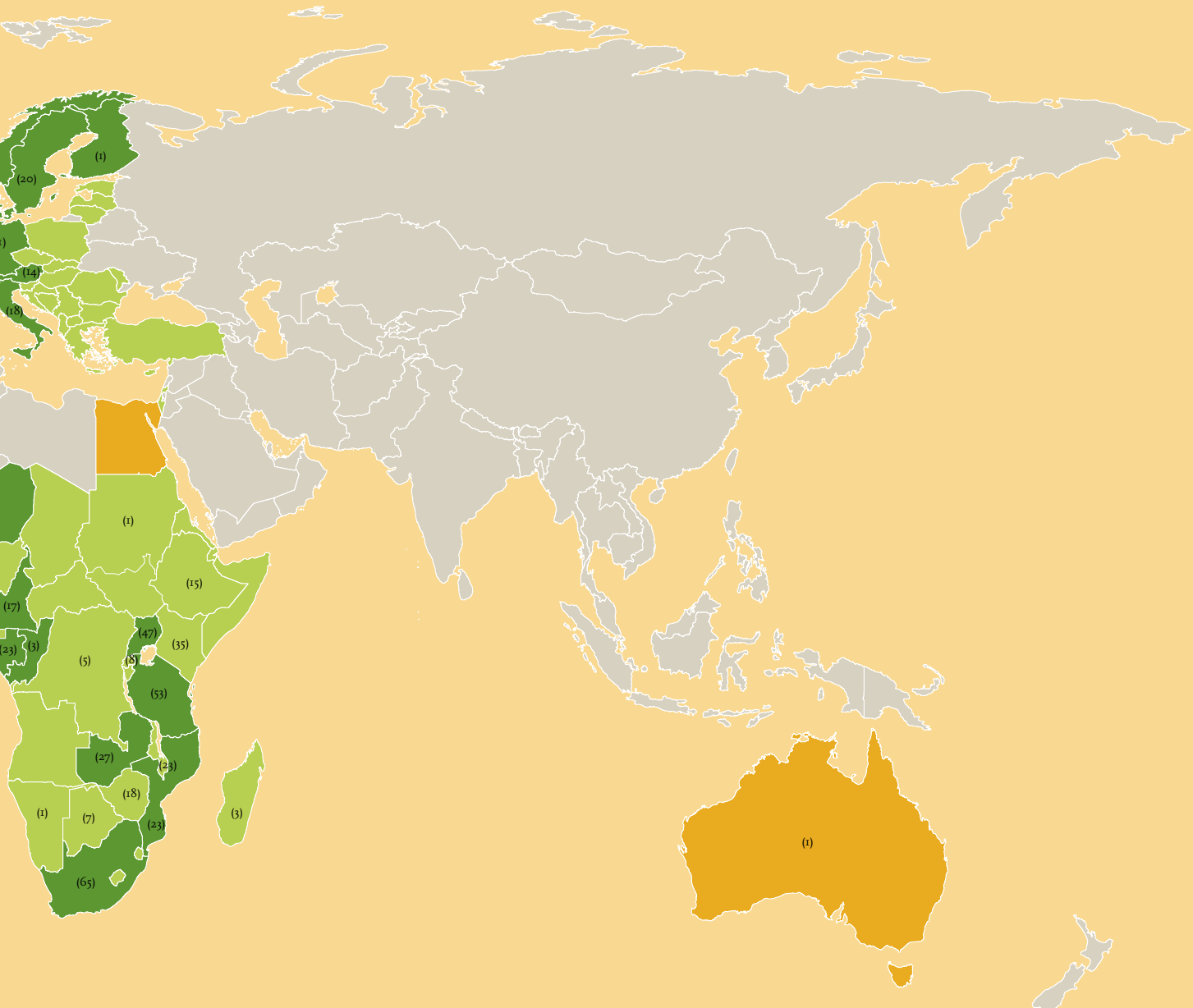
Collaboration in



The map gives an overview of the number of EDCTP projects in which each country collaborates

- EDCTP Participating States (as of July 2015) and eligible to receive EDCTP funding
- Countries eligible to receive EDCTP funding
- Countries involved in EDCTP-funded projects but not eligible to receive EDCTP funding
- Countries not eligible to receive EDCTP funding

EDCTP projects



EDCTP Governance

EDCTP General Assembly meeting on 5-6 May 2014 in The Hague, Netherlands

The EDCTP-EEIG is the legal structure for the first EDCTP programme (2003-2015);

the EDCTP Association is the legal structure for the second EDCTP programme (2014-2024).

Both legal entities have been running in parallel since 10 April 2014.

Member and observer countries of the EDCTP-EEIG in 2014

There were 16 European member countries: Austria, Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

There were two European observer countries: Finland and Latvia.

Member countries of the EDCTP Association in 2014

There were 11 African Members (or Participating States) of the Association: Cameroon, Congo, The Gambia, Ghana, Mozambique, Niger, Senegal, South Africa, Tanzania, Uganda and Zambia.

There were 13 European Members (or Participating States) of the Association: Austria, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain and the United Kingdom.

There was one Aspirant Member of the Association: Switzerland.

EDCTP General Assembly representatives and deputy representatives (EEIG and Association)

Country	GA representative	Deputy GA representative
Austria	**Dr Christiane Druml** *Medical University of Vienna*	**Dr Hemma Bauer** *Austrian Federal Ministry of Science and Research*
Belgium	**Prof. Bruno Gryseels** *Institute for Tropical Medicine*	**Ms Margarida Freire MSc** *Belgian Science Policy Office*
Cameroon	**Prof. Sinata Koulla Shiro** *Ministry of Public Health*	**Prof. Anne/Cécile Zoung/Kanyi Bissek** *Ministry of Public Health*
Congo	**Prof. Deby Gassaye** *University Marien Ngouabi*	**Prof. Francine Ntoumi** (Association Board member) *University Marien Ngouabi*
Denmark	**Dr Mikkel Lyndrup** *Statens Serum Institute*	
Finland	**Dr Jarmo Wahlfors** *Academy of Finland*	**Dr Sirpa Nuotio** *Academy of Finland*
France	**Prof. Patrice Debré** *Institut national de la santé et de la recherche médicale (INSERM), succeeded by* **Prof. Jean-François Delfraissy** *Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS); Institut de microbiologie et des maladies infectieuses (IMMI)*	**Dr Bernadette Murgue** *Institut national de la santé et de la recherche médicale (INSERM)* **Mr Guillaume Fusai** *Ministère de l'éducation nationale, de l'enseignement supérieur et de la recherche*
The Gambia	**Hon. Omar Sey** *Ministry of Health and Social Welfare*	**Dr Makie Taal** *Ministry of Health and Social Welfare*
Germany	**Dr Joachim Klein** *Bundesministerium für Bildung und Forschung*	**Dr Detlef Böcking** (Vice-Chair EEIG / Association) *Deutsches Zentrum für Luft und Raumfahrt e.V.*

Country	GA representative	Deputy GA representative
Ghana	**Prof. John Gyapong** (Association Board member) *University of Ghana*	**Prof. Kwadwo Koram** *University of Ghana*
Greece	**Prof. Evangelia Ntzani** *University of Ioannina School of Medicine*	**Mrs Eleni Stavrianoudaki** *General Secretariat for Research and Technology*
Ireland	**Mr Patrick Empey** *Irish Aid, Department of Foreign Affairs*	
Italy	**Prof. Stefano Vella** (Vice-Chair EEIG/ Association) *Istituto Superiore di Sanità (ISS)*	**Dr Benedetta Mattioli** *ISS*
Latvia	**Dr Modra Murovska** *Augusta Kirhensteina - Microbiology and Virology Institute, Riga Stradins University*	**Dr Zane Kalnina** *Ministry of Education and Science of the Republic of Latvia* **Dr Uldis Berkis** *Ministry of Science and Education*
Luxembourg	**Dr Carlo Duprel** *Fonds National de la Recherche*	
Mozambique	**Dr Ilesh Jani** *Ministry of Health*	**Dr Eusebio Macete** *Health Research Centre of Manhiça*
Netherlands	**Dr Eva Rijkers** *NACCAP-NWO*	**Dr Marcel de Kort** *Ministry of Foreign Affairs*
Niger	**Mrs Sakina Habou Ocquet** *Ministry of Public health*	**Dr Odile Ouwe Missi Oukem** *Centre de Recherche Médicale et Sanitaire (CERMES)*
Norway	**Dr Sigurd Røtnes** *Norwegian Directorate of Health*	**Dr Wenche Dageid** *The Research Council of Norway*
Portugal	**Dr Paula Elyseu Mesquita** *succeeded by* **Dr Ricardo Pereira** *Foundation for Science and Technology (FCT)*	**Dr Ana Quartin** *FCT*
Senegal	**Prof. Alioune Dieye** *University Cheikh Anta Diop*	
South Africa	**Mr Mmboneni Muofhe** *Department of Science and Technology (DST)*	**Mr Daan du Toit** *DST* **Mrs Mamohloding Tlhagale** *Council for Scientific and Industrial Research (CSIR)*
Spain	**Dr Rafael De Andrés Medina** *Instituto de Salud Carlos III*	**Mr Tomas López-Peña Ordoñez** *Instituto de Salud Carlos III*
Sweden	**Prof. Hannah Akuffo** *Swedish International Development Agency (Sida)*	**Prof. Olle Stendahl** (retired) *Faculty of Health Sciences, University of Linköping*
Switzerland	**Dr Isabella Beretta** *State Secretariat for Education and Research*	
Tanzania	**Dr Hassan Mshinda** *Tanzania Commission for Science and Technology (COSTECH)*	**Dr Flora Tibazarwa** *(COSTECH)*
Uganda	**Dr Sam Okware** *Uganda National Health Research Organisation (UNHRO)*	**Prof. Pontiano Kaleebu** *Uganda Virus Research Institute*
United Kingdom	**Dr Mark Palmer** (Chair EEIG/Association) *Medical Research Council*	**Dr Morven Roberts** *Medical Research Council*
Zambia	**Dr Elizabeth Chizema-Kawesha** *Ministry of Health*	**Prof. Nkandu Luo** *Ministry of Gender and Child Development.*

Expectations for the second EDCTP programme

Dr Mark Palmer,
Chairperson, EDCTP General Assembly

EDCTP has always been a partnership between European countries, African countries and the European Union. For many years, the EDCTP funding strategy has aimed to integrate clinical trials with research capacity development in Africa. Furthermore, EDCTP has stimulated African research leadership through its Senior Fellowships at the individual level. At the same time, it has invested at the institutional level in research infrastructure, for example by supporting Networks of Excellence, ethics review committees or the Pan African Clinical Trials registry (PACTR). This strategy is pursued from the conviction that it is essential for African countries to develop their research capacity and have ownership of their research agenda.

The EDCTP Association, established in April 2014, is designed to enable African countries to participate in the governance of the EDCTP programme and to promote a good alignment of its research with their national health policy agendas.

The main goal of EDCTP remains the same in the second programme. We will continue to fight major poverty-related diseases through financing clinical research that aims to develop or improve means of treatment, prevention and diagnostics. But important changes have been made as well. First, we have a wider scope now. The second EDCTP programme will fund not only research regarding HIV/AIDS, tuberculosis and malaria but also on the neglected infectious diseases and emergent infectious diseases, such as Ebola Virus Disease, relevant to sub-Saharan Africa. The programme also allows for funding health systems optimisation. This serves to make sure that the results of the research supported by EDCTP and other international organisations get translated into health care for all patients. The global health community has become more and more aware of the fact that development of a product as such does not guarantee that it will reach all the patients who might need it.

Secondly, we hope and endeavour to attract much more direct support from the private sector than in the first programme. The ambitious goal is to attract approximately €500 million in support from private parties, including pharmaceutical and biotechnological companies. We want to develop much closer partnerships with the private sector, which is one of the stakeholders in global health improvement.

EDCTP2 will continue to fund large clinical research in sub-Saharan Africa that is necessary to establish the safety and efficacy of new interventions against poverty-related infectious diseases. We will continue the strategy of supporting collaborative research and integrating research capacity development with the studies we fund. Moreover, we will certainly look for innovative approaches to and faster development of new interventions, for example through smart trial design.

As for many international organisations, an important challenge for EDCTP is to improve its decision-making and administrative processes, and make them as efficient as possible. The ultimate challenge is of course to invest the means that European and African countries as well as the European Union entrust us with, are well spent and get the results we all hope for.

We have much work to do and challenges to overcome in the coming ten years. Research is notoriously unpredictable but I am confident that a well-aligned research agenda will bring solid results for individual patients and health care systems alike. I hope that the research we fund will result into better health care, contributing to a more prosperous future for sub-Saharan Africa and all of us.

Observers to the EDCTP EEIG and Association General Assembly

Dr Line Matthiessen-Guyader, Head of Infectious Diseases and Public Health, DG Research & Innovation
Dr Gianpietro van de Goor, Principal Policy Officer for International Cooperation, DG Research & Innovation
Ms Veronique Lorenzo, Head of Unit B4 'Education, Health, Research, Culture', DG Development Cooperation (DEVCO)
Dr Walter Seidel, Head of Sector 'Health', Unit B4, DG DEVCO
Dr Eric Sattin, Policy Officer for Development Cooperation on Global Health, Unit B4, DG DEVCO
Dr Olawale Maiyegun, Director for Social Affairs of the African Union (AU) Commission of Social Affairs
Dr Joseph Cabore, Director for Programme Management, World Health Organisation African Region
Dr Delanyo Dovlo, Director of Health Systems and Services, World Health Organisation African Region
Prof. Tumani Corrah, Chair of the EDCTP Strategic Advisory Committee.

Strategic Advisory Committee in 2014

The Strategic Advisory Committee (SAC) is the principal advisory group to EDCTP, providing strategic and scientific advice to the General Assembly (GA) and the Secretariat, as well as oversight of the scientific integrity of the EDCTP programme, in order to assist EDCTP to achieve its mission and objectives. In January 2014, the SAC was expanded to include 15 members in order to ensure expert representation from the fields related to the remit of EDCTP2. The SAC acts exclusively in the interest of achieving the mission and objectives of EDCTP.

Prof. Tumani Corrah (Chair)	The Gambia
Dr Salim Abdulla	Tanzania
Dr Eleni Aklillu (vice-Chair)	Sweden
Prof. Moses Bockarie	United Kingdom
Dr Marilyn Bonnet	France
Prof. Simon Croft	United Kingdom
Prof. Knut Fylkesness	Norway
Prof. Stefan Kaufmann	Germany
Dr Maria Fraga Oliveira Martins	Portugal
Prof. Clara Menéndez Santos	Spain
Prof. Marie-Louise Newell	United Kingdom
Prof Gita Ramjee	South Africa
Prof. Philippe Sansonetti	France
Mr Jean Marie Talom	Cameroon
Prof. Ali Zumla (vice-Chair)	United Kingdom

External observers to the Strategic Advisory Committee

Dr Line Matthiessen	European Commission, DG research & Innovation
Dr Gianpietro van de Goor	European Commission, DG Research & Innovation
Dr Vasee Moorthy	World Health Organisation
Dr Martin O.C. Ota	World Health Organisation African Region

EDCTP Secretariat staff in 2014

Prof. Charles Mgone	Executive Director
Abdoulie Barry	Director of Finance and Administration
Dr Michael Makanga	Director South-South Cooperation and Head of Africa Office
Dr Ole F. Olesen	Director of North-North Cooperation
Dr Pauline Beattie	Operations Manager
Dr Gabrielle Breugelmans	North-North Networking Manager
Dr Thomas Nyirenda	South-South Networking and Capacity Development Manager
Hager Bassyouni	Project Officer
Dr Montserrat Blázquez Domingo	Project Officer
Chris Bruinings	Financial Officer
Ana Lúcia Cardoso	North-North Networking Officer
Mary Jane Coloma-Egelink	Grants Financial Assistant
Dr Christy Comeaux	Administrative Assistant (left July 2014)
Lucien de Corte	Information Technology (IT) Officer
Nuraan Fakier	Project Officer
Jean Marie Vianney Habarugira	Project Officer
Suzanne Hoogervorst	Travel and Events co-ordinator
Suzanne Ignatia	Human Resources (HR) Advisor
Nancy Kensmil	Administrative Officer & HR Assistant
Gert Onne van de Klashorst	Communications Officer
Mariska Louw	Senior Administrative Officer
Wendy Morrill	Administrative Officer (left September 2014)
Pete Murphy	Project Officer
Michelle Nderu	Project Officer
Lara Pandya	North-North Networking Officer
Daniela Pereira	Assistant Communications & IT Officer
Emma Qi	Grants Financial Assistant
Dr Monique Rijks-Surette	Project Officer
Sayma Siddiqui	Financial Assistant
Jennifer Stamatelos	Administrative Officer (started November 2014)
Dr Lidwien van der Valk	Legal Officer
Jing Zhao	Grants Financial Assistant

Summary financial statements 2014 and Auditor's Report

Statement of financial performance and other comprehensive income for the year ended 31 December 2014

Expressed in thousands ('000) of Euro

	Restricted EC 2014	Restricted Donor 2014	Total 2014	Total 2013
INCOME				
Contributions	6,129	10,337	16,466	41,612
Finance income	45	56	101	303
Total income	6,174	10,393	16,567	41,915
Expenditure				
Grants expenditure	749	(10,838)	(10,089)	(33,146)
Other expenditure	(7,260)	(575)	(7,835)	(6,791)
Governance expenditure	(133)	(140)	(273)	(267)
Total expenditure	(6,644)	(11,553)	(18,197)	(40,204)
Result of the year	(470)	(1,160)	(1,630)	1,711

EDCTP-EEIG has no other comprehensive income.

All income and expenditure relates to continuing activities.

	2014 € '000	2013 € '000
Result attributable to:		
EC	(470)	547
Donor	(1,160)	1,164
	(1,630)	1,711

Statement of financial position as at 31 December 2014 (After appropriation of result)

Expressed in thousands ('000) of Euro

Assets	31 December 2014	31 December 2013
Non-current assets		
Property Plant & Equipment	–	–
Debtors	–	–
Total non-current assets	–	–
Current assets		
Debtors and other receivables	1,166	10,086
Cash and cash equivalents	19,828	18,914
Total current assets	20,994	29,000
Total assets	20,994	29,000
Equity		
Restricted reserve: EC	(162)	308
Restricted reserve: Donors	1,903	3,063
Total equity	1,741	3,371
Non-current liabilities		
Grant payables	–	3,819
Total non-current liabilities	–	3,819
Current liabilities		
Grant payables	11,990	18,590
EC Creditors	4,640	–
Other payables	2,623	3,220
Total current liabilities	19,253	21,810
Total equity and liabilities	20,994	29,000

The financial statements were approved by the Executive Secretariat on behalf of the EDCTP-EEIG General Assembly by:

Professor Charles Mgone

Dated 5 June 2015

Statement of Changes in Equity for the year ended 31 December 2014

Expressed in thousands ('000) of Euro

	Restricted reserve: EC	Restricted reserve: Donor	Total
Balance as at 31 December 2012	(239)	1,899	1,660
Result of the year 2013	547	1,164	1,711
Balance as at 31 December 2013	308	3,063	3,371
Result of the year 2014	(470)	(1,160)	(1,630)
Balance as at 31 December 2014	(162)	1,903	1,741

EDCTP has no unrestricted reserves.

Statement of cash flows for the year ended 31 December 2014

Expressed in thousands ('000) of Euro

	2014	2013
Cash flows from operating activities		
Result for the year	(1,630)	1,711
Adjustment for:		
Finance income	(101)	(303)
(Increase) decrease in debtors and other receivables	8,913	6,382
Increase (decrease) in grant and other payables	(6,376)	(21,109)
Net cash flows from (used in) operating activities	806	(13,319)
Cash flows from investing activities		
Interest received	108	499
Net cash flows from investing activities	108	499
Net increase (decrease) in cash and cash equivalents	914	(12,820)
Cash and cash equivalents at 1 January	18,914	31,734
Cash and cash equivalents at 31 December	19,828	18,914

Notes to the summary financial statements

1. Basis of preparation

The summary financial statements, including the 2013 comparative figures, comprising the statement of financial position as at 31 December 2014, the statements of comprehensive income, changes in equity and cash flows for the year then ended, have been extracted from the annual financial statements of EDCTP-EEIG for the year ended 31 December 2014. These financial statements have been prepared in accordance with International Financial Reporting Standards as adopted by the European Union (hereafter EU-IFRS).

2. Accounting policies

The summary financial statements omit the notes comprising the significant accounting policies and other explanatory information as required by EU-IFRS. Therefore, to obtain a full understanding of the financial statements, the summary financial statements should be read in conjunction with the annual financial statements from which the summary financial statements were extracted.

The annual financial statements can be obtained from the EDCTP website (www.edctp.org).

Independent auditor's report

To: The General Assembly of EDCTP-EEIG

The accompanying Summary financial statements, as included on pages 69 to 72 of the Annual Report 2014, which comprise the statement of financial position as at 31 December 2014, the statements of comprehensive income, changes in equity and cash flows for the year then ended, and notes, comprising a summary of the significant accounting policies and other explanatory information, are derived from the audited financial statements of EDCTP-EEIG 2014. We expressed an unqualified audit opinion on those financial statements in our report dated 5 June 2015. Those financial statements, and the Summary financial statements, do not reflect the effects of events that occurred subsequent to the date of our report on those financial statements.

The Summary financial statements do not contain all the disclosures required by International Financial Reporting Standards as adopted by the European Union (EU-IFRS). Reading the Summary financial statements, therefore, is not a substitute for reading the audited financial statements of EDCTP-EEIG.

The directors's responsibility

The directors are responsible for the preparation of a summary of the audited financial statements on the basis described in note 1 (Basis of preparation) of the Summary financial statements.

Auditor's responsibility

Our responsibility is to express an opinion on the Summary financial statements based on our procedures, which were conducted in accordance with Dutch law, including the Dutch Standard on Auditing 810 'Engagements to report on Summary financial statements'.

Opinion

In our opinion, the Summary financial statements derived from the audited financial statements of EDCTP-EEIG 2014, as included on pages 69 to 72 of the Annual Report 2014, are consistent, in all material respects, with those financial statements, on the basis described in note 1 (Basis of preparation) of the Summary financial statements.

The Hague, 17 July 2015
KPMG Accountants N.V.

C. den Besten RA

Photo acknowledgement

All photographs by Africa Interactive unless otherwise indicated.

Cover: Laboratory staff at Ahero sub-district Hospital in Nyanza, Kenya, part of the PfSPZ Challenge study (led by Dr Bernhards Ogutu)
Page 4: Professor Charles Mgone, EDCTP Executive Director (photo by Hans Hordijk, the Netherlands)
Page 9: Dr Mark Palmer, EDCTP General Assembly Chairperson, Prof. John Gyapong, representative in the EDCTP Association for Ghana, and Prof. Charles Mgone (photo by Hans Hordijk, The Netherlands)
Page 10: Carlos Moedas, European Commissioner for Research, Innovation and Science, speaks at the welcome reception of the High-Level Event to launch the second EDCTP programme on 1 December 2014
Page 11-12: Laboratory staff at the KAVI-Kenyatta National Hospital in Nairobi, Kenya, part of the HIV-CORE004 project (led by Prof. Tomáš Hanke)
Page 14: Medical staff and volunteer at the KAVI-Kangemi Health Centre in Nairobi, Kenya, part of the HIV-CORE004 project (led by Prof. Tomáš Hanke)
Page 20-21: Clinical staff and study volunteer at the Charles De Gaulle University Hospital, in Ouagadougou, Burkina Faso, part of the MONOD project (led by Dr Valériane Leroy)
Page 22: Medical staff and volunteer at the Kibong'oto National TB Hospital in Tanzania, part of the PanACEA-MAMS project (led by Prof. Martin Boeree, Prof. Michael Hoelscher and Prof. Stephen Gillespie)
Page 27: Medical staff at the Kibong'oto National TB Hospital in Tanzania, part of the PanACEA-MAMS project (led by Prof. Martin Boeree, Prof. Michael Hoelscher and Prof. Stephen Gillespie)
Page 30-31: Laboratory staff at the Kilimanjaro Clinical Research Institute (KCRI)-Kilimanjaro Christian Medical Centre (KCMC), part of the PanACEA-MAMS project (led by Prof. Martin Boeree, Prof. Michael Hoelscher and Prof. Stephen Gillespie)
Page 32: Medical staff and research volunteer at the Regional Hospital of Banfora, Burkina Faso, part of the WANECAM project (led by Prof. Abdoulaye Djimdé)
Page 38: Laboratory staff at the KAVI-Kenyatta National Hospital in Nairobi, Kenya, part of the HIV-CORE004 project (led by Prof. Tomáš Hanke)
Page 40: Study volunteer at Ahero sub-district Hospital in Nyanza, Kenya, part of the PfSPZ Challenge stufy (led by Dr Bernhards Ogutu)
Pages 46-47: Study volunteers at the KAVI-Kangemi Health Centre in Nairobi, Kenya, part of the HIV-CORE004 project (led by Prof. Tomáš Hanke)
Page 48: Project staff meeting at the Ubuntu Clinic in Khayelitsha, South Africa, part of the PredART project (led by Dr Graeme Meintjes)
Page 51: Laboratory staff at the Charles De Gaulle University Hospital, in Ouagadougou, Burkina Faso, part of the MONOD project (led by Dr Valériane Leroy)
Page 54: Medical staff at the Centro de Investigação e Treino em Saúde da Polana Caniço in Mozambique, as part of the TaMoVacII project (led by Prof. Eligius Lyamuya)
Page 56: Study volunteer at the Centro de Investigação e Treino em Saúde da Polana Caniço in Mozambique, as part of the TaMoVacII project (led by Prof. Eligius Lyamuya)
Page 58: Dr Renate Loskill at the Seventh EDCTP Forum's opening address
Page 62: EDCTP General Assembly members in 2014 (photo by Hans Hordijk, The Netherlands)
Page 65: Dr Mark Palmer, EDCTP General Assembly Chairperson (photo by Hans Hordijk, The Netherlands)
Page 68: Blood samples for the TaMoVacII project (led by Prof. Eligius Lyamuya)

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Printing Kapsenberg van Waesberge

The Hague, July 2015
European & Developing Countries Clinical Trials Partnership

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