# EDCTP Portfolio

# Fellowship and training schemes

# 1 Career Development/Senior fellowships

## 1.1 HIV/AIDS Career Development and Senior Fellowships

| Project Acronym (Coordinator) | Study classification /design | Product(s) | Manufacturer/ Developer | Study population | Status |
|---|---|---|---|---|---|
| Alabi SF -HIV | Laboratory assay development | In-house viral load assays | In-house (based on Roche HIV version) | none | Completed |
| Ekouevi SF - HIV | Phase II multicentre open label trial | Truvada (Emtricitabine + Tenofivir), Niverapine and Zudovudine/Azidothymid | Gilead Sciences, Boehringer Ingelheim and Tübingen respectively | 60 mother-child pairs per step (10 per site and per step in Abidjan, Côte d'Ivoire, Soweto, South Africa and Phnom Penh in Cambodia | Completed |
| Serwanga (Kebba) - CDF | Prospective cohort study on protective HIV immunity | none | Not applicable | 200 HIV serodiscordant couples with particular interest in the seronegative partners at high risk for HIV-1 infection. | Completed |
| Sevene - CDF | Prospect cohort safety study | Sulphadoxine-Pyrimithamine + standard regimen (Stavudine, lamuvidine and niverapine) | WHO pre-qualified drugs | The pregnant women from first ante-natal visit to deliverly, and both mother and baby followed until the child is 12 months old | Completed |
| Njai- SF | Longitudinal study on HIV immunology | none | Not applicable | The proposed study will use the unique Rural Clinical Cohort established in 1990 | Completed |
| Ndembi -SF | Prospective cohort study on determinants of dual infection with HIV strains | none | Not applicable | A rural clinical cohort (RCC) of over 500 individuals (HIV+ and HIV-) established in 1990 | Completed |
| Mwinzi - SF | Prevalence study on IRIS in schistomiasis on | standard regimen (Stavudine, lamuvidine and | WHO pre-qualified drugs | HIV-schistosome co-infection patients undergoing HAART In western Kenya. | Completed |

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| | HAART | niverapine) | | | |
| Kiepela - SF | Laboratory analyses of HIV mucosal immunity and KIR:HAL genes | none | Not applicable | | Ongoing |
| Kityo -SF | Prospective cohort study on drug resistance in children | standard regimen (Stavudine, lamuvidine and niverapine) | WHO pre-qualified drugs | 360 HIV-infected children under 12 years of age in three JCRC clinics already participating in the established PASER network monitoring HIVDR in adults | Ongoing |
| Burgers -SF | Laboratory study on the effect of HIV on lung immunity in TB patients | None | Not applicable | 70 adult latent TB patients: 35 HIV+ with CD4 counts >400 and 35 HIV- persons | Completed |
| Mduluza –SF | Prospective cohort study on the evolution of neutrolising antibodies in HIV – C | None | Not applicable | Stored samples of 70 individuals aged between 15 - 55 years old with acute/recent stages of HIV-1C infection followed up to day 440 in Botswana | Completed |
| Kayondo –SF | Laboratory analyses for ART resistace in treatment naïve patients | Combivir + niverapine or tenofivir | ?? prequalified formulations | Stored samples from structured treatment interrupted (STI) and continuous treatment (CT) arms of the DART of Combivir + Nevirapine or Tenofovir combination regimen | Ongoing |
| Kennedy -SF | Capacity building for HIV/STI prevention trials in a post-conflict Liberia | None | Not applicable | none | Completed |
| Kinyanda – SF | Prevalence study of mental health among clinical trials participants in HIV/AIDS | None | Not applicable | HIV patients on HAART in Uganda | Ongoing |
| Ndounga - SF | Establishment of a HIV positive cohort for site preparation | None | Not applicable | HIV infected individuals | Ongoing |

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| | for HIV and malaria clinical trials in the Republic of Congo | | | | |
| Delany Moretlwe - SF | Prospective cohort study on HPV and genital warts in HIV-1 negative and HIV-1 positive men taking ART in South Africa. | None | Not applicable | Men having sex with men | Ongoing |
| Nchinda - SF | Laboratory pre-clinical evaluation of dendritic cell antigens and HIV gag protein vaccines | None | Not applicable | In vitro studies (samples from chronically HIV infected patients in Cameroon) | Ongoing |

### 1.1.1 Abraham Alabi

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| EDCTP Project Coordinator: | Abraham Alabi (Medical Research Council (MRC) Laboratories, The Gambia) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Development and evaluation of high throughput, cheap and reliable assays for monitoring HIV-1 and HIV-2 viral loads in ARV programmes and clinical trials in developing countries |
| EDCTP Project Code: | TA.2004.40200.001 |
| EDCTP Project Start Date: | 1 January 2005 |
| EDCTP Project End Date: | 28 September 2008 |
| Collaborators: | • Steve Kaye (MRC Laboratories, The Gambia)<br>• Samuel McConkey (MRC Laboratories, The Gambia) |
| Site Principal Investigator(s): | • Clayton Onyango (The Gambia)<br>• Modou Camara (The Gambia)<br>• Steve Kaye (The Gambia)<br>• Samuel MacConkey (The Gambia)<br>• Sarah Rowland Jones (The Gambia)<br>• Simon Agwale (Nigeria) |
| Goal: | To develop robust and affordable in-house virus load assays for quantifying HIV-1 and HIV-2 RNA in the blood of an infected individual; with similar sensitivity, specificity, and reproducibility to currently available commercial HIV viral load assays. A secondary objective is to train scientists in the West Africa sub-region to encourage a wider use of the assay |
| Collaborating site(s): | Medical Research Council (UK) |
| Study design: | Laboratory assay development and validation |
| Product(s): | In-house viral load assay |
| Manufacturer/Developer: | Roche proto-type |
| Status: | Completed |
| Results and Outcomes: | The project produced a locally validated HIV viral load assay. 10 scientists from West Africa and 9 from Eastern Africa were trained in the course. Six publications resulted from the grant. |
| Publications: | 1. Hansmann A, Schim van der Loeff MF, Kaye S, Awasana AA, Sarge-Njie R, O'Donovan D, Ariyoshi K, Alabi A, et al. Baseline plasma viral load and CD4 cell percentage predict survival in HIV-1 and HIV-2-infected women in a community-based cohort in The Gambia. *J. Acquir Immune Defic. Syndr.* 2005; 38: 335-341.<br>2. Gillespie GM, Pinheiro S, Sayeid-Al-Jamee M, Alabi A, et al. CD8+ T cell responses to human immunodeficiency viruses type 2 (HIV-2) and type 1 (HIV-1) gag proteins are distinguishable by magnitude and breadth but not cellular phenotype. *Eur. J Immunol.* 2005; 35:1445-53.<br>3. Duvall MG, Jaye A, Dong T, Brenchley JM, Alabi AS et al., Maintenance of HIV-specific CD4+ T cell help distinguishes HIV-2 from HIV-1 infection. *J Immunol.* 2006; 176: 6973-81<br>4. Jallow S, Kaye S, Alabi A et al., Virological and immunological response to Combivir and emergence of drug resistance mutations in a cohort of HIV-2 patients in The Gambia. *AIDS 2006*; 20:1455-8.<br>5. Leligdowicz A, Yindom LM, Onyango C, Sarge-Njie R, Alabi A et al., Robust Gag-specific T cell responses characterize viremia control in HIV-2 infection. *J Clin Invest*. 2007; 17: 3067-3074<br>6. Damond F, Benard A, Ruelle J, Alabi A, Kupfer B, Gomes P, Rodes B, Albert J, Böni J, Garson J, Ferns B, Matheron |

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| | S, Chene G, Brun-Vezinet F; ACHIEV2E Collaboration on HIV-2 Infection Study Group., Quality control assessment of human immunodeficiency virus type 2 (HIV-2) viral load quantification assays: results from an international collaboration on HIV-2 infection in 2006. *J. Clin. Microbiol.* 2008; 46:2088-91. |

### 1.1.2 Didier Ekouevi

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| EDCTP Project Coordinator: | Didier Ekouevi (Centre Hospitalier Universitaire (CHU) de Treichville, Cote d'Ivoire) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Phase II multicentre open label trial to evaluate the pharmacokinetics and the safety and toxicity of the Tenofovir-Emtricitabine combination in pregnant women and infants in Africa and Asia |
| EDCTP Project Code: | TA.2004.40200.003 |
| EDCTP Project Start Date: | 1 January 2005 |
| EDCTP Project End Date: | 30 October 2007 |
| Collaborators: | • Gerard Allou (Centre Hospitalier Universitaire (CHU) de Treichville, Cote d'Ivoire)<br>• Patricia Fassinou (CHU de Treichville, Cote d'Ivoire)<br>• Appolinaire Horo (CHU de Treichville, Cote d'Ivoire)<br>• Hassan Toure (CHU de Treichville, Cote d'Ivoire)<br>• Ida Viho (CHU de Treichville, Cote d'Ivoire) |
| Site Principal Investigator(s): | • Thérèse N'dri-Yoman (Côte d'ivoire)<br>• Eric Nerrienet (Cambodia)<br>• Leang Sim Kruy (Cambodia)<br>• James Mcintyre (South Africa)<br>• Marie-Laure Chaix (France)<br>• Christine Rouzioux (France)<br>• Jean-Marc Treluyer (France)<br>• Elisabeth Rey (France)<br>• Stéphane Blanche (France)<br>• Elise Arrive (France) |
| Clinical Trial/Study Sponsor: | French National Research Agency (France) |
| Trial/Study title: | Phase II multicentre open label trial to evaluate the pharmacokinetics and the safety and toxicity of the Tenofovir-Emtricitabine combination in pregnant women and infants in Africa and Asia |
| Objective(s): | To assess safety, pharmacokinetics (PK) and resistance profile of Truvada® (tenofovir disporoxyl fumarate [TDF 300 mg] + Emtricitabine [FTC 200 mg]), an alternative ARV regimen for PMTCT in resource-limited settings in HIV-infected pregnant women and their infants |
| Clinical Trial/Study site(s): | Centre Hospitalier Universitaire (CHU) de Treichville (Cote d'Ivoire) |
| Study design: | Phase II trial |
| Number of subjects: | 60 mother-child pairs |
| Product: | • Truvada (Emtricitabine + Tenofivir)<br>• Niverapine<br>• Zudovudine/Azidothymid |
| Manufacturer/Developer: | • Gilead Sciences (USA)<br>• Boehringer Ingelheim (Germany)<br>• University of Tübingen (Germany) |
| Cofunders: | National Agency for AIDS Research (ANRS, France |
| Trial Registration number(s): | NCT00334256 |
| Status: | Completed |
| Results and Outcomes: | This study laid a foundation for collaboration in PMTCT trials between South Africa, Ivory Coast and Cambodia. The study showed that emtricitabine (FTC) achieves adequate blood levels in mothers and their neonates. Three publications have |

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| | come out of the studies. |
| Publications: | 1. The TEmAA ANRS 12109 Study group. Tolerance and viral resistance after single-dose nevirapine with tenofovir and emtricitabine to prevent vertical transmission of HIV-1. *AIDS 2009*, Vol 23 No 7. 825-33.<br>2. D Hirt, S Urien, DK Ekouévi, E Rey, E Arrivé, S Blanche, C Amani-Bosse, E Nerrienet, G Gray, M Kone, SK Leang, J McIntyre, F Dabis and J-M Tréluyer. Population Pharmacokinetics of Tenofovir in HIV-1-Infected Pregnant Women and Their Neonates (ANRS 12109). *Clinical pharmacology & Therapeutics*. 5 November 2008; 1-5<br>3. De´borah Hirt, Saik Urien, Elisabeth Rey, Elise Arrive´, Didier K. Ekoue´vi, Patrick Coffie´, Sim Kruy Leang, Sarita Lalsab, Divine Avit, Eric Nerrienet, James McIntyre, Ste´phane Blanche, Francois Dabis, and Jean-Marc Tre´luyer. Population Pharmacokinetics of Emtricitabine in Human Immunodeficiency Virus Type 1-Infected Pregnant Women and Their Neonates. *Antimicrobial agents and chemotherapy*, Mar. 2009, p. 1067–1073 |

### 1.1.3 Jenifer Serwanga

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| EDCTP Project Coordinator: | Jenifer Serwanga (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda) |
| EDCTP Project Call: | Career Development Fellowship |
| EDCTP Project Title: | Pattern of HIV-induced T-cell response influencing viral load course following HIV infection |
| EDCTP Project Code: | TA.2005.40203.003 |
| EDCTP Project Start Date: | 30 October 2006 |
| EDCTP Project End Date: | 23 May 2010 |
| Collaborators: | • Jill Gilmour (International AIDS Vaccine Initiative, Netherlands)<br>• Martin Grobusch (University of the Witwatersrand, South Africa)<br>• Pontiano Kaleebu (MRC/UVRI, Uganda)<br>• Andrew McMichael (University of Oxford, UK) |
| Site Principal Investigator(s): | • Heiner Grosskurth (Uganda)<br>• Pontiano Kaleebu (Uganda)<br>• Pietro Pala (Uganda)<br>• Daniel Bugembe Lule (Uganda)<br>• Andrew McMicheal (UK) |
| Trial/Study title: | Pattern of HIV-induced T-cell response influencing viral load course following HIV infection |
| Objective(s): | 1. To determine the plasma viral load pVL trajectory from primary infection through viral set point and beyond<br>2. To evaluate the relationship between HLA class I polymorphisms and pVL trajectory<br>3. To evaluate the pattern and magnitude of HIV-1 specific CD8 T-cell response longitudinally following infection<br>4. To sequence the virus at specified intervals following HIV-1 infection to assess viral evolution and escape from HIV specific responses. |
| Study design: | Prospective cohort study on protective HIV immunity |
| Number of subjects: | 200 |
| Status: | Completed |
| Results and Outcomes: | The study investigated how T cell responses in the early phase of HIV-1 infection may influence the course of disease. The results showed that different persons have different levels of both conserved (sustained) and temporary responses to HIV infection. Six staff (Daniel Lule, Kenneth Musinguzi, Ekii Obuku, Samuel Okurut, Andrew Ekii and Pietro Pala) were trained in various short courses including good clinical practices. |
| Publications: | |

### 1.1.4 Esperança Sevene

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| EDCTP Project Coordinator: | Esparanca Sevene (Eduardo Mondlane University, Mozambique) |
| EDCTP Project Call: | Career Development Fellowship |
| EDCTP Project Title: | Intensive safety monitoring of antimalarial and anti-retroviral drugs used during pregnancy in Manhiça |
| EDCTP Project Code: | TA.2005.40203.007 |
| EDCTP Project Start Date: | 23 April 2010 |
| EDCTP Project End Date: | 27 February 2010 |
| Collaborators: | • Xavier Carne (Hospital Clinic of Barcelona, Spain)<br>• Catarina David (Manhiça Health Research Center, Mozambique)<br>• Alexander Dodoo (University of Ghana)<br>• Sureia Hassamo (Mozambique)<br>• Lidia Laço (Mozambique)<br>• Sonia Machevo (Mozambique)<br>• Alda Mariano (Eduardo Mondlane University, Mozambique)<br>• Clara Menendez (University of Barcelona, Spain)<br>• Ana Sofia Roberto (Mozambique)<br>• Joaquina do Rosário (Mozambique) |
| Goal: | To describe potential adverse drug reactions to anti-malarial and anti-retroviral drugs in pregnant women including adverse pregnancy outcomes |
| Objective(s): | To measure the incidence of these adverse drug reactions and to determine risk factors that may contribute to the development of adverse drug reactions to anti-retroviral and antimalarial drugs in the pregnant women |
| Study design: | Prospect cohort safety study |
| Number of subjects: | 2041 |
| Product: | Sulphadoxine-Pyrimithamine + standard regimen (Stavudine, lamuvidine and niverapine) |
| Manufacturer/Developer: | WHO prequalified regimen drugs |
| Status: | Completed |
| Results and outcomes: | A total of 2041 pregnant woman were recruited in the study. Of these 1608 delivered at the hospital. After delivery, 1473 and 877 mothers presented their babies for assessment at second and twelfth month respectively. Fifteen pregnant women presented adverse drug reactions to drugs used during pregnancy but all recovered without sequelae. The study team attended four courses on pharmacovigilance and data management during the course of the projects. Nine papers have been published of which eight are in indexed journals. |
| Publications: | 1. E Sevene, A Bardají, A Mariano, S Machevo, E Ayala, B Sigaúque, P Alonso, X Carné, C Menendez. Drug exposure and pregnancy outcomes in Mozambique. *Paediatr Drugs*. 2012 Feb 1;14(1):43-9. doi: 10.2165/11591270<br>2. Sevene E, González R, Menéndez C. Current knowledge and challenges of antimalarial drugs for treatment and prevention in pregnancy. *Expert Opin Pharmacother*. 2010 Jun;11(8):1277-93.<br>3. Julie Cliff; Simon Lewin; Godfrey Woelk; Benedita Fernandes; Alda Mariano; Esperanca Sevene; Karen Daniels; Sheillah Matinhure; Andrew Oxman; John Lavis. Policy development in malaria vector management in Mozambique, South Africa and Zimbabwe. *Health Policy and Planning* 2010; doi: 10.1093/heapol/czq008.<br>4. Woelk G, Daniels K, Cliff J, Lewin S, Sevene E, Fernandes |

B, Mariano A, Matinhure S, Oxman AD, Lavis JN, Stålsby Lundborg C. Translating research into policy: Lessons learned from eclampsia treatment and malaria control in three southern African countries. *Health Research Policy and Systems* 2009, 7:31. doi:10.1186/1478-4505-7-31

5. John J Aponte, David Schellenberg, Andrea Egan, Alasdair Breckenridge, Ilona Carneiro, Julia Critchley, Ina Danquah, Alexander Dodoo, Robin Kobbe, Bertrand Lell, Jürgen May, Zul Premji, Sergi Sanz, Esperanza Sevene, et al. Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. *The Lancet* September 17, 2009.
6. Karen Daniels, Simon Lewin, Practihc Policy Group (Sevene E, Mariano A). Translating research into maternal health care policy: a qualitative case study of the use of evidence in policies for the treatment of eclampsia and pre-eclampsia in South Africa. *Health Res Policy Syst*. 2008 Dec 17;6:12. doi: 10.1186/1478-4505-6-12.
7. Sevene E, Mariano A, Mehta U, Machai M, Dodoo A, Vilardell D, Patel S, Barnes K, Carné X. Spontaneous Adverse Drug Reaction Reporting in Rural Districts of Mozambique. *Drug Safety.* 2008; 31 (10): 867-876.
8. Bardagí A, Sigaúque B, Bruni L, Romagosa C, Sanz S, Mabunda S, Mandomando I, Aponte J, Sevene E, Alonso PL, Menendez C. Clinical malaria in African pregnant women. *Malar J*. 2008; 7 (27): 1-7.
9. Ward SA, Sevene EJP, Hastings IM, Nosten F, Mcgready R. Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance. *The Lancet infect Dis* 2007;7:136-44.

### 1.1.5 Harr Freeya Njai

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| EDCTP Project Coordinator: | Harr Freeya Njai (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Characterisation of neutralizing antibody responses in Chronic clades A and D Human Immunodeficiency Virus Type 1 (HIV-1) infections and the relationship with established markers of disease progression – A longitudinal study in rural Uganda |
| EDCTP Project Code: | TA.2007.40200.001 |
| EDCTP Project Start Date: | 13 August 2008 |
| EDCTP Project End Date: | 12 August 2010 |
| Collaborators: | • Sunita Balla (Prince Leopold Institute of Tropical Medicine (ITM), Belgium)<br>• Heiner Grosskurth (MRC/UVRI, Uganda)<br>• Pontiano Kaleebu (MRC/UVRI, Uganda)<br>• Anatoli Kamali (MRC/UVRI, Uganda)<br>• David Montefiori (Duke University, USA) |
| Site Principal Investigator(s): | • Heiner Grosskurth (Uganda)<br>• Pontiano Kaleebu (Uganda)<br>• Anatoli Kamali (Uganda) |
| Objective(s): | To identify and assess the prevalence and potency of broadly neutralising antibodies in a cohort of non-B HIV chronically infected individuals in rural Uganda. |
| Collaborating site(s): | • Helen Donners (Belgium)<br>• David Montefiori (USA) |
| Study design: | Longitudinal study on HIV immunology |
| Cofunders: | • Duke University Medical Center (Uganda)<br>• ITM (Belgium)<br>• MRC/UVRI (Uganda) |
| Status: | Completed |
| Results and Outcomes: | Magnitude of the NAb response against SF162.LS (subtype B) and MW965.26 (subtype C) varied but was relatively potent in most cases (ID50 titers >1,000, range 20->43740). Between 5-10 years of infection, samples neutralized MW965.26 more than SF162 with a median of 6,243 at T2; at infections more than 10 years the same neutralization profile is seen (i.e. MW965 is more neutralized than SF162). In infections between 5-10 years median neutralization property was significantly higher at T1 than at T2 among those aged between 5-10 years, p values 0.0048 (MW965.26) and 0.012 (SF162.LS). One publication has come out of this work. |
| MSc study: | Topic: PCR and sequencing assays<br>Candidate: Juma Magambo (MRC/UVRI, Uganda) |
| Publications: | 1. HF Njai, K Tomusange, B Sokolik-Wolak, D Montefiori, S Balla, G Vanham, J Levin, D Maher, A Kamali, H Grosskurth, P Pala and P Kaleebu. 2009. Prevalence of neutralizing antibody responses in chronic clades A and D human immunodeficiency virus type 1 (HIV-1) infections. *Retrovirology* 2009, 6(Suppl 3):P39. |

### 1.1.6 Nicaise Ndembi

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| EDCTP Project Coordinator: | Nicaise Ndembi (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Frequency and determinants of dual infection with different strains of HIV-1 in low- and high-risk populations in Uganda |
| EDCTP Project Code: | TA.2007.40200.011 |
| EDCTP Project Start Date: | 31 July 2008 |
| EDCTP Project End Date: | 30 July 2010 |
| Collaborators: | • Eric Arts (ase Western Reserve University, USA)<br>• Frances Gotch (Imperial College London, UK)<br>• Heiner Grosskurth (MRC/UVRI, Uganda)<br>• Pontiano Kaleebu (MRC/UVRI, Uganda)<br>• Philippe Lemey (Katholieke Universiteit Leuven, Belgium)<br>• Pietro Pala (MRC/UVRI, Uganda)<br>• Deogratius Ssemwanga<br>• Annemie Vandamme (Katholieke Universiteit Leuven, Belgium)<br>• Carolyn Williamson (University of Cape Town, South Africa) |
| Site Principal Investigator(s): | Pontiano Kaleebu (Uganda) |
| Primary Objective(s): | To evaluate the frequency and determinants of dual infection with different strains of HIV-1 in low- and high- risk populations in Uganda. This study had four major objectives and 1 minor:<br>• Implement and validate novel sequence analysis methods developed at the Rega Institute (Belgium) for the detection of instances of co-infection and superinfection in longitudinally collected samples<br>• Determine the clinical consequences of dual infection by comparing disease progression (viral loads and CD4+ counts) between those with and without dual infection<br>• Determine the course of virologic recombination that occurs after dual infection<br>• Determine the immunologic correlates of dual infection<br>• Determine the prevalence of HIV-1 drug resistance among recently infected commercial sex workers. |
| Collaborating site(s): | George Shaw (UK) |
| Study design: | Prospective cohort study on determinants of dual infection with HIV strains |
| Number of subjects: | 500 |
| Status: | Completed |
| Results and Outcomes: | Various methodologies have been optimised and used for the detection and confirmation of dual infection. The study was unable to determine the incidence of co-infection and superinfection but was able to show HIV-1 subtype distribution, multiple infections, sexual networks and partnership histories in Commercial Sex Workers in Kampala. The prevalence of transmitted drug resistance among newly infected commercial sex workers was done among 42 women that seroconverted in the high risk population. DNA sequencing work still continues. Two articles from the project have been published in high impact journals |
| Publications: | 1. Ssemwanga D, Lyagoba F, Ndembi N, Mayanja BN, Larke N, Wang S, Baalwa J, Williamson C, Grosskurth H, Kaleebu P. Multiple HIV-1 infections with evidence of |

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| | recombination in heterosexual partnerships in a low risk Rural Clinical Cohort in Uganda. *Virology*. 2011 Mar 1;411(1):113-31. Epub 2011 Jan 15.<br>2. Ndembi N, Hamers RL, Sigaloff KC, Lyagoba F, Magambo B, Nanteza B, Watera C, Kaleebu P, Rinke de Wit TF. Transmitted antiretroviral drug resistance among newly HIV-1 diagnosed young individuals in Kampala. *AIDS*. 2011 Apr 24;25(7):905-10 |

### 1.1.7 Pauline Mwinzi

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| EDCTP Project Coordinator: | Pauline Mwinzi (Kenya Medical Research Institute (KEMRI), Kenya) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Immune reconstitution inflammatory syndrome (IRIS) in schistosomiasis patients undergoing HAART |
| EDCTP Project Code: | TA.2008.40200.007 |
| EDCTP Project Start Date: | 24 November 2009 |
| EDCTP Project End Date: | 24 November 2011 |
| Collaborators: | • Robert Colebunders (Prince Leopold Institute of Tropical Medicine (ITM), Belgium)<br>• Diana Karanja (KEMRI, Kenya)<br>• Luc Kestens (ITM, Belgium)<br>• Erick Muok (KEMRI, Belgium)<br>• Katja Polman (ITM, Belgium) |
| Site Principal Investigator(s): | • Diana Karanja (Kenya)<br>• Erick Muok (Kenya) |
| Objective(s): | To study the Immunopathogenesls, clinical aspects and management of manifestation of IRIS in HIV-schistosome co-infection patients undergoing HAART In western Kenya. Schistosome infections are common in the same areas where HIV prevalence is also high. |
| Collaborating site(s): | Bob Colebunders (Belgium), Luc Kestens (Belgium), Katja Polman(Belgium) (Belgium) |
| Study design: | Prevalence study on IRIS in schistomiasis on HAART |
| Product: | Standard regimen (Stavudine, lamuvidine and niverapine) and anti-schtistosmes |
| Status: | Completed |
| Results and Outcomes: | 622 HIV positive patients were followed. In the first year of follow up 12 patients expressed signs and symptoms of IRIS of whom two met the case definition of IRIS. As a requirement for all staff participants on this project, GCP/GCLP training was provided online from the EDCTP-sponsored AMANET online courses. |
| PhD study | Title: Immunology of Schistosoma associated IRIS<br>Candidate: Eric Muok (Kenya) |
| MSc studies: | Title: Pathogenesis of Schistosomiasis/HIV Co-Infection: Polymorphisms in IL-23 Receptor in Schistosomiasis Patients Undergoing Highly Active Antiretroviral Therapy (HAART)"<br>Candidate: George Ogola |
| | Title: Role of vitaminD3 (1-ALPHA, 25-Dihydroxyvitamin D3) in Schistosoma -IRIS<br>Candidate: Elses Simuyu |
| | Caroline Mukiimi was attached to the project as an intern. |
| Publications: | |

### 1.1.8 Photini Kiepela

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| EDCTP Project Coordinator: | Photini Kiepela (Medical Research Council South Africa (MRC), South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Training in mucosal immunity and the evaluation of KIR:nHLA genes in HIV-1 clade c infection: key components to HIV vaccine design |
| EDCTP Project Code: | TA.2008.40200.015 |
| EDCTP Project Start Date: | 25 March 2010 |
| EDCTP Project End Date: | 31 December 2013 |
| Collaborators: | • S. Ganesh (MRC, South Africa)<br>• Sharika Gappoo (MRC, South Africa)<br>• R. Govinden (MRC, South Africa)<br>• Thumbi Ndungu'U (University of KwaZulu-Natal, South Africa)<br>• Thesla Palanee (MRC, South Africa)<br>• Jo-Ann Passmore (University of Cape Town, South Africa)<br>• Gita Ramjee, (MRC, South Africa) |
| Site Principal Investigator(s): | • S Ganesh (South Africa)<br>• Sharika Gappoo (South Africa)<br>• R Govinden (South Africa)<br>• Thumbi Ndung'U (South Africa)<br>• Thesla Palanee (South Africa) |
| Objective(s): | To answer questions relating to the role of host HLA and KIR genotype as HLA class I contributes to both the innate and adaptive immune responses |
| Study design: | Laboratory analyses of HIV mucosal immunity and KIR:HAL genes |
| Status: | Ongoing |
| Results and outcomes: | KIR: HLA project protocol was developed and ethics approval obtained and the e-learning workshops have completed. Statistical training in Methods in HIV Vaccine Trial Design and Evaluation took place on 28-30 March 2012. |
| Publications: | |

### 1.1.9 Cissy Kityo Mutuuluza

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| EDCTP Project Coordinator: | Cissy Kityo (Joint Clinical Research Center (JCRC), Uganda) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Evaluating antiretroviral drug resistance in HIV infected children in Africa |
| EDCTP Project Code: | TA.2008.40200.022 |
| EDCTP Project Start Date: | 23 November 2009 |
| EDCTP Project End Date: | 23 November 2011 |
| Collaborators: | • Diana Gibb (Medical Research Council (MRC), UK)<br>• Joshua Kayiwa (JCRC, Uganda)<br>• Peter Mugyenyi (JCRC, Uganda)<br>• Victor Musiime (JCRC, Uganda)<br>• Lillian Nakatudde (JCRC, Uganda)<br>• Tobias Rinke de Wit (International Centre of Reproductive Health (ICRH), Netherlands) |
| Site Principal Investigator(s): | • Joshua Kiyiwa (Uganda)<br>• Peter Mugyenyi (Uganda)<br>• Victor Musiime (Uganda)<br>• Lillian Nakatudda (Uganda) |
| Objective(s): | To determine what proportion of a paediatric cohort prevent HIV drug resistance (HIVDR) as measured by viral load suppression, and what HIVDR mutations and mutational patterns are observed in patients not achieving undetectable viral load. |
| Clinical Trial/Study site(s): | |
| Collaborating site(s): | MRC (UK) |
| Study design: | Prospective cohort study on drug resistance in children |
| Number of subjects: | 360 |
| Product: | Standard regimen (Stavudine, lamuvidine and niverapine) |
| Manufacturer/Developer: | Prequalified regimens |
| Status: | Ongoing |
| Results and outcomes: | Study in progress. Under a no cost extension until November 2012 |
| Publications: | |

### 1.1.10 Wendy Burgers

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| EDCTP Project Coordinator: | Wendy Burgers (University of Cape Town, South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | The effect of HIV co-infection on the immune response to *Mycobacterium tuberculosis* (*M.tb*) in the lung |
| EDCTP Project Code: | TA.2008.40200.020 |
| EDCTP Project Start Date: | 9 October 2009 |
| EDCTP Project End Date: | 9 October 2011 |
| Collaborators: | • Willem Hanekom (University of Cape Town, South Africa)<br>• Barbara Kalsdorf (Research Center Borstel, Germany)<br>• Gerhard Walzl (Stellenbosch University, South Africa)<br>• Robert Wilkinson (University of Cape Town, South Africa) |
| Site Principal Investigator(s): | • Willem Hanekom<br>• Barbara Karlsdof<br>• Gerhard Walzl<br>• Robert Wilkinson |
| Objective(s): | To examine the effect of HIV co-infection on the immune response to *Mycobacterium tuberculosis*. The proposed research aims to identify aspects of the immune response to *M.tb* which differ in persons latently infected with TB in the presence or absence of HIV co-infection. |
| Study design: | Laboratory study on the effect of HIV on lung immunity in TB patients |
| Number of subjects: | 70 |
| Status: | Completed |
| Results and outcomes: | By the end of the project 75% of the intended study volunteers were recruited, all samples stored and all planned analyses done. The project has also been successful in being awarded funds (R90,000 for 1 year) from a local South African source, the NHLS Trust, with the Senior Fellow Wendy Burgers as PI (Principal Investigator). This grant will allow completion of the remaining sample collection and analysis on this project, and perform (limited) additional analyses focusing on innate immune dysfunction, in particular alveolar macrophage function in the lungs, as well as establish links with TB researchers at UKZN and Harvard Medical School, Boston, USA.<br><br>Trainees attached to the project were: Rubina Bunjun, a student from Mauritius/Botswana who is now involved in an PhD (2012); Zekarias Ginbot; and a MSc student recruited from Tanzania (Narjis Khatoon Thawer) who joined the laboratory in 2012. |
| PhD study: | Rubina Bunjun (Mauritius/Botswana) |
| MSc study | Narjis Khatoon Thawer (Tanzania) |
| PostDoc study: | |
| Publications: | |

### 1.1.11 Takafira Mduluza

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|---|---|
| EDCTP Project Coordinator: | Takafira Mduluza (University of Zimbabwe) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Evolution of neutralizing antibodies among acute to early HIV Subtype C infected individuals in Botswana: one year longitudinal study. |
| EDCTP Project Code: | TA.2009.40200.005 |
| EDCTP Project Start Date: | 14 May 2010 |
| EDCTP Project End Date: | 14 May 2012 |
| Collaborator(s): | • Joseph Makhema (Botswana Harvard Partnership (BHP), Botswana)<br>• Keikantse Matlhagela (BHP, Botswana)<br>• Rosemary Musonda (BHP, Botswana) |
| Site Principal Investigator(s): | • Joseph Makhema (Botswana)<br>• Keikantse Mathlagela (Botswana)<br>• Sikhulile Moyo<br>• Rosemary Musonda (Botswana)<br>• Vladmir Novitsky |
| Objective(s): | To characterise the evolution of neutralising antibodies against HIV-1 subtype C gp 120 molecular envelope clones from acute/and early heterosexual acquired HIV-1 subtype C infections in Botswana |
| Study design: | Prospective cohort study on the evolution of neutrolising antibodies in HIV –C |
| Number of subjects: | 72 |
| Status: | Completed |
| Results and outcomes: | Using stored samples collected from 72 HIV-infected patients in 2005-2008, 50 plasma samples were analysed. Results so far show that broadly neutralizing antibodies are indeed present during pregnancy and at selected time points during the course of infection in the case of acute and recently infected individuals. Most plasmas have 50% neutralizing capacity, but the majority fail to exhibit 90% neutralisation. There was no strong inhibition of IN93, an HIV-1C strain similar to the predominant subtype C in the region. There is potential of identifying samples that show broad inhibition of various virus strains; with some samples showing high inhibition of subtype B (BR92). |
| MSc studies: | Candidate: Keabetswe Bedi |
| | Candidate: Sheron Dzoro |
| Publications: | |

### 1.1.12 Jonathan Kayondo

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|---|---|
| EDCTP Project Coordinator: | Jonathan Kayondo (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Evolution of HIV-1 ARV drug resistance mutations in ART naïve individuals during therapy; threshold frequency levels and linkage context associated with treatment failure in Uganda |
| EDCTP Project Code: | TA.2009.40200.011 |
| EDCTP Project Start Date: | 30 March 2010 |
| EDCTP Project End Date: | 31 December 2012 |
| Collaborators: | • Pontiano Kaleebu (MRC/UVRI, Uganda)<br>• Jean Mbisa (Health Protection Agency (HPA), UK)<br>• Chris Parry (MRC/UVRI, Uganda)<br>• Deenan Pillay (University College London/HPA, UK) |
| Objective(s): | To complement the just commenced Wellcome Trust-funded Uganda Virus Research Institute postdoctoral research, which looks at issues related to Nevirapine induced HIV-1 drug resistance, by including in-depth investigations on the evolution of drug resistance mutations in ART-naïve individuals. |
| Collaborating site(s): | HPA (UK) |
| Study design: | Laboratory analyses for ART resistance in treatment naïve patients |
| Number of subjects: | Unspecified stored samples |
| Product: | Combivir plus niverapine or tenofivir |
| Manufacturer/Developer: | Prequalified formulations |
| Status: | Completed |
| Results and Outcomes: | Single genome sequencing has been established by the Principal Investigator (PI) at the UVRI laboratory. The Institute has also acquired phylogenetic and sequence analysis software packages. Four patients that had persistent viraemia during combivir/nevirapine therapy are being followed in the study. |
| Publications: | |

### 1.1.13 Stephen Kennedy

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| EDCTP Project Coordinator: | Steven Kennedy (University of Liberia) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Building Research Infrastructure and Capacity to Implement an HIV/STD Prevention Trial in Post-Conflict Liberia |
| EDCTP Project Code: | TA.2009.40200.023 |
| EDCTP Project Start Date: | 7 May 2010 |
| EDCTP Project End Date: | 7 May 2012 |
| Objective(s): | To support research infrastructure, training and partnerships to prevent HIV/AIDS in rural Liberia and to implement and evaluate an HIV/AIDS programme for high risk rural youth in post-conflict Liberia. |
| Study design: | Capacity building for HIV/STI prevention trials in a post-conflict Liberia |
| Number of subjects: | 250 |
| Status: | Completed |
| Results and Outcomes: | HIV and STI baseline data have been collected in post-conflict Liberia. A total of 118 males and 132 females (n=250) were initially enrolled into the programs. The 3-month follow-up survey was administered to 115 males and 126 females (n=241) in both programs from the four communities, thus constituting an overall retention rate of 96% (i.e. attrition rate 4%). The 9-month follow-up survey was administered to 111 males and 113 female (n=224), constituting an overall retention rate of 90% (i.e. attrition rate 10%), respectively. |
| Publications: | 1. Katharine A. Atwood, Stephen B. Kennedy, Steve Shamblen,Jemee Tegli, Salome Garber, Pearl W. Fahnbulleh, Prince M. Korvah,Moses Kolubah, Comfort Mulbah-Kamara, and Shannon Fulton. Impact of school-based hiv prevention program in post-conflict Liberia. *AIDS Education and Prevention*, 24(1), 68–77, 2012<br>2. Katharine A. Atwood, Stephen B. Kennedy, Steve Shamblen, Curtis H. Taylor, Monica Quaqua, Ernree M. Bee, Mawen E. Gobeh, Daisajou V. Woods and Barclay Dennis. Reducing sexual risk taking behaviors among adolescents who engage in transactional sex in post-conflict Liberia. *Vulnerable Children and Youth Studies*. Vol. 7, No. 1, March 2012, 55–65 |

### 1.1.14 Eugene Kinyanda

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|---|---|
| EDCTP Project Coordinator: | Eugene Kinyanda (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Clinical trials in HIV/AIDS in Africa: Should they routinely control for mental health factors? |
| EDCTP Project Code: | TA.2010.40200.011 |
| EDCTP Project Start Date: | 12 April 2011 |
| EDCTP Project End Date: | 12 April 2013 |
| Collaborators: | • Heiner Grosskurth (LSHTM, UK/Mwanza Intervention Trials Unit (MITU), Tanzania)<br>• Jonathan Levin (MRC/UVRI Uganda Research Unit on AIDS, Uganda)<br>• Vikram Patel (London School of Hygiene and Tropical Medicine (LSHTM), UK/Sangath Centre Porvorim, India) |
| Objective(s): | The study aims to answer the following questions:<br>1. What is the prevalence of mental health problems associated with major depressive disorders (MDD) and maladaptive coping style (MACS) among HIV-infected patients in Uganda, and what is the incidence of MDD in HIV/AIDS?<br>2. Do mental health problems associated with MDD and MACS significantly impact on HIV disease progression in an Ugandian socio-cultural environment including through non-adherence to ART?<br>3. What would be the potential impact of MDD and MACS mental health covariates on HIV disease progression on the DART trial results under a range of possible differential treatment effects in the subgroups of patients with and without psychological problems? |
| Study design: | Prevalence study of mental health among clinical trials participants in HIV/AIDS |
| Status: | Ongoing |
| Results and Outcomes: | So far 230 clients (Entebbe =140; Masaka =90) have been recruited. The rate of major depressive disorder in Masaka site (n= 25) is 4%. An MSc student (Alan Kalungi) has developed the proposal, 'Association between serotonin transporter gene polymorphisms and suicidality in HIV/AIDS in a Ugandan population'. In the MSc project DNA will be extracted in Uganda and the genetic analysis will be done in South Africa. The fellow has developed an extensive network within and outside Uganda. |
| MSc study | Title: Association between serotonin transporter gene polymorphisms and suicidality in HIV/AIDS in a Ugandan population<br>Candidate: Alan Kalungi (Makerere University, Uganda) |
| Publications: | |

### 1.1.15 Mathieu Ndounga

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| EDCTP Project Coordinator: | Mathieu Ndounga (Centre d'Etudes sur les Ressources Végétales (CERVE), Congo) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Establishment of a HIV positive cohort for site preparation for HIV and malaria clinical trials in the Republic of Congo |
| EDCTP Project Code: | TA.2010.40200.011 |
| EDCTP Project Start Date: | 29 April 2011 |
| EDCTP Project End Date: | 29 April 2013 |
| Collaborators: | • Roth Cecile Laure Mapapa Miakassissa (CERVE, Congo)<br>• Rock Fabien Niama (Laboratoire Nationale de Sante Publique, Congo)<br>• Francine Ntoumi (Organization for the Coordination of Endemic Disease Control in Central (OCEAC), Cameroon)<br>• Mayengue Issamou Pembe (University Marien Ngouabi of Brazzaville, Congo)<br>• Celine Samba Louka (CERVE, Congo) |
| Goal: | This project aims at developing capacities for the conduct of clinical trials on HIV/AIDS, malaria and tuberculosis in Central Africa as part of CANTAM |
| Objective(s): | • To investigate the effect of HIV infection on clinical malaria infections<br>• To evaluate the impact of clinical malaria on HIV infection<br>• To develop human capacities in the conduct of clinical research for future HIV clinical trials in Brazzaville |
| Study design: | Clinical site development |
| Number of subjects: | 101 children aged from 9 months to 10 years |
| Status: | Ongoing |
| Results and outcomes: | By end of 2012 a cohort of 101 HIV infected children has been established in Brazzaville. Preliminary results show that all the HIV-infected children did not present with positive blood smear after 4 months of follow up. |
| PhD study: | Topic: Investigate viral load through the Laboratoire national de santé Publique in Brazzaville<br>Candidate: Laure Ghoma Linguissi (Fondation Congolaise Pour La Recherche Médicale, Congo) |
| Publications: | |

### 1.1.16 Sinead Delany Moretlwe

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| EDCTP Project Coordinator: | Sinead Delany Moretlwe (University of the Witwatersrand, South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | HPV in Men (HIM): Natural history of human papillomavirus (HPV) infection and genital warts in HIV-1 negative men, HIV-1 positive men not yet taking ART, and HIV-1 positive men taking ART in South Africa. |
| EDCTP Project Code: | TA.2010.40200.034 |
| EDCTP Project Start Date: | 8 June 2011 |
| EDCTP Project End Date: | 8 June 2013 |
| Collaborators: | • David Lewis (National Institute for Communicable Diseases, South Africa)<br>• Philippe Mayaud (London School of Hygiene and Tropical Medicine (LSHTM), UK) |
| Goal: | To show the epidemiology of HPV infection in men by HIV status and to provide data to inform mathematical models that predict the impact of HPV vaccination (e.g. using Gardasil) in various African settings, including South Africa. |
| Objective(s): | **Primary objective**<br>To determine the prevalence of HPV disease (anogenital and oropharyngeal), type distribution of low risk (LR)- and high risk (HR)-HPV DNA, and HPV seroprevalence in men in South Africa over a 12 -18 month period.<br><br>**Secondary objectives**<br>To determine:<br>1. The incidence of HPV disease and infection in this cohort over a maximum of 18 months<br>2. The persistence of HPV disease and infection (presence of HPV DNA) in this cohort followed for a maximum of 18 months<br>3. Socio-demographic, behavioural and clinical factors associated with HPV infection and disease in this cohort<br>4. Acceptability of anal swabbing in this population of presumed predominantly heterosexual African young men; and knowledge and acceptability of vaccine and factors associated with vaccine acceptability in this cohort. |
| Study design: | Cohort study on HPV and genital warts in HIV-1 negative and HIV-1 positive men taking ART in South Africa |
| Number of subjects: | 150 |
| Status: | Ongoing |
| Results and outcomes: | Clinical trial: by end of 2012 recruitment of HIV negative cohort was completed (150 men recruited and 93% retained at 12 months). Plans for recruiting HIV positive cohort in place; preliminary community engagement activities include presentation to CAB, radio activities and community education events.<br><br>Capacity building: eight staff have received GCP/GCLP training; one MSc student completed her MSc thesis; one PhD student has joined the study; exchange visits with European collaborators planned for November 2012; 7 staff received HIM-SA protocol training in May 2012.<br><br>An MSc student funded y another programme (Dr Jo Gibbs) is |

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| | working with the project to conduct a study entitled “A Study Examining The Natural History Of Human Papillomavirus In HIV-Seropositive Men In South Africa”. She also provided literature review used in the project. |
| MSc study: | Candidate: Jo Gibbs (LSHTM, UK)<br>Supervisor: Sinead Delany Moretlwe and Philippe Mayaud |
| Publications: | |

### 1.1.17 Godwin Nchinda

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|---|---|
| EDCTP Project Coordinator: | Godwin Nchinda (International Reference Centre Chantal Biya (CIRCB), Cameroon) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Pre-clinical evaluation of dendritic cell targeted consensus B, C, CRFO2_AG and MOSAIC HIV gag protein vaccines in PBMC from chronically infected patients in Central Africa |
| EDCTP Project Code: | TA.2010.40200.016 |
| EDCTP Project Start Date: | 10 March 2011 |
| EDCTP Project End Date: | 10 March 2013 |
| Collaborators: | • Vittorio Colizzi, (CIRCB, Cameroon)<br>• Ralph Steinman (The Rockefeller University, USA)<br>• Klaus Uerberla (Ruhr University Bochum, Germany) |
| Goal: | This project will verify if a consensus B based HIV gagP24 vaccine targeted to dendritic cells would be able to recall *in vitro* similar gag specific T cell responses in PBMCs from people chronically infected with the prevalent strains of HIV-1 in Africa. |
| Objective(s): | 1. To examine if a DC targeted consensus B HIV gag p24 protein vaccine could recall in vitro pre-existing gag specific T cells in PBMCs of subjects chronically infected with unrelated HIV-1 strains prevalent in Africa<br>2. To compare in terms of magnitude, breadth, and depth T cell responses recalled in vitro in PBMCs of subjects chronically infected with HIV-1 in central Africa by 4 four different DC targeted HIV gag p24 protein vaccines based on CRFO2_AG, C, B and MOSAIC HIV gag sequences, which are designed to address the problems associated with HIV-1 diversity. |
| Collaborating site(s): | • Rokerfeller University (USA)<br>• Ruhr University (Germany) |
| Study design: | Laboratory pre-clinical evaluation of dendritic cell antigens and HIV gag protein vaccines |
| Status: | Ongoing |
| Results and outcomes: | The project is contributing to training of 4 PhD students, 2 MSc and 1 nurse. The EDCTP funds have been used to purchase of a number of equipments. The project has established links with University of Yaounde 1, Institut Pasteur Cameroon, Case Western Reserve University and Tromsø Science Park of Norway. |
| PhD studies | Candidate: Georgia Ambada |
| | Candidate: Carol Ngaye |
| | Candidate: Tchaji Colin |
| | Candidate: Benson Nyachongi |
| MSc studies | Candidate: Nja Nadesh |
| | Candidate: Archille Nague |
| Publications: | |

## 1.2 Tuberculosis Career Development and Senior fellowships

| Project Acronym (Coordinator) | Type of study / Phase of trial | Product(s) | Manufacturer / Developer | Study population | Status |
|---|---|---|---|---|---|
| Mukhtar - SF | Epidemiology of TB | None | Not applicable | 100 villages randomly selected from five geographical regions in eastern Sudan, 100 households from each village resulting in recruitment of about 70,000 individuals | Closed |
| Hanekom - SF | Prospective cohort analyses | None | Not applicable | 5,675 neonates | Closed |
| Rangaka - CDF | Immunology of TB reconstitution in HIV | None | Not applicable | Over 200 patients with HIV and TB | Closed |
| Adetifa -CDF | Comparison of immunological and molecular TB diagnostics techniques | None | Not applicable | 188 stored samples (73 smear positive, 93 smear negative, 22 progressors) | Completed |
| Dheda - SF | Immunology of TB Lung innate immunity pathways | None | Not applicable | 74 TB patients and health contacts | Completed |
| Nicol - SF | Point of care genotypic diagnosis of TB and drug resistance | GeneXpert | Cepheid, Sunnyvale, CA, USA | 2522 patients | Completed |
| Nachega -SF | Phase II: Randomised placebo control trial for prevention of TB-IRIS with non-steroidal anti-inflammatory drugs | Meloxicam and omeprazole | Not applicable – generic formulations | TB patients on HAART | Ongoing |
| Oyakhirome - SF | TB, TB-HIV and MDR prevalence in preparation for future trials | None | Not applicable | General population | Completed |
| Hatherill -SF | Epidemiology of TB and intestinal helminthes infection | None | Not applicable | 800 children in South Africa and Kenya | Ongoing |
| Worodria -SF | Monitoring treatment outcomes of TB patients on ART | None | Not applicable | 230 TB patient on HAART in Kampala | Ongoing |

### 1.2.1 Maowia Mukhtar

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|---|---|
| EDCTP Project Coordinator: | Maowia Mukhtar (University of Khartoum, Sudan) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | The burden of tuberculosis in eastern Sudan: epidemiology and drug resistance patterns *of Mycobacterium tuberculosis* isolates |
| EDCTP Project Code: | TA.2004.40200.005 |
| EDCTP Project Start Date: | 1 January 2005 |
| EDCTP Project End Date: | 30 June 2007 |
| Collaborators: | • Greet Dieltiens Prince Leopold Institute of Tropical Medicine (ITM), Belgium<br>• Nageed Saeed (Federal Ministry of Health, Sudan)<br>• Patrick van der Stuyft (ITM, Belgium) |
| Goal: | To conduct epidemiological studies to identify suitable sites for future diagnostic, treatment and vaccine trials on tuberculosis in Sudan |
| Primary Objective(s): | • To study and map the burden of tuberculosis in Eastern Sudan<br>• To understand the epidemiology of pulmonary TB<br>• To determine the drug resistance pattern of *Mycobacterium tuberculosis* isolates. |
| Study design: | Epidemiological survey |
| Status: | Completed |
| Results and outcomes: | The project has produced epidemiological understanding of TB in Sudan which provides a foundation for future trials in TB |
| Publications: | |

### 1.2.2 Willem Hanekom

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| EDCTP Project Coordinator: | Willem Hanekom (University of Cape Town, South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | The BCG-induced immune correlates of protection against tuberculosis |
| EDCTP Project Code: | TA.2004.40200.004 |
| EDCTP Project Start Date: | 1 January 2005 |
| EDCTP Project End Date: | 6 October 2008 |
| Collaborators: | • Adrian Hill (University of Oxford, UK)<br>• Gregory Hussey (University of Cape Town, South Africa)<br>• Gilla Kaplan (New Jersey Medical School, USA) |
| Goal: | To identify BCG immune correlates of protection against TB in children whose understanding is critical for TB vaccine development |
| Objective(s): | 1. To determine whether the post-vaccination number, function and/or antigenic repertoire of specific conventional CD4+ and CD8+ T cells correlate with protection against TB<br>2. To determine whether the post-vaccination number and/or function of specific regulatory CD4+ T cells correlate with protection against TB<br>3. To determine whether the post-vaccination gene expression and cytokine secretion profiles of whole blood, and of PBMC, correlate with protection against TB. |
| Clinical Trial/Study site(s): | |
| Collaborating site(s): | • New Jersey Medical School (USA)<br>• University of Oxford (UK) |
| Study design: | Prospective cohort analyses |
| Number of subjects: | 5662 children |
| Status: | Completed |
| Results and outcomes: | There were no differences in plasma levels of interferon-gamma, a cytokine commonly used to measure vaccination outcome, or any other cytokine, between the TB protected and TB non-protected children. However, when combinations of cytokines were evaluated, a model that included fractalkine, interleukin 12p40 and epidermal growth factor allowed correct discrimination in 82% of “protected” and “unprotected” infants. Combinations of cytokines from plasma from blood incubated for 7 hours without antigen also allowed correct discrimination between the 2 groups. The studies on correlates of protective immunity from BCG have strengthened laboratories at SATVI which has since been awarded several EDCTP grants for TB vaccine studies and trials. The fellowship was a re-entry fellowship to support the return of Willem Hanekom tore-establish his research career in South Africa. |
| Publications: | 1. Mark Hatherill, Tony Hawkridge, Andrew Whitelaw, Michele Tameris, Hassan Mahomed, Sizulu Moyo, Willem Hanekom and Gregory Hussey. Isolation of Non-Tuberculous Mycobacteria in Children Investigated for Pulmonary Tuberculosis. *PLoS ONE*, December 2006;1:e21.<br>2. Hanekom WA. The immune response to BCG vaccination of newborns. *Ann N Y Acad Sci*. 2005 Dec;1062:69-78.<br>3. Murray RA, Mansoor N, Harbacheuski R, Soler J, Davids V, Soares A, Hawkridge A, Hussey GD, Maecker H, Kaplan G, Hanekom WA. Bacillus Calmette Guerin vaccination of human newborns induces a specific, functional CD8+ T |

cell response. *J Immunol*. 2006 Oct 15;177(8):5647-51.
4. Hanekom WA, Abel B, Scriba TJ. Immunological protection against tuberculosis. *S Afr Med J*. 2007 Oct;97(10 Pt 2):973-7.
5. Hussey G, Hawkridge T, Hanekom W. Childhood tuberculosis: old and new vaccines. *Paediatr Respir Rev*. 2007 Jun;8(2):148-54.
6. Scriba TJ, Kalsdorf B, Abrahams D-A, Isaacs F, Hofmeister J, Black G, Hassan HY, Wilkinson RJ, Walzl G, Gelderbloem SG, Mahomed H, Hussey GD, Hanekom WA. Distinct, specific IL-17 and IL-22-producing CD4+ T cell subsets contribute to the human anti-mycobacterial immune response. *J Immunol*. 2008, 180: 1962-1970.
7. Natalie E.R. Beveridge, Helen A. Fletcher, Jane Hughes, Ansar A. Pathan, Thomas J. Scriba, Angela Minassian, Clare R. Sander, Kathryn T. Whelan, Hazel M. Dockrell, Adrian V.S. Hill, Willem A. Hanekom and Helen McShane. A comparison of IFNy detection methods used in tuberculosis vaccine trials. *Tuberculos*. November 2008;88(6):631-640.
8. M Hatherill, T Hawkridge, H J Zar, A Whitelaw, M Tameris, L Workman, L Geiter, W A Hanekom and G Hussey. Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis? *Arch. Dis. Child*. 2009;94;195-201; originally published online 1 Oct 2008.
9. Soares AP, Scriba TJ, Joseph S, Harbacheuski R, Murray RA, Gelderbloem SJ, Hawkridge A, Hussey GD, Maecker H, Kaplan G, Hanekom WA. Bacille Calmette Guerin vaccination of human newborns induces T cells with complex cytokine and phenotypic profiles. *J Immunol*. 2008 Mar 1;180(5):3569-77.

### 1.2.3 Molebogang Rangaka

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|---|---|
| EDCTP Project Coordinator: | Molebogang Rangaka (University of Cape Town, South Africa) |
| EDCTP Project Call: | Career Development Fellowship |
| EDCTP Project Title: | Immunological investigation of the HIV-tuberculosis associated immune reconstitution |
| EDCTP Project Code: | TA.2005.40203.005 |
| EDCTP Project Start Date: | 15 December 2006 |
| EDCTP Project End Date: | 31 January 2009 |
| Collaborators: | • Gary Maartens (University of Cape Town, South Africa)<br>• Graeme Ayton Meintjes (University of Cape Town, South Africa)<br>• Katalin Andrea Wilkinson (University of Cape Town, South Africa)<br>• Robert Wilkinson (University of Cape Town, South Africa) |
| Goal: | To determine the frequency of *M.tb* specific T cells and serum cytokine agonist/antagonist ratios amongst IRIS cases compared to controls. The effect of steroid or placebo therapy on these variables was also studied. |
| Objective(s): | To understand the immune dysregulation that underlies HIV-Tuberculosis associated immune reconstitution inflammatory syndrome (TB IRIS). |
| Study design: | Laboratory investigations in a cohort of TB-HIV patients |
| Status: | Completed |
| Results and outcomes: | The study has contributed to the establishment of well characterised cohorts of TB/HIV co-infected individuals in parts of Cape Town. Dr Rangaka competed for and was awarded a Wellcome Trust Training Fellowship at the end of the EDCTP award. |
| Publications: | 1. Meintjes G, Rangaka M.X et al. Novel Relationship between Tuberculosis Immune Reconstitution Inflammatory Syndrome and Antitubercular Drug Resistance. *Clin Infect Dis*. 2009 Mar 1;48(5):667-76. doi: 10.1086/596764<br>2. Meintjes G, Wilkinson K.A, Rangaka M.X et al. Type 1 Helper T Cells and FoxP3-positive T Cells in HIV–Tuberculosis-associated Immune Reconstitution Inflammatory Syndrome. *Am J Respir Crit Care Med*. 2008 Nov 15;178(10):1083-9. doi: 10.1164/rccm.200806-858OC. Epub 2008 Aug 28<br>3. Dominique J. Pepper, Suzaan Marais, Gary Maartens, Kevin Rebe, Chelsea Morroni, Molebogeng X. Rangaka, Tolu Oni, Robert J. Wilkinson, and Graeme Meintjes. Neurologic Manifestations of Paradoxical Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome: A Case Series. *Clinical Infectious Diseases* 2009:48 (1 June)<br>4. Katalin A. Wilkinson, Ronnett Seldon, Graeme Meintjes1, Molebogeng X. Rangaka, Willem A. Hanekom, Gary Maartens, and Robert J. Wilkinson. Dissection of Regenerating T-Cell Responses against Tuberculosis in HIV-infected Adults Sensitized by Mycobacterium tuberculosis. *American Journal of Respiratory and Critical Care Medicine* Vol 180. pp 674–683, 2009<br>5. Graeme Meintjes, Robert J Wilkinson, Chelsea Morroni, Dominique J Pepper, Kevin Rebe, Molebogeng X Rangaka, Tolu Oni, Gary Maartens. Randomized placebo-controlled trial of prednisone for paradoxical TB-associated immune |

reconstitution inflammatory syndrome. *AIDS*. 2010 Sep 24;24(15):2381-90. doi: 10.1097

6. Rebecca Tadokera, Graeme Meintjes, Keira H Skolimowska, Katalin A Wilkinson, Kerryn Matthews, Ronnett Seldon, Novel N Chegou, Gary Maartens, Molebogeng Xheedha Rangaka , Kevin Rebe, Gerhard Walzl, Robert J Wilkinson. Hypercytokinaemia accompanies HIV-tuberculosis immune reconstitution inflammatory syndrome. *Eur Respir J*. 2011 May;37(5):1248-59. doi: 10.1183/09031936.00091010. Epub 2010 Sep 3.

### 1.2.4 Ifedayo Adetifa

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| EDCTP Project Coordinator: | Ifedayo Adetifa (Medical Research Council (MRC) Laboratories, The Gambia) |
| EDCTP Project Call: | Career Development Fellowship |
| EDCTP Project Title: | Immunologic, diagnostic and epidemiologic studies for improved phenotyping of Mycobacterium tuberculosis infection and disease for a double blind, placebo controlled randomized trial of vitamin A supplementation for modulation of Mycobacterium tuberculosis immune responses in children aged 5-14 years with latent Tuberculosis |
| EDCTP Project Code: | TA.2005.40203.001 |
| EDCTP Project Start Date: | 15 March 2007 |
| EDCTP Project End Date: | 1 July 2010 |
| Collaborators: | • Richard Adegbola (MRC Laboratories, The Gambia)<br>• Martin Antonio (MRC Laboratories, The Gambia)<br>• Philip Hill (MRC Laboratories, The Gambia) |
| Objective(s): | To provide additional evidence for the performance of novel diagnostics for latent tuberculosis and TB case detection in adults and children especially those with paucibacillary disease in a TB endemic country; and to identify differences in immune responses may improve our understanding of what constitutes protection against progression to TB in those latently infected |
| Study design: | Immunological studies in TB immunity |
| Number of subjects: | |
| Status: | Completed |
| Results and Outcomes: | In a cross sectional study, the ELISPOT test was more sensitive than the QFT-GIT for diagnosing TB disease but both tests performed similarly in the diagnosis of LTBI in TB contacts. In an extension of this study to two newly licensed commercial IGRAs, it was found that both IGRAs and the TST responded in a similar manner to a gradient of exposure to TB. In addition, each IGRA in combination with TST increased sensitivity for diagnosis of LTBI but was also associated with a loss of specificity. Also tested were Hain Sciences Line probe assay, MTBDRplus ® in a 2 step-procedure. On 93 smear negative culture positive samples, the LPA had a sensitivity of 45.2% (42 of 93) and over half of the results were blank. There was no relationship between the results from post decontamination ZN concentration staining and failed LPA results. In assessing gene expression for cytokines protective against TB disease progression IFN-γ was significantly lower in progressors compared to both non-progressors and TB cases ($p=0.0328$ and $p=0.0062$ respectively). For other cytokines-IL-10 and IL-12 similar levels were seen between the groups. IL-18 was significantly higher in progressors compared to non-progressors and confirmed TB cases ($p<0.001$ for both). |
| Publications: | 1. Adetifa IM, Lugos MD, Hammond A, et al. Comparison of two interferon gamma release assays in the diagnosis of Mycobacterium tuberculosis infection and disease in The<br>2. Lugos MD, Adetifa IM, Donkor S, Hill PC, Adegbola RA, Ota MO. Evaluation of the contribution of major T cell subsets to IFN-gamma production in TB infection by ELISPOT. *Immunol Invest*. 2009; 38: 341-9.<br>3. Adetifa IM, et al. Commercial interferon gamma release assays compared to the tuberculin skin test for diagnosis of latent Mycobacterium tuberculosis infection in childhood contacts in the Gambia. *Pediatr Infect Dis J*. |

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| | 2010; 29:439-43.<br>4. Adetifa IM, Ota MO, Walther B, et al, Hill PC. Decay kinetics of an interferon gamma release assay with anti-tuberculosis therapy in newly diagnosed tuberculosis cases. *PLoS One*. 2010. Sep 1;5(9). pii: e12502. |

### 1.2.5 Keertan Dheda

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| EDCTP Project Coordinator: | Keertan Dheda (University of Cape Town, South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Human lung innate immune pathways regulating the stasis and killing of *M. tuberculosis* in a high burden setting |
| EDCTP Project Code: | TA.2007.40200.010 |
| EDCTP Project Start Date: | 28 July 2008 |
| EDCTP Project End Date: | 27 July 2010 |
| Collaborators: | • Gregory Hussey (University of Cape Town, South Africa)<br>• Graham Rook (University College London, UK)<br>• Alimuddin Zumla (University College London, UK) |
| Objective(s): | 1. To compare compartment-specific IFN- antigen-specific responses in TB versus non-TB patients<br>2. To procure and bank biological material (alveolar lavage fluid and cells) from HIV negative close contacts (of sputum smear positive patients) that have laboratory evidence of LTBI (TST+, IGRA+ i.e. converters) versus those that do not (TST-, IGRA- i.e. non-converters)<br>3. To compare expression and function of innate markers of protective immunity (pathogen recognition molecules/ receptors, cytokines, humoral factors and cell phenotypes) in converters and non-converters |
| Collaborating site(s): | University College London (UK) |
| Study design: | Immunological studies |
| Status: | Completed |
| Results and outcomes: | Rapid diagnosis of TB meningitis by smear microscopy and PCR is problematic and the diagnostic delay can often translate into increased morbidity and mortality due to the poor sensitivity of these assays. The TB-specific quantitative T cell ELISPOT assay, when using CSF mononuclear cells and in conjunction with other rapid confirmatory tests (Gram stain and cryptococcal latex-agglutination) is an accurate and rapid rule-in test for TBM in a TB and HIV endemic setting. The RD-1, but not the purified-protein-derivative, cerebrospinal fluid-lymphocyte IFN-γ ELISPOT response is a useful rapid immunodiagnostic test for TBM. Further studies are continuing from the work described above. |
| Publications: | 1. Patel VB, Singh R, Connolly C, ,Coovadia Y, Peer A, Parag P, Kasprowicz V, Zumla A, Ndung"u T, Dheda K. Cerebrospinal T cell responses aid the diagnosis of tuberculous meningitis in a HIV and TB endemic population. *AJRCCM* 2010 May 4. [Epub ahead of print] PMID: 20442433<br>2. Patel VB, Bhigjee AI, Paruk HF, Singh R, Meldau R, Connolly C, Ndung'u T, Dheda K. Utility of a novel lipoarabinomannan assay for the diagnosis of tuberculous meningitis in a resource-poor high-HIV prevalence setting. *Cerebrospinal Fluid Research* 2009 November,2;6:13. PMID: 19878608<br>3. Cashmore TJ , Peter GJ, van Zyl-Smit RN, Semple PL, Maredza A, Meldau R, Zumla A, Nurse B, Dheda K. Feasibility and diagnostic utility of antigen-specific interferon-gamma responses for rapid immunodiagnosis of tuberculosis using induced sputum. *PLoS One*. 2010 Apr 28;5(4):e10389. PMID: 20442850?<br>4. Dheda K, van Zyl-Smit RN, Sechi LA, Badri M, Meldau R, Meldau S, Symons G, Semple L, Maredza A, Dawson R, |

Wainright H, Whitelaw A, Vallie Y, Raubenheimer P, Bateman ED, Zumla A. Utility of quantitative T cell responses versus unstimulated IFN-{gamma} for the diagnosis of pleural tuberculosis. *Respir J*. 2009 Nov;34(5):1118-26. Epub 2009 Apr 22. PMID: 19386693

5. Dheda K, Van-Zyl Smit RN, Sechi LA, Badri M, Meldau R, Symons G, Khalfey H, Carr I, Maredza A, Dawson R, Wainright H, Whitelaw A, Bateman ED, Zumla A. Clinical diagnostic utility of IP-10 and LAM antigen levels for the diagnosis of tuberculous pleural effusions in a high burden setting. *PLoS One*. 2009;4(3):e4689. Epub 2009 Mar 11. PMID: 19277111
6. Dheda K, Smit RZ, Badri M, Pai M. T-cell interferon-gamma release assays for the rapid immunodiagnosis of tuberculosis: clinical utility in high-burden vs. low-burden settings. *Curr Opin Pulm Med*. 2009 May;15(3):188-200. Review. PMID: 19387262
7. Dheda K, van Zyl-Smit RN, Meldau R, Meldau S, Symons G, Khalfey H, Govender N, Rosu V, Sechi LA, Maredza A, Semple PL, Whitelaw A, Wainright H, Badri M, Dawson R, Bateman ED, Zumla A. Quantitative lung T cell responses aid the rapid diagnosis of pulmonary tuberculosis. *Thorax*. 2009 Oct;64(10):847-53. Epub 2009 Jul 9. PMID: 19592392
8. van Zyl-Smit RN, Dheda K, Meldau R. Quantitative Pulmonary T-Cell Responses for the Diagnosis of Active Tuberculosis. *Am J Respir Crit Care Med*. 2010 Feb 1;181(3):289; author reply 289-90. PMID: 20093656
9. van Zyl-Smit RN, Pai M, Peprah K, Meldau R, Kieck J, Juritz J, Badri M, Zumla A, Sechi LA, Bateman ED, Dheda K (senior and corresponding author). Within-subject variability and boosting of T-cell interferon-gamma responses after tuberculin skin testing. *Am J Respir Crit Care Med*. 2009 Jul 1;180(1):49-58. Epub 2009 Apr 2. PMID: 19342414
10. van Zyl-Smit RN, Zwerling A, Dheda K, Pai M. Within-subject variability of interferon-gamma assay results for tuberculosis and boosting effect of tuberculin skin testing: a systematic review. *PLoS One*. 2009 Dec 30;4(12):e8517. Review. PMID: 20041113
11. Dheda K, Schwander SK, Zhu B, Van Zyl-Smit RN, Zhang Y. The immunology of tuberculosis: From bench to bedside. *Respirology*. 2010 Apr;15(3):433-50. PMID: 20415982

### 1.2.6 Mark Nicol

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| EDCTP Project Coordinator: | Mark Nicol (University of Cape Town, South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | The impact of rapid genotypic detection of multi-drug resistant tuberculosis on treatment outcome in a semi-rural region of South Africa |
| EDCTP Project Code: | TA.2007.40200.009 |
| EDCTP Project Start Date: | 29 August 2008 |
| EDCTP Project End Date: | 20 September 2011 |
| Collaborators: | • Willem Hanekom (University of Cape Town, South Africa)<br>• Gregory Hussey (University of Cape Town, South Africa)<br>• Lizette Phillips (Brewelskloof Hospital, South Africa)<br>• Danie Theron (Brewelskloof Hospital, South Africa)<br>• Tommie Victor (Stellenbosch University, South Africa)<br>• Robert Wilkinson (University of Cape Town, South Africa) |
| Goal: | To assess the impact of a novel rapid molecular diagnostic test for tuberculosis and the presence of rifampicin resistance (Xpert MTB/RIF) on patient and health services outcomes. |
| Objective(s): | To determine whether the detection of tuberculosis by GeneXpert MTB/Rif testing in place of the routine diagnostic algorithm will lead to a reduction in: number of clinic visits prior to appropriate TB treatment; time to appropriate treatment for TB and reduced morbidity and mortality due to undiagnosed TB; number of TB cultures requested per patient; TB-related clinic workload and TB-related laboratory workload |
| Clinical Trial/Study site(s): | Blewelskloof Hospital, Khayelitsa, Worcester (South Africa) |
| Study design: | TB point of care diagnosis |
| Number of subjects: | 1577 |
| Product: | GeneXpert |
| Manufacturer/Developer: | Cepheid, Sunnyvale (USA) |
| Status: | Completed |
| Results and outcomes: | 1577 patients with suspected TB were recruited. GeneXpert improves accuracy and shortens duration of diagnosis to treatment. The preliminary results of this study formed a substantial component of a report submitted to the WHO Strategic and Technical Advisory Group for Tuberculosis which in September 2010 issued a recommendation that Xpert MTB/RIF replace smear microscopy as the first line diagnostic test for TB in areas with high prevalence of MDR-TB or HIV. South-North networking in the project was well established working with the Foundation for Innovative New diagnostics (FIND) and TB Clinical Diagnostics Research Consortium of Johns Hopkins University and Boston Medical Centre. Other collaborative projects included development of a novel point-of-care diagnostics for TB with North-western University, USA. In the south the project links with EDCTP funded TB-NEAT consortium (PI Keertan Dheda), Wellcome Trust project in Malawi and Zimbabwe. |
| Publications: | 1. Catharina C Boehme, Mark P Nicol, Pamela Nabeta, Joy S Michael, Eduardo Gotuzzo, Rasim Tahirli, Ma Tarcela Gler, Robert Blakemore, William Worodria, Christen Gray, Laurence Huang, Tatiana Caceres, Rafail Mehdiyev, Lawrence Raymond, Andrew Whitelaw, Kalaiselvan Sagadevan, Heather Alexander, Heidi Albert, Frank Cobelens, Helen Cox, David Alland, Mark D Perkins, Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis |

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| | of tuberculosis and multidrug resistance: a multicenter implementation study. *Lancet* 2011 Apr 30; 377(9776):1495-505) |

### 1.2.7 Jean Nachega

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| EDCTP Project Coordinator: | Jean Nachega (Stellenbosch University, South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | A Multi-Site Double-Blind Placebo Controlled Randomised Clinical Trial to Prevent Immune Reconstitution Inflammatory Syndrome with Non-Steroid Anti-Inflammatory Drugs |
| EDCTP Project Code: | TA.2008.40200.021 |
| EDCTP Project Start Date: | 9 February 2010 |
| EDCTP Project End Date: | 31 December 2013 |
| Collaborators: | • Robert Colebunders (Prince Leopold Institute of Tropical Medicine (ITM), Belgium)<br>• Mzileni Olga Mogiyana (University of Limpopo, South Africa)<br>• Ingrid Wilson (Stellenbosch University, South Africa) |
| Goal: | To investigate immune-modulation of non-steroidal anti-inflammatory treatment in TB IRIS among HIV infected patients |
| Objective(s): | 1. Evaluate the impact of NSAIDs compared to placebo on preventing TB-IRIS in a TB-HIV infected South African Adults<br>2. Evaluate the impact of NSAIDs compared to placebo on CD4+ T-cell count recovery following initiation of ART in TB-HIV infected South African Adults<br>3. Evaluate the impact of NSAIDs compared to placebo on HIV-1 RNA response following initiation of ART in TB-HIV infected South African Adults<br>4. Evaluate the impact of NSAIDs compared to placebo on adherence of both TB and HIV medication following initiation of ART in TB-HIV infected South African Adults<br>5. Assess the impact of NSAIDs compared to placebo on quality of life following initiation of ART in TB-HIV infected South African Adults |
| Collaborating site(s): | ITM (Belgium) |
| Study design: | Phase II: Randomised placebo control trial for prevention of TB-IRIS with non-steroidal anti-inflammatory drugs |
| Product: | Meloxicam and omeprazole |
| Manufacturer/Developer: | Generic formulations |
| Cofunders: | Stellenbosch University (South Africa) |
| Status: | Ongoing |
| Results and outcomes: | Enrolment into the study started in September 2012. |
| Publications: | |

### 1.2.8 Sunny Oyakhirome

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| EDCTP Project Coordinator: | Sunny Oyakhirome (Albert Schweitzer Hospital, South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Career development and strengthening institutional capacity for clinical research in TB at the Faculty of Health Sciences in Brazzaville |
| EDCTP Project Code: | TA.2009.40200.010 |
| EDCTP Project Start Date: | 13 April 2010 |
| EDCTP Project End Date: | 13 April 2012 |
| Collaborators: | • Michel Bitemo (CERVE)<br>• Vladimir Malonga (Fondation Congolaise pour al Recherche Médicale (FCRM)/Faculté des sciences de la santé (FSSA), Congo)<br>• Pembe Issamou Mayengue (FCRM/FSSA, Congo)<br>• Mitawa Missontsa (FCRM/FSSA, Congo)<br>• Benjamin Mordmüller (Albert Schweitzer Hospital, Gabon)<br>• Francine Ntoumi (FCRM/FSSA, Congo)<br>• Veronique Penlap Beng (University of Yaounde, Cameroon) |
| Objective(s): | To determine the prevalence of TB, TB/HIV co-infection and multi drug resistant TB (MDR) infections in the Congolese population and identify groups most at risk for recent TB transmission in urban areas of Brazzaville in the Republic of Congo. A follow up will be set up for evaluating TB transmission in Congo; quantify the problem of recent transmission and characterized circumstances and settings for transmission |
| Collaborating site(s): | • University of Yaounde (Cameroon)<br>• Albert Schweitzer Hospital (Gabon) |
| Study design: | Trial site development |
| Status: | Ongoing |
| Results and outcomes: | Preliminary reports show that the EDCTP grant in Congo supported personnel, maintenance of laboratory equipment with their consumables and reagents. A TB research team formed as the result of the grant included a molecular biologist (Dr Pembe), a biostatistician (Mr Bitemo) and a local physician (Dr Mitawa). In the project period the newly formed team devoted time to the preparation of standards operating procedures necessary for handing TB and TB-HIV samples (from recruitment of patients to data analysis). The TB project has established collaboration with the TB CANTAM site at University Yaounde1 in Cameroon (Contact: Prof Penlap), University of Tübingen (contact: Dr Matthias Frank) and Medical research Unit of Albert Schweitzer Hospital in Lambarene, Gabon (Dr Safi and Dr Lell) |
| Publications: | |

### 1.2.9 Mark Hatherill

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| EDCTP Project Coordinator: | Mark Hatherill (University of Cape Town, South Africa) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | The risk of pulmonary tuberculosis associated with intestinal helminth infection among children at two tuberculosis vaccine trial sites in sub-Saharan Africa |
| EDCTP Project Code: | TA.2009.40200.015 |
| EDCTP Project Start Date: | 20 April 2010 |
| EDCTP Project End Date: | 31 December 2013 |
| Collaborators: | • Willem Hanekom (University of Cape Town, South Africa)<br>• Gregory Hussey (University of Cape Town, South Africa)<br>• Pauline Mwinzi (Kenya Medical Research Institute (KEMRI), Kenya)<br>• Videlis Nduba (KEMRI, Kenya) |
| Objective(s): | Primary objectives:<br>1. To determine whether prevalent infection with intestinal helminths is associated with increased risk of pulmonary tuberculosis disease in children<br>2. To determine whether maternal infection with intestinal helminths is associated with increased risk of pulmonary tuberculosis disease in children<br>3. To compare the risk of pulmonary tuberculosis disease associated with prevalent infection with intestinal helminths between the research site in Breede Valley, South Africa, and the research site in Siaya District, Kenya.<br><br>Secondary specific aims<br>1. To determine whether prevalent infection with intestinal helminths is associated with increased risk of LTBI in children<br>2. To determine whether maternal infection with intestinal helminths is associated with increased risk of LTBI in children. |
| Collaborating site(s): | KEMRI (Kenya) |
| Study design: | Epidemiology of TB |
| Number of subjects: | 800 (target) in both Kenya and South Africa |
| Status: | Ongoing |
| Results and outcomes: | The first participant was enrolled at the UCT site on 7 March 2011 where 32 mothers were also approached and 6 (19%) consented to participation. By the end of 2011 total of 135 infants had been enrolled (42% of the 325 target for Year 1). Health system strengthening has resulted in increased use of anthelmintic treatment in the community, with the result that 198 (32%) of 610 screened infants were excluded for this reason. To achieve the final target of 650 infants enrolled in the study from South Africa a no cost extension to 31 December 2013. |
| Publications: | |

### 1.2.10 William Worodria

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| EDCTP Project Coordinator: | William Worodria (Makerere University, Uganda) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Short- and long-term clinical and immunological outcomes of patients with HIV/TB coinfections on ART |
| EDCTP Project Code: | TA.2010.40200.007 |
| EDCTP Project Start Date: | 11 April 2011 |
| EDCTP Project End Date: | 11 April 2014 |
| Collaborators: | • Frank Cobelens (KNCV Tuberculosis Foundation, Netherlands)<br>• Robert Colebunders (Prince Leopold Institute of Tropical Medicine (ITM), Belgium)<br>• Jean Pierre van Geertruyden (ITM, Belgium)<br>• Luc Kestens (ITM, Belgium)<br>• Robert Lukande (Makerere University, Uganda)<br>• Yukari Manabe (Makerere University, Uganda)<br>• Harriet Mayanja-Kizza (Makerere University, Uganda)<br>• Alice Nakiwogga-Mawanga (Infectious Diseases Institute, Uganda) |
| Clinical Trial/Study Sponsor: | University of Amsterdam (Netherlands) |
| Objective(s): | To study short-term effects of TB and ART treatment (the incidence, predictors and clinical characteristics of TB-IRIS, side effects of the therapy, causes of early mortality) and long term effects of ART after completing TB treatment (clinical events such as infections, late-onset IRIS, adverse effects of therapy or immunological and virological events such as changes in CD4 counts, CD4 %; viral load, viral resistance). Also to study possible factors influencing these outcomes such as adherence and factors affecting them, TB relapse and mycobacteriological factors, immunological defects and social factors that are associated with a recurrent TB episode and causes of mortality |
| Collaborating site(s): | • ITM (Belgium)<br>• KNCV Tuberculosis Foundation (Netherlands) |
| Study design: | Treatment monitoring |
| Number of subjects: | 280 (target) |
| Product: | Prequalified TB regimens and HAART |
| Status: | Ongoing |
| Results and outcomes: | By 30 July 2012 the project had enrolled 79 study participants of which 44 were enrolled in the study. 29 of those enrolled in the study are on both HAART and TB treatment. Patient follow-up is continuing. |
| Publications: | |

## 1.3 Malaria Career Development and Senior fellowships

| Project Acronym (Coordinator) | Study classification /design | Product(s) | Manufacturer / Developer | Study population | Status |
|---|---|---|---|---|---|
| Djimde - SF | Phase IV randomised trial Mali | AS/AQ, AS/SP and AR-L | Pre-qualified drugs | 780 subjects in which 2463 malaria episodes studied | Completed |
| Nzila - SF | Laboratory study to investigate the mechanism of piperaquine resistance | DHA-piperaquine and artemether-lumefantrine | Not applicable (used samples from completed clinical trials) | In-vitro cultures of Plasmdium falciparum | Completed |
| Talisuna - SF | Phase IV: Pharmacovigilance of anti-malarial drugs in Uganda | | Not applicable | None (training of health staff and comparison by health facility/region) | Completed |
| Nebie -SF | Immunological studies on the role of T cells in malaria endemicity | None | Not applicable | 219 adults and children in Burkina Faso | Completed |
| Moukoko -CDF | Malaria virulence markers | None | Not applicable | In vitro assays | Completed |
| Nwakanma - SF | PCR diagnosis of malaria | None | Not applicable | Out patients with malaria symptoms in Gambia | Completed |
| Cisse - SF | Phase III: IPT with community participation | Pyrimethamine/Sulphamethopyrazine (Dualkin); DHA and Piperaquine; and AS and AQ | Pre-qualified drugs | 1893 children | Completed |
| Dodoo - SF | In-vitro assessment of | None | Not applicable | In vitro assays | Completed |

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| | malaria antibodies | | | | |
| Happi - SF | Biomarkers of artemesinin resistance | None | Not applicable | In vitro and in vivo assays | Completed |
| Phiri - SF | Phase II trial of oral iron therapy for treatment of post-malaria iron-deficiency anaemia in children | Iron and iron isotopes | International Atomic Energy Agency | Children under 3 with malaria | Completed |
| Achidi - SF | Baseline studies for clinical trials site develpment | None | Not applicable | General population in Cameroon | Completed |
| Tiono - SF | Phase IV: Cluster randomised trial: Impact of nets, home management and rapid diagnosis on malaria mortality in children | | | 40 clusters of 40 children each and followed for 2 years | Ongoing |
| Byakika Kibwika - SF | Phase II: Safety, efficacy, PK and interaction with ART of iv artesunate and iv quinine | IV artsunate and (Quinine, ACT (Artemether-Lumefantrine or Dihydroartemisinin-piperaquine) | Gilead (for iv artesunate only). And prequalified for oral ACT (Artemether-Lumefantrine or Dihydroartemisinin-piperaquine) and Quinine | 330 adult patients | Ongoing |
| Kouriba - SF | Immunological cohort studies: Role of monocytes in protection against malaria in Mali | None | Not applicable | In vitro assays | Ongoing |
| Toure - SF | In-vitro studies: | None | Not applicable | In vitro assays | Ongoing |

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| | Evaluation of malaria immunity and merozoite vaccine candidates | | | | |
| Ndiaye - SF | Cluster randomised Trial: IPT and home management of malaria in Senegal | None | Not applicable | 24 clusters of villages randomised to each intervention | Ongoing |

### 1.3.1 Abdoulaye Djimde

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| EDCTP Project Coordinator: | Abdoulaye Djimde (Malaria Research & Training Center, Mali) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Assessment of the Public Health Benefit of artemisinin based combination therapies for uncomplicated malaria treatment in Mali |
| EDCTP Project Code: | TA.2004.40200.003 |
| EDCTP Project Start Date: | 1 January 2005 |
| EDCTP Project End Date: | 8 February 2009 |
| Collaborators: | • Demba Dembele (Malaria Research & Training Center, Mali)<br>• Bakary Fofana (Malaria Research & Training Center, Mali)<br>• Bakari Sidibe (Malaria Research & Training Center, Mali)<br>• Sekou Toure (Malaria Research & Training Center, Mali) |
| Objective(s): | 1. To test hypothesis that repeated administration of artesunate/amodiquine (AS/AQ), artesunate pyrimethamine (AS/SP) and coartem (AR-L) for treatment of consecutive episodes of uncomplicated malaria reduces the incidence of uncomplicated malaria and attributable malaria<br>2. To measure the impact of repeated administration of the drugs on malarial immunity and malaria transmission |
| Study design: | Phase IV randomised trial |
| Number of subjects: | 780 |
| Product: | AS/AQ, AS/SP and AR-L |
| Manufacturer/Developer: | Prequalified drugs |
| Status: | Completed |
| Results and outcomes: | A total of 780 subjects were included to the study with 260 per treatment arm. Collectively, they experienced 2463 episodes of malaria. Combined therapy of Arsucam or Arsumax reduced malaria incidence more than Coartem. Dr Djimde is the Project Coordinator of the WANECAM project (IP.2007.31060.002) |
| Publications: | 1. Kaddouri H., Djimdé A.A., Dama S., Kodio A., Tekete M., Hubert V., Koné A., Maiga H., Yattara O., Fofana B., Sidibe B., Sangaré C.P.O, Doumbo O.K. and Le Bras J. Baseline in vitro efficacy of ACT component drugs on Plasmodium falciparum clinical isolates of Mali. *Int J Parasitol*. 2008 Jun;38(7):791-8. Epub 2008 Jan 3<br>2. Djimdé A.A., Fofana B., Sagara I., Sidibe B., Toure S., Dembele D., Dama S., Ouologuem D., Dicko A., and Doumbo O.K. Efficacy, Safety, and Selection of Molecular Markers of Drug Resistance by two ACTs in Mali. *Am. J. Trop. Med. Hyg*., 78(3), 2008, pp. 455–461<br>3. Tekete M, Djimde AA, Beavogui AH, Maiga H, Sagara I, Fofana B, Ouologuem D, Dama S, Kone A, Dembele D, Wele M, Dicko A, Doumbo OK. Efficacy of chloroquine, amodiaquine and sulphadoxine-pyrimethamine for the treatment of uncomplicated falciparum malaria: revisiting molecular markers in an area of emerging AQ and SP resistance in Mali. Malar J. 2009 Feb 26;8:34.<br>4. Barger B., Maiga H., Traore O.B., Tekete M., Timbine A., Dara A, Traore Z.I., Gantt S., Doumbo O.K. and Djimde A.A. Intermittent preventive treatment using artemisinin-based combination therapy reduces malaria morbidity among school-aged children in Mali. *Trop Med Int Health*. 2009 May 26. PMID: 19497079 |

### 1.3.2 Alexis Nzila

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| EDCTP Project Coordinator: | Alexis Nzila (Kenya Medical Research Institute (KEMRI), Kenya) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Understanding the mechanism of piperaquine PQ) resistance |
| EDCTP Project Code: | TA.2004.40200.003 |
| EDCTP Project Start Date: | 1 January 2005 |
| EDCTP Project End Date: | 25 November 2008 |
| Collaborators: | • Xin-zhuan Su (National Institute of Health (NIH), USA)<br>• Steve Ward (University of Liverpool, UK) |
| Goal: | To understand the mechanisms of PQ-resistance, with the overall goal to identify molecular markers that could be used to predict PQ resistance |
| Objective(s): | 1. Assess the selective pressure of the PQ following the use of ArtekinTM<br>2. Select PQ resistance in vitro: by continuously culturing of parasites in presence of increasing concentrations of PQ<br>3. Identify molecular markers associated with piperaquine resistance. |
| Collaborating site(s): | • NIH (USA)<br>• University of Liverpool (UK) |
| Study design: | Laboratory based investigations: In-vitro drug resistance studies |
| Product: | • PQ, Lumofantrine (LM)<br>• Dihydroxyartemisin (DHA) |
| Status: | Completed |
| Results and outcomes: | The study collected baseline information on the activity of several antimalarials, PQ, Lumofantrine (LM) and Dihydroxyartemisin (DHA) in *P.falciparum* isolates in Kilifi, Kenya. 10 to 20% of isolates had reduced susceptibility to LM, yet this drug has just been introduced in the country; The use of PQ (as part of the use of Artekin®) selected for isolates with higher IC50s to LM, implying that the use of Artekin® may be associated with reduced Coartem® susceptibility. Wild type pfcrt-76 and pfmdr1-86 are associated with increasef LM IC50s. These genes could contribute to LM-resistance, although it is likely that other genes are also involved. Dr Nzila has been the recipient 2006 Royal Society Pfizer Award and 2009 EDCTP Senior Outstanding Scientist Award. He also successfully mentored Dr Leah Mwai who completed her EDCTP funded PhD in 2011. |
| Publications: | 1. Laura K Certain, Marnie R Briceño, B.A.; Steven M Kiara, Alexis M Nzila, William M Watkins, Carol H Sibley. Limited genetic diversity in pyrimethamine resistant strains of Plasmodium falciparum from Kenya. *J Infect Dis*. 2008. 197(12):1743-51<br>2. Eunice Nduati, Abdi Diriye, Ommeth Sheila, Leah Mwai, Steven Kiara, Victor Masseno, Gilbert Kokwaro and Alexis Nzila. Effect of folate derivatives on the activity of antifolate drugs used against malaria and cancer. *Parasitology Research* 2008, 102 (6): 1227-1234.<br>3. Leah Mwai, Edwin Ochong, Abdulrahman Abdi, Stevens Murithi, Steve Ward, Kevin Marsh, Gilbert Kokwaro, Phillip Sassy, Steffen Boormann and Alexis Nzila. Chloroquine resistance before and after its withdrawal in Kenya. *Malar J.* 2009 May 18;8:106. doi: 10.1186/1475-2875-8-106.<br>4. D.M. Kiboi, B. N. Irungu, B. Langat, S. Wittlin, R. Brun, J.Chollet, O. Abiodun J. K. Nganga, V.C.S. Nyambati, G. |

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| | M. Rukunga, A. Bell and A. Nzila. Plasmodium berghei ANKA: Selection of resistance to piperaquine and lumefantrine in a mouse model. *Exp Parasitol*. 2009 Jul;122(3):196-202. doi: 10.1016/j.exppara.2009.03.010. Epub 2009 Mar 24<br>5. Philip Sasi, Abdi Abdulrahaman, Leah Mwai, Judith Straimer, Elise Schieck, Anja Rippert, Mahfudh Bashraheil, Amina Salim, Judith Peshu, Ken Awuondo, Brett Lowe, Munir Pirmohamed, Peter Winstanley, Steve Ward, Alexis Nzila, Steffen Borrmann. In vivo and in vitro efficacy of amodiaquine against Plasmodium falciparum in an area of continued use of 4-aminoquinolines in East Africa. *J Infect Dis*. 2009 Jun 1;199(11):1575-82. doi: 10.1086/598862. |

### 1.3.3 Ambrose Talisuna

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| EDCTP Project Coordinator: | Ambrose Talisuna (Ministry of Health, Uganda) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Safety of artemisinin derivatives-based combination therapy in children with uncomplicated malaria and population-based pharmacovigilance (PV): a capacity strengthening proposal for pharmacovigilance of antimalarial drugs in Africa |
| EDCTP Project Code: | TA.2005.40200.001 |
| EDCTP Project Start Date: | 25 May 2007 |
| EDCTP Project End Date: | 1 June 2010 |
| Collaborators: | • Umberto D'Alessandro (Prince Leopold Institute of Tropical Medicine-ITM, Belgium)<br>• Moses Kamya (Makerere University, Uganda)<br>• Fred Wabwire (Makerere University, Uganda) |
| Site Principal Investigator(s): | Moses Kamya, Makerere University, Uganda; Fred Wabwire-Mangen, Makerere University, Uganda |
| Objective(s): | The objective was to develop a PV system for monitoring the safety of antimalarial treatment at health facilities and within communities.<br>A mixed model of a large multicentre trial at 12 sites (EDCTP funded) and a population based cohort at 2 Ugandan sentinel sites were used to detect signals and test hypotheses on the causal relationship between treatments and AEs. |
| Collaborating site(s): | ITM (Belgium) |
| Study design: | Phase IV (Pharmacovigilance) |
| Status: | Completed |
| Results and outcomes: | A total of 973 antimalarial treatments given either individually or in combination were followed-up. The highest prescriptions were for AL (59 %) followed by quinine (25%), SP (7%), AQ (4%), CQ (3 %), AS monotherapy (0.7%) and DHAPQP (0.1%). In total, 443 AEs were documented in the active surveillance. Pregnancy registration was implemented between January and December 2009. A total of 808 pregnant women were followed with 568 completing follow up. The key success factors were firstly the availability of focal personnel to collect and distribute the forms as well as provide feedback on a monthly basis, Secondly, linkage to existing schemes such as the health management information system and sentinel surveillance. |
| Publications: | |

### 1.3.4 Issa Nebie

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| EDCTP Project Coordinator: | Issa Nebie (Centre national de recherche de Formation sur le Paludisme (CNRFP), Burkina Faso) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Understanding the mechanisms underlying the difference in susceptibility to malaria in an area of hyperendemic malaria in Burkina Faso: The potential role of regulatory T cells |
| EDCTP Project Code: | TA.2005.40200.008 |
| EDCTP Project Start Date: | 30 October 2006 |
| EDCTP Project End Date: | 31 May 2010 |
| Collaborators; | • Diadier Diallo (CNRFP, Burkina Faso)<br>• Amidou Diarra (CNRFP, Burkina Faso)<br>• David Modiano (University of Rome La Sapienza, Italy)<br>• Sodiomon Sirima (CNRFP, Burkina Faso)<br>• Maria Gabriella Torcia (University of Florence, Italy) |
| Goal: | To contribute to the understanding of the role of T cell in susceptibility/resistance to malaria that might help improving or designing new malaria control tools such as malaria vaccine |
| Objective(s): | • To compare the proportion of regulatory T cells in population living in malaria endemic areas<br>• To estimate the number of Foxp3 and GITR expressing cells as indicators of functional activities of T-reg in populations living in malaria endemic areas<br>• To estimate the number of cells producing regulatory cytokine (IFN-gamma, IL-10 and TGF-β) in populations living in malaria endemic areas<br>• To strengthen research capacity of CNRFP (Burkina Faso) through equipment of laboratories and training of young scientists in cellular immunology. |
| Collaborating site(s): | • University of Rome La Sapienza (Italy)<br>• University of Florence (Italy) |
| Study design: | Immunological studies |
| Status: | Completed |
| Results and outcomes: | CD4+CD25+high subpopulations which contain the majority of T-reg cells were predominant in Fulani ethnic group ( statistical significance (P=0.045)). The proportion of CD4+ subsets and CD4+CD25+IL10+ among CD25+ subpopulation which produced the Th2 type cytokine IL10 were more prevalent in Mossi ethnic group compared to Fulani ethnic group (P=0.05 and P=0.03 respectively). The proportion of CD127low and Foxp3+ subpopulations were similar in both ethnic groups. In sub-cohort 2, CD4+CD25+high and Cd4+CD25+IL10+ among CD4+IL10+ were predominant in children with severe malaria compare to asymptomatic children and the observed differences were statistically significant (P=0.01 and P<0.001 respectively). Mr Sanou Guillaume Sylvestre (CNRFP PhD student) trained in on flow in the labs of the University of Florence (Italy) and University of Bordeaux II (France). Three workshops were organised to standardise the assays and to analyse the data. Personnel have been also recruited (one lab technician, 5 nurses), two physicians had been appointed for the project and 2 students (1PhD and 1 master) were registered to complete their training. |
| Publications: | |

### 1.3.5 Emboumbou Moukoko

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| EDCTP Project Coordinator: | Emboumbou Moukoko (University of Buea, Cameroon) |
| EDCTP Project Call: | Career Development Fellowship |
| EDCTP Project Title: | Identification of *Plasmodium falciparum* parasite virulence markers for the evaluation of the impact of malaria control intervention according to the local parasite populations |
| EDCTP Project Code: | TA.2005.40203.006 |
| EDCTP Project Start Date: | 21 November 2006 |
| EDCTP Project End Date: | 20 November 2008 |
| Collaborators: | • Eric Akum Achidi (University of Buea, Cameroon)<br>• Ogobara Doumbo (University of Bamako, Mali)<br>• Albert Same Ekobo (University of Yaoundé, Cameroon)<br>• Peter Kremsner (University of Tübingen, Germany)<br>• Christophe Rogier (Research Unit in Parasite Biology and Epidemiology, France) |
| Goal: | To strengthen previous evidences, to determine more accurately the location of loci associated with pathogenicity, and to identify the *P. falciparum* gene(s) and genotypes that affect(s) the susceptibility to severe malaria (SM). |
| Objective(s): | To perform the combined epidemiological, clinical and genetic analysis (gene mapping of several loci of *P. falciparum* whole-genome and genotyping human haemoglobin) to identify parasite and human genetic markers associated with higher risk of severe disease (including cerebral malaria, severe malaria related anaemia, convulsion and hyperparasitaemia) compared to uncomplicated malaria (UCM)<br><br>Secondary objectives:<br>1. To identify *P. falciparum* gene(s) and genotypes that affect(s) the pathogenicity (i.e. to severe malaria) using a genome wide gene mapping approach<br>2. To identify and control in the statistical the human genetic factors of malaria susceptibility to SM (i.e. haemoglobin and G6PD abnomalies)<br>3. To identify parasite genotypes associated with drug resistance. |
| Collaborating site(s): | • University of Bamako (Mali)<br>• Research Unit in Parasite Biology and Epidemiology (France)<br>• University of Tübingen (Germany) |
| Study design: | Malaria virulence markers |
| Number of subjects: | 956 |
| Status: | Completed |
| Results and outcomes: | A total number of patients 956 of malaria were recruited from September 2007 to January 2009. Most of the data concerning the age, the sex, the clinical phenotype, the biological data and the clinical outcome were collected. The verification of the data bases was completed in participating countries of Cameroon, Mali and Gabon. The project enabled the grantee to set up molecular epidemiology expertise in his laboratory and he consequently got a lecturer position at University of Douala in Cameroon |
| Publications: | |

### 1.3.6 Davis Nwakanma

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| EDCTP Project Coordinator: | Davis Nwakanma (Medical Research Council (MRC) Laboratories, The Gambia) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Evaluation and implementation of high throughput PCR-based method for diagnosis and measurement of P. falciparum parasitaemia in clinical trials |
| EDCTP Project Code: | TA.2005.40200.006 |
| EDCTP Project Start Date: | 27 November 2006 |
| EDCTP Project End Date: | 27 May 2009 |
| Collaborators: | • David Conway (MRC, The Gambia)<br>• Natalia Escobar-Gomez (MRC, The Gambia)<br>• Michael Walther (MRC, The Gambia) |
| Goal: | To evaluate a number of different quantitative real-time PCR (qPCR) methods to determine and establish a suitable protocol for routine application in malaria diagnosis and measurement of parasite density |
| Objective(s): | • To establish the application of qPCR determination of malaria parasitaemia for clinical trials<br>• To evaluate parasite density estimates obtained from qPCR amplification of parasite DNA in blood sample for agreement with blood film slide microscopy<br>• To conduct a cost comparison of qPCR with slide microcopy for the determination of malaria parasitaemia. |
| Study design: | Point of care diagnostics |
| Status: | Completed |
| Results and outcomes: | qPCR detected more infections than microscopy (22% vs 18%) but overall the coefficient of agreement between both methods was very high (κ = 0.86). Parasite density estimates by the two methods were very similar with near-perfect concordance (rho_c = 0.968). At 72h post-treatment it was possible to detected parasites by qPCR in ~20% of patients in whom microscopy failed to detect any infection. Median parasite clearance time was 16h by microscopy and 24h by qPCR. Parasite survival curves estimated by the two methods were significantly different (X2. =34.43; p=<.0001). Eleven PhD and MSc students were trained on short courses in the project. One article was published. |
| Publications: | 1. Nwakanma D, Gomez-Escobar N, Walther M, Crozier S, Dubovsky F, Malkin E, Locke E, Conway D. (2009) Quantitative detection of Plasmodium falciparum DNA in saliva, blood and urine. *J Infect Dis* 199: 1567-1574. |

### 1.3.7 Badara Cisse

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| EDCTP Project Coordinator: | Badara Cisse (University Cheikh Anta Diop, Senegal) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | A pilot study of the Implementation of Seasonal Intermittent Preventive Treatment with Community Participation in Senegal |
| EDCTP Project Code: | TA.2005.40200.004 |
| EDCTP Project Start Date: | 14 May 2007 |
| EDCTP Project End Date: | 8 August 2010 |
| Collaborators: | • Pierre Gazin (Institut de Recherche pour le Développement, Senegal)<br>• Omar Gaye (University of Dakar, Senegal)<br>• Brian Greenwood (London School of Hygiene and Tropical Medicine (LSHTM), UK)<br>• Paul Milligan (LSHTM, UK)<br>• Pape Moussa Thior (Ministry of Health and Medical Prevention, Senegal)<br>• Jean-François Trape (Institut de Recherche pour le Développement, Senegal) |
| Clinical Trial/Study Sponsor: | University Cheikh Anta Diop (Senegal) |
| Primary Objective(s): | To compare the effectiveness of Dualkin (cure rate at 28 and 42 days) compared to amodiaquine plus artesunate (e.g. Falcimon*) which is the used ACT for the treatment of uncomplicated Plasmodium falciparum. Falcimon* is a combination of amodiaquine plus artesunate. The secondary objectives of this study were to compare delay to fever and parasitemia clearance and to determine the prevalence of gametocyte carriage at day 14, 28 and 42. Other objectives included to assess the clinical efficacy (delay to fever and parasite clearance and prevalence of gametocytes carriage after treatment). |
| Collaborating site(s): | • LSHTM (UK)<br>• Institut de Recherche pour le Développement (Senegal) |
| Study design: | Phase III |
| Number of subjects: | 1893 children |
| Product: | Dualkin to amodiaquine plus artesunate |
| Status: | Completed |
| Results and outcomes: | This study provided evidence that seasonal IPTc with SP+PQ among children is highly effective and well tolerated. The combination of two long-acting drugs is optimal for malaria prevention and is most effective in the face of an emergence of resistant parasite genotypes. It was also demonstrated that amendments to age-based dosing of SP-Amodiaquine had the potential of increasing dosing accuracy and improve tolerability of the IPTc. Two scientific papers were published. The work has been an important reference for the WHO scientific advisory group. One junior physician, 2 nurses and 45 community volunteers were trained. The grantee also recruited an MSc student in parasitology and he was also a recipient of second Senior Fellowship grant from Malaria Capacity Development Consortium. Two more EDCTP funded projects are now linked to the ground work of this project. These are a Senior Fellowship to Jean Louis Ndiaye and the Malaria Vectored Vaccines Consortium - IP_08_31100_001, which were both awarded in 2010. |
| Publications: | 1. Cisse B, Cairns M, Faye E, et al. Randomised Trial of Piperaquine with Sulfadoxine-Pyrimethamine or |

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| | Dihydroartemisinin for Malaria Intermittent Preventive Treatment in Children. *PloS one.* 2009;4(9):e7164<br>2. M Cairns, B Cisse, C Sokhna, et al. Amodiaquine dosage and tolerability for intermittent preventive treatment to prevent malaria in children. *Antimicrobial Agents and Chemotherapy*. March 2010, p. 1265-1274, Vol. 54, No. 3. |

### 1.3.8 Daniel Dodoo

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| EDCTP Project Coordinator: | Daniel Dodoo (Noguchi Memorial Institute for Medical Research, Ghana) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Assessment of functionality of antibodies that associate with protection from clinical malaria using the in-vitro P.falciparum growth inhibition assay |
| EDCTP Project Code: | TA.2007.40200.012 |
| EDCTP Project Start Date: | 24 July 2008 |
| EDCTP Project End Date: | 30 March 2011 |
| Collaborators: | • Klavs Berzins (Stockholm University, Sweden)<br>• Michael Theisen (Statens Serum Institut (SSI), Denmark) |
| Goal: | To measure GLURP and MSP3 isotype and IgG subclass antibodies by ELISA in relation to susceptibility or protection from clinical malaria; establishment and field validation of the in vitro parasite growth inhibition assays using purified GLURP specific antibodies from selected individuals whose ELISA antibody responses to GLURP associate with protection against or susceptibility to clinical malaria after correcting for potential confounders. |
| Objective(s): | 1. To establish in the field, the *in vitro* parasite growth inhibition assays with or without the presence of monocytes, using microscopy and flowcytometric readouts to assess parasite growth inhibition<br>2. To assess by ELISA, antibody responses to GLURP and MSP3 in relation to protection against or susceptibility to clinical malaria correcting for potential confounders such as age, socio-economic status, area of residence in study area, duration of residence in study area among others<br>3. To determine the functionality of purified antibodies in individuals who had malaria and those who did not have malaria during the study period by the *in vitro* parasite growth inhibition assay with or without the presence of monocytes. |
| Collaborating site(s): | • Stockholm University (Sweden)<br>• SSI (Denmark) |
| Study design: | Laboratory based immunological and molecular biology investigations: in-vitro assays |
| Status: | Completed |
| Results and outcomes: | The acquired Growth Inhibition Assay technique by the project staff has been established at the Immunology laboratory of Noguchi Memorial Institute and used in assessing the functionality of antibodies that correlate with protection from clinical malaria in the ELISA procedure. 8 individuals at the centre have been trained in GIA. |
| Publications: | |

### 1.3.9 Christian Happi

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| EDCTP Project Coordinator: | Christian Happi (University of Ibadan, Nigeria) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Validation of New Biomarkers for Monitoring *Plasmodium falciparum* Reduced susceptibility/Tolerance or Resistance to Artemisinin Derivatives and Partner Drugs in Nigeria. |
| EDCTP Project Code: | TA.2007.40200.016 |
| EDCTP Project Start Date: | 13 December 2008 |
| EDCTP Project End Date: | 12 December 2010 |
| Goal: | To identify and validate new biomarkers/molecular determinants of parasites response to artemisinin derivatives (ARTs) and partner drugs *in vitro* and *in vivo.* |
| Objective(s): | 1. Evaluate clinical treatment response parameters, *in vitro* and *in vivo* efficacy and drug blood levels of artemether-lumefantrine (AL) and artesunate-amodiaquine (AS-AQ) combinations in patients' infected with *P. falciparum* in Ibadan, Southwest Nigeria<br>2. Use the PCR, DNA sequencing approaches to identify new biomarkers/ molecular determinants of P. falciparum response to ARTs and Partner drugs *in vitro* and *in vivo*.<br>3. Validate the role of new biomarkers/molecular determinants of *P. falciparum* response to ARTs and partner drugs by collating SNPs/SNPs patterns in parasite genes with clinical treatment response parameters, patients' treatment outcome, blood drug levels and in vitro quantitative responses (phenotypes). |
| Study design: | *In vitro* and *in vivo* bio-markers studies |
| Status: | Completed |
| Results and Outcomes: | 5 major sub-studies were completed and four publications produced from the fellowship. The capacity building programme at grantee's laboratory at the College of Medicine, University of Ibadan in Nigeria has been improved and has been used to train Dr Obaro Michael (a clinician) a former Master's Degree Programme student for his fellowship; Dr Onikepe Folarin a post-doctoral Fellow to attend the Genome Epidemiology Meeting in Hinxton, UK and Miss Titilola Okuboyejo a PhD student partly being supported by this project to undergo a 3 months training on quantitative qPCR for gametocyte sex ratio determination |
| Publications: | 1. Akintunde Sowunmi, Elsie O Adewoye, Grace O Gbotosho, Christian T Happi, Abayomi Sijuade, Onikepe A Folarin, Titilope M Okuboyejo and Obaro S Michael. (2010). Factors contributing to delay in parasite clearance in uncomplicated *falciparum* malaria in children. *Malaria Journal.* 9(1):53<br>2. Grace O. Gbotosho, Christian Happi, Onikepe Folarin, Ochuko Keyamo, Akintunde Sowunmi, and Ayoade MJ Oduola. (2010). Rapid Detection of Lactate Dehydrogenase and Genotyping of *Plasmodium falciparum* in Saliva of Children with Acute Uncomplicated Malaria. *Am. J. Trop. Med. Hyg*. 83 (3): 496-501<br>3. Obaro S Michael, Grace O Gbotosho, Onikepe A Folarin, Titilope Okuboyejo, Akintunde Sowunmi, Ayoade MJ Oduola and Christian T Happi. (2010). Early variations in *Plasmodium falciparum* dynamics in Nigerian children after treatment with two artemisinin-based combinations: implications on delayed parasite clearance. *Malaria* |

*Journal*. 9:335.
4. Daria Van Tyne, Daniel J. Park, Stephen F. Schaffner, Daniel E. Neafsey, Elaine Angelino, Joseph F. Cortese, Kayla G. Barnes, David M. Rosen, Amanda K. Lukens, Rachel F. Daniels, Danny A. Milner, Jr, Charles A. Johnson, Ilya Shlyakhter, Sharon R. Grossman, Justin S. Becker, Daniel Yamins, Elinor K. Karlsson, Daouda Ndiaye, Ousmane Sarr, Souleymane Mboup, Christian Happi, Nicholas A. Furlotte, Eleazar Eskin, Hyun Min Kang, Daniel L. Hartl, Bruce W. Birren, Roger C. Wiegand, Eric S. Lander, Dyann F. Wirth, Sarah K. Volkman, Pardis C. Sabeti. (2011). Identification and Functional Validation of the Novel Antimalarial Resistance Locus PF10_0355 in *Plasmodium falciparum*. *PLoS Genet*. E1001383.doi:10.1371/journal.pgen.1001383.

### 1.3.10 Kamija Phiri

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| EDCTP Project Coordinator: | Kamija Phiri (University of Malawi) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | A randomised controlled trial of oral iron therapy for treatment of post-malaria iron-deficiency anaemia in Malawian children com paring immediate post-discharge versus delayed treatment on iron uptake and haematological response |
| EDCTP Project Code: | TA.2008.40200.016 |
| EDCTP Project Start Date: | 29 September 2009 |
| EDCTP Project End Date: | 29 September 2011 |
| Collaborators: | • Patrick van Rheenen (University Medical Center Groningen, Netherlands)<br>• Feiko ter Kuile (University of Liverpool, UK)<br>• Sarah White (Malawi-Liverpool-Wellcome Trust Research Programme, Malawi) |
| Clinical Trial/Study Sponsor: | College of Medicine, University of Malawi |
| Objective(s): | To determine whether delaying oral iron therapy in post-malaria iron deficiency anaemia for at least two weeks improves iron absorption and reduces the risk of iron-induced intestinal inflammation |
| Clinical Trial/Study site(s): | |
| Collaborating site(s): | • University Medical Center Groningen (Netherlands)<br>• University of Liverpool (UK) |
| Study design: | Phase II trial: Evaluation of different forms of oral iron for treatment of post malaria iron deficiency anaemia |
| Number of subjects: | 245 |
| Product: | Iron tonic/ iron isotopes |
| Manufacturer/Developer: | International Atomic Energy Agency |
| Status: | Completed |
| Results and Outcomes: | In 2010 protocol changes increased the required the sample size increased from 400 to 600. Due to slow recruitment at original study site (Ndirande Health Centre in Blantyre) the study was moved to another district (Zomba) with a reported higher rate of potential study participants. Between September 2011 and end of February 2012 a total of 148 participants had been recruited bringing the total to 245 study participants (41% of required sample). The fellow had also successfully managed to source funds ($100,000) from Malaria Capacity development Consortium (MCDC) of the London School of Hygiene and Tropical Medicine to establish a Tropical Haematology Research Unit (THRU) in the Haematology Department, College of Medicine. A sub-study investigating iron absorption and incorporation into the blood cells has been planned to be carried out in collaboration with partners at the Swiss Federal Institute of Technology (ETH) Institute of Food in Switzerland (Prof Richard Hurrell and team). |
| Publications: | |

### 1.3.11 Eric Achidi

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| EDCTP Project Coordinator: | Eric Achidi (University of Buea, Cameroon) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Malaria baseline studies towards characterising and establishing a clinical trial site at Mutengene, South West Region of Cameroon |
| EDCTP Project Code: | TA.2009.40200.008 |
| EDCTP Project Start Date: | 22 March 2010 |
| EDCTP Project End Date: | 22 March 2012 |
| Collaborators: | • Julius Atashili (University of Buea, Cameroon) |
| Objective(s): | The epidemiological study is designed to provide data on baseline malariometric parameters valuable for future intervention studies aimed at validating disease control tools. The specific objectives include conducting a population census of the study area, determining the malaria prevalence rates and density in cross sectional surveys, helminth and malaria co-infection rates and densities, number of episodes per year in cohort longitudinal studies, vectors transmitting parasites, their dynamics and inoculation rates, natural immune responses to malaria parasite exposure and prevalence of some genetic traits that protect against malaria. |
| Clinical Trial/Study site(s): | Mutengene, Fako Division (Cameroon) |
| Study design: | Epidemiological studies for clinical trials site develpment |
| Number of subjects: | 15,344 |
| Status: | Completed |
| Results and Outcomes: | At the end of the project a total of 15,344 individuals had been included and a series of baseline studies were conducted. These included studies household mosquito net ownership, prevalence of fever, prevalence of malaria parasitaemia by season, prevalence of intestinal helminthes by season, prevalence of anaemia, the prevalence of the sickle cell trait (HbAS) in the study group and levels of Plasmodium falciparum specific IgE/IgG2 antibodies in study participants. The project is well integrated within the EDCTP funded central African network of excellence, CANTAM and also received additional funding from the European Virtual Institute for Malaria Research (EVIMalaR). Eight members of the study team received various short term trainings. |
| PhD study: | Candidate: Njua Clarisse Yafi |
| Publications: | 1. Eric A. Achidi, Tobias O. Apinjoh, Judith K. Anchang-Kimbi,Clarisse N. Yafi, Richard Besingi, Nancy W. Awah and Marita Troye-Blomberg. (2012). Plasmodium falciparum Specific IgE, IgG and Anti-GPI IgG Antibodies in Cameroonian Children with Severe and Uncomplicated Malaria. *International Journal of Tropical Disease and Health*. June 2012. 2(3): 157-172<br>2. Eric A Achidi, Tobias O Apinjoh, Judith K Anchang-Kimbi, Regina N Mugri, Andre N Ngwai, Clarisse N Yafi. (2012). Severe and uncomplicated falciparum malaria in children from three regions and three ethnic groups in Cameroon: prospective study. *Malar J.* 2012 Jun 24;11:215.<br>3. Gervais Gouana Tchinda, Julius Atashili, Eric A Achidi, Henri L Kamga, Anna L Njunda, Peter M Ndumbe (2012). Impact of malaria on hematological parameters in people living with HIV/AIDS attending the Laquintinie Hospital in Douala, Cameroon. *PLoS One*. 2012;7(7):e40553. doi: 10.1371/journal.pone.0040553. Epub 2012 Jul 10 |

### 1.3.12 Alfred Tiono

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| EDCTP Project Coordinator: | Alfred Tiono (Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Burkina Faso) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Phase IV: A cluster-randomised controlled trial to assess the impact of combined strategies (impregnated bed nets + Home management of malaria oriented by Rapid Diagnosis Test) on severe malaria morbidity in children aged 6 to 59 months in Burkina Faso |
| EDCTP Project Code: | TA.2009.40200.019 |
| EDCTP Project Start Date: | 29 April 2010 |
| EDCTP Project End Date: | 28 February 2013 |
| Collaborators: | • Issa Ouedraogo Nebie (CNRFP, Burkina Faso)<br>• Sodiomon Bienvenu Sirima (CNRFP, Burkina Faso) |
| Objective(s): | To show the additional benefit in terms of reduction of severe malaria morbidity by adding the HMM to bed nets for children aged 6-59 months living in a seasonal malaria transmission area and to estimate the incidence of severe malaria in children aged 6-59 months living under Insecticides impregnated bed nets with access to home based management of malaria strategy in a seasonal malaria transmission area |
| Clinical Trial/Study site(s): | CNRFP (Burkina Faso) |
| Study design: | Cluster randomised trial of bed nets and home management |
| Number of subjects: | 40 clusters (8860 children) |
| Status: | Ongoing |
| Results and outcomes: | At the end of first year of the project the following have been achieved and in accordance with the approved work plan:<br>• Approval of the study by the community and ethics review board<br>• Definition of study clusters<br>• Purchase and distribution of bed nets<br>• Training of staff<br>• Conduct 2 of the planned 4 cross sectional studies<br><br>The remaining activities include:<br>• Third cross sectional study<br>• Fourth cross sectional study<br>• Data analysis<br>• Publications |
| Publications: | |

### 1.3.13 Pauline Byakika Kibwika

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| EDCTP Project Coordinator: | Pauline Byakika Kibwika (Infectious Diseases Institute, Makerere University College Of Health Sciences (Uganda) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Comparison of efficacy, safety and pharmacokinetics of intravenous artesunate and intravenous quinine followed by oral artemisinin combination therapy for severe malaria treatment in Uganda AND evaluation of pharmacokinetic drug interactions of artesunate, quinine, lumefantrine and piperaquine with antiretroviral drugs |
| EDCTP Project Code: | TA.2009.40200.020 |
| EDCTP Project Start Date: | 14 March 2011 |
| EDCTP Project End Date: | 14 March 2013 |
| Collaborators: | • Jane Achan (Makerere University, Uganda)<br>• Moses R. Kamya (Makerere University (Uganda)<br>• Elly Katabira (Makerere University, Uganda)<br>• Noah Kiwanuka (Makerere University, Uganda)<br>• Mohammed Lamorde (Makerere University, Uganda)<br>• Harriet Mayanja-Kizza (Makerere University, Uganda)<br>• Concepta Merry (Makerere University, Uganda/Trinity College, Ireland) |
| Clinical Trial/Study Sponsor: | Institute of Infectious Diseases (Uganda) |
| Goal: | To evaluate the effectiveness of IV artesunate plus ACT and IV quinine plus ACT as well as to study the pharmacokinetics of artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) for treatment of severe malaria in adults and children in Tororo district hospital, Uganda. |
| Objective(s): | 1. To compare treatment outcome (measured as risk of recurrent parasitaemia and risk of recurrent symptomatic malaria) following treatment with IV quinine followed by oral ACT (Artemether-Lumefantrine or Dihydroartemisinin-piperaquine) and IV artesunate followed by oral ACT (AL or DP) for treatment of severe malaria in Ugandan patients<br>2. To compare parasite clearance time following treatment with IV quinine followed by oral ACT (AL or DP) and IV artesunate followed by oral ACT (AL or DP) for treatment of severe malaria in Ugandan patients<br>3. To investigate the pharmacokinetic parameters of IV quinine, IV artesunate, oral AL and oral DP during severe malaria treatment in Ugandan patients and correlate these with treatment outcome<br>4. To investigate the pharmacokinetic drug interactions of quinine, artesunate, lumefantrine and piperaquine with the antiretroviral drugs (Nevirapine, Efavirenz, Lopinavir/ritonavir) in Ugandan patients. |
| Collaborating site(s): | University of Liverpool (UK) |
| Study design: | PK and drug interaction studies |
| Number of subjects: | 400 (target) |
| Product: | Quinine, ACT (Artemether-Lumefantrine or Dihydroartemisinin-piperaquine) and IV artesunate |
| Manufacturer/Developer: | Gilead (for iv artesunate only) |
| Cofunders: | International Society of Infectious Diseases (Uganda) |
| Status: | Ongoing |
| Results and Outcomes: | By mid-2012 the project had screened 57 patients, recruited |

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| | 39 and had 1 lost to follow up. The target sample size is 400. |
| Publications: | |

### 1.3.14 Bourema Kouriba

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| EDCTP Project Coordinator: | Bourema Kouriba (University of Bamako, Mali) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Role of functionally distinct monocyte subpopulations in protection against clinical Plasmodium falciparum malaria in people living in endemic area of Mali |
| EDCTP Project Code: | TA.2010.40200.007 |
| EDCTP Project Start Date: | 13 May 2011 |
| EDCTP Project End Date: | 13 May 2013 |
| Collaborators: | • Charles Aarama (Malaria Research & Training Center, Mali)<br>• Issa Diarra (Malaria Research & Training Center, Mali)<br>• Abdoulaye Kone (Malaria Research & Training Center, Mali)<br>• Amadou Niangaly (Malaria Research & Training Center, Mali)<br>• Mahamadou S. Sissoko (Malaria Research & Training Center, Mali)<br>• Kourane Sissoko (Malaria Research & Training Center, Mali) |
| Objective(s): | To assess the role of monocytes activation by infected red blood cell in the protection against clinical falciparum malaria in endemic area and determine the frequency of monocytes subpopulations according to the clinical outcome (asymptomatic, mild and severe) of malaria infection |
| Study design: | Immunological cohort studies |
| Number of subjects: | 210 children |
| Status: | Ongoing |
| Results and outcomes: | A cohort of 210 children aged 1-15 years was established in May 2011. Three cross-sectional studies will be conducted on this cohort before completion of the project. |
| Publications: | |

### 1.3.15 Aissatou Toure

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| EDCTP Project Coordinator: | Aissatou Toure (Pasteur Institute of Dakar, Senegal) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Optimization and standardization of the new functional antibody dependant respiratory burst (ADRB) assay to evaluate anti-malarial immunity in endemic populations and merozoite based vaccine candidates |
| EDCTP Project Code: | TA.2010.40200.027 |
| EDCTP Project Start Date: | 26 April 2011 |
| EDCTP Project End Date: | 26 April 2013 |
| Collaborators: | • Sylvie Bay (Institut Pasteur, France)<br>• Shirley Longacre (Institut Pasteur, France)<br>• Adama Tall (Institut Pasteur de Madagascar) |
| Objective(s): | 1. To optimize and standardize a "new" functional assay developed recently in our research unit, the Antibody Dependant Respiratory Burst (ADRB) assay detected by chemiluminescence, which has been correlated with clinical protection against malaria<br>2. To compare ADRB results with those of other commonly used functional assays such as the growth inhibition assay (GIA)<br>3. To use the ADRB assay as a tool to evaluate the level of malaria immunity in different endemic populations and to validate merozoite surface antigen vaccine candidates |
| Study design: | Laboratory based investigations: *in vitro* immunological and molecular biological assays |
| Status: | Ongoing |
| Results and outcomes: | In the first year of the project the team studied mononuclear cells in comparison with polymorphonuclear neutrophils but concluded that using freshly isolated polymorphonuclear neutrophils give better results. Conditions of Ph for optimising the ADRB assay were also studied and the conclusion is that better results are obtained with alkaline Ph. The team finished by studying different strains of *P. falciparum* in the ADRB using the Palo Alto strain of *P. falciparum* as reference in comparison with local adapted *P. falciparum* strain. They observed that the ADRB is significantly higher when the merozoites originated from local *P. falciparum* strains. After comparing optimized ADRB using the data bank and sera collection available in the Pasteur Institute associated with the Dielmo project monitoring the immune status of two endemic populations the results showed again a correlation between high level of ADRB and a lower risk of malaria attack that confirm our previous results. |
| Publications: | |

### 1.3.16 Jean Louis Ndiaye

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| EDCTP Project Coordinator: | Jean Louis Ndiaye (University Cheikh Anta Diop of Dakar, Senegal) |
| EDCTP Project Call: | Senior Fellowship |
| EDCTP Project Title: | Intermittent preventive treatment in children combined with malaria home management in an area with persisting high malaria prevalence in Senegal |
| EDCTP Project Code: | TA.2010.40200.032 |
| EDCTP Project Start Date: | 11 April 2011 |
| EDCTP Project End Date: | 11 April 2013 |
| Collaborators: | • Badara Cisse (University Cheikh Anta DIOP de Dakar (UCAD), Senegal)<br>• Oumar Gaye ((UCAD, Senegal)<br>• Paul Milligan (London School of Hygiene and Tropical Medicine (LSHTM), UK)<br>• Youssoupha Ndiaye (Ministere de la sante et de la prevention medicale, Senegal)<br>• Pape Moussa Thior (Ministere de la sante et de la prevention medicale, Senegal) |
| Clinical Trial/Study Sponsor: | University Cheik Anta Diop de Dakar (Senegal) |
| Objective(s): | To determine whether seasonal IPTc with sulfadoxine-pyrimethamine plus amodiaquine provide added benefit in populations with access to prompt effective treatment through home–based management; whether IPTc has previously been shown effective when give for three months in areas with a short transmission season and whether seasonal IPTc is safe and acceptable when given for a longer period in areas with a longer transmission season. To also show the cost-effectiveness of adding seasonal IPTc to home management of malaria (HMM) |
| Collaborating site(s): | London School of Hygiene and Tropical Medicine (LSHTM, UK) |
| Study design: | Phase IV: Cluster randomised trial |
| Number of subjects: | 4554 |
| Status: | Ongoing |
| Results and outcomes: | Twenty four Community Health Workers and malaria volunteers were trained by the department of Parasitology to do thick and thin blood smear to confirm all malaria cases in the 24 villages involved in that EDCTP research project. Out of 4554 chldren enrolled in the study approximately 2000 children have received IPTc at fifth month (97% of intended sample of intervention group). |
| MSc studies | Candidate: Dr Mamadou Sarifou |
| | Candidate: Mr Cheikh Tidiane Ba |
| Publications: | |

# 2 PhD and MSc scholarships

Stand-alone (individual) PhD and MSc scholarships in HIV/AIDS, tuberculosis and malaria supported by EDCTP. Other PhD and MSc grants are included under their respective integrated/clinical trial projects

| Project Acronym (Coordinator) | Disease area | Project details | Study population | Status of project |
|---|---|---|---|---|
| Jobe - MSc | HIV | Master of Science in Reproductive and Sexual Health Research | TBD | Completed |
| Oyakhirome - MSc | | Public Health | Not applicable | Completed |
| Sikateyo - PhD | HIV | Informed consent process in HIV trials in Zambia | Participants in an HIV vaccine trial in Lusaka | Completed |
| Yindom - PhD | HIV | Immunogenetics for HIV vaccine design | 600 unrelated adults in Gambia | Completed |
| Yimer - PhD | TB | TB drug and ART interaction and metabolism | 758 ART naïve TB, TB-HIV and HIV infected individuals | Completed |
| Mthiyane - PhD | TB | Interferon gamma responses in TB-HIV coinfected individuals | TB-HIV infected patients | Completed |
| Mwai - PhD | Malaria | Lumefantrine resistance | 250 in vitro culture isolates | Completed |
| Ramatoulie - PhD | Malaria | Pharmcogenetics of chlorproguanil in adults and children | Malaria patients in Gambia | Completed |
| Arama - PhD | Malaria | Immungenetic factors in malaria prevention | 77 patients in Mali | Completed |

## 2.1 Alasan Jobe

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| EDCTP Project Coordinator: | Alasan Jobe (National Malaria Control Program, Department of State for Health and Social Welfare, The Gambia) |
| EDCTP Call Title: | MSc Studentship |
| EDCTP Project Title: | Masters in Reproductive and Sexual Health Research |
| EDCTP Project Code: | TA.2005.40205.001 |
| EDCTP Project Start Date: | 10 August 2006 |
| EDCTP Project End Date: | 30 October 2007 |
| Status: | Completed |
| Results and Outcomes: | The MSc training from the London School of Hygiene & Tropical Medicine on Reproductive & Sexual Health Research was completed in August 2007. |

## 2.2 Sunny Oyakhirome

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| EDCTP Project Coordinator: | Sunny Oyakhirome (Medical Research Unit, Albert Schweitzer Hospital, Gabon) |
| EDCTP Call Title: | MSc Studentship |
| EDCTP Project Title: | MSc in Public Health |
| EDCTP Project Code: | TA.2005.40205.002 |
| EDCTP Project Start Date: | 27 June 2006 |
| EDCTP Project End Date: | 27 June 2007 |
| Institution: | London School of Hygiene and Tropical Medicine (LSHTM, UK), Distance learning in MSc in public health |
| Supervisor(s): | • Saadou Issifou (Medical Research Unit, Albert Schweitzer Hospital, Gabon)<br>• Peter Kremsner (University of Tübingen, Germany)<br>• Bertrand Lell (Medical Research Unit, Albert Schweitzer Hospital, Gabon) |
| Goal: | Candidate aim: Improvement in the health of populations, communities and particular groups within them (eg children), through the evaluation of practical, effective interventions against major public health diseases: Malaria, Tuberculosis; AIDS. With emphasis on evidence based methods of analysis of treatment and care; investigation, development and critical evaluation of conceptual models. |
| Objectives: | To provide a sound ability to apply knowledge of the core disciplines; statistics, epidemiology, health economics, and social research, to real health problems. In addition, graduates should be able to:<br>1. Demonstrate knowledge and understanding of the principle theories, methods and interventions used in health promotion<br>2. Demonstrate knowledge and understanding of the development of health promotion internationally and its evolution as a multidisciplinary field<br>3. Assess the appropriate use of population-wide versus targeted health promotion interventions<br>4. Consider how to develop health promotion policy and practice that is relevant to varying public health issues in diverse contexts<br>5. Show competence in critically evaluating and communicating research evidence<br>6. Apply the knowledge and analytical skills they have gained to inform health promotion policy-making, programme planning, implementation and evaluation, and research design. |
| Status: | Completed |
| Results and Outcomes: | The MSc training from the London School of Hygiene & Tropical Medicine on Public Health was completed in June 2007. |

## 2.3 Bornwell Sikateyo

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| EDCTP Project Coordinator: | Bornwell Sikateyo (Central Board of Health, Zambia) |
| EDCTP Call Title: | PhD Studentship |
| EDCTP Project Title: | Understanding participants' consent undertaken by in an Entero-Toxigenic vaccines trial in Misisi Township in Lusaka, Zambia |
| EDCTP Project Code: | TA.2005.40204.026 |
| EDCTP Project Start Date: | 1 November 2006 |
| EDCTP Project End Date: | 30 March 2011 |
| Supervisor(s): | • Roger Beech (University of Keele, UK)<br>• Nancy E. Kass (Johns Hopkins Bloomberg School of Public Health, USA)<br>• Douglas Wassenaar (University of KwaZulu-Natal, South Africa) |
| Objectives: | The specific objectives of this PhD project were: (a) To describe the interactions between research staff and participants in which "consent" is negotiated and maintained, (b) to explore participants' social and economic characteristics, everyday life and situations as these impact the "consent process" and (c) to assess how negotiations of participant consent evolve and change over the course of the trial in view of the complex procedures. |
| Status: | Completed |
| Results and Outcomes: | This study found that study participants in a vaccine trial in Missi in Zambia enrolled to gain access to the resources necessary for survival. These included improved health care and cash incentives. |

## 2.4 Louis Marie Yindom

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| EDCTP Project Coordinator: | Louis Marie Yindom (Medical Research Council (MRC) Laboratories, The Gambia) |
| EDCTP Call Title: | PhD Studentship |
| EDCTP Project Title: | The role of Human leukocyte antigen (HLA) and killer immunoglobulin-like receptor (KIR) in HIV-2 infection: a key component to HIV vaccine design and its evaluation in Africa |
| EDCTP Project Code: | TA.2005.40204.013 |
| EDCTP Project Start Date: | 1 August 2006 |
| EDCTP Project End Date: | 31 August 2009 |
| Supervisor(s): | • Assan Jaye (MRC Laboratories, The Gambia)<br>• Sarah Rowland-Jones (MRC Laboratories, The Gambia)<br>• Giorgio Sirugo (MRC Laboratories, The Gambia) |
| Goal: | To comprehensively characterise the distribution of HLA class I molecules in populations in the Gambia and Guinea-Bissau and to look at immunogenetic associations, focusing on HLA and KIR genotypes, with clinical outcome in HIV-2 infection which is largely confined to West Africa and provides a valuable model of attenuated HIV disease |
| Objectives: | The major objectives of this project are to:<br>1. Determine the distribution of HLA class I and KIR genes among HIV-2 cases and healthy individuals in Caio (Guinea-Bissau) and Fajara (Gambia)<br>2. Study the association of individual HLA-A, HLA-B, HLA-C, and KIR genes with susceptibility or resistance to HIV-2 infection<br><br>The secondary objectives are to:<br>1. Determine the epistatic effect between HLA and KIR gene variants in HIV-2 disease outcome using indicators of disease<br>2. Progression such as CD4+ T cell count and plasma viral load (PVL)<br>3. Develop sequence specific techniques for subsequent detection of KIR and HLA alleles from genomic DNA |
| Status: | Completed |
| Results and outcomes: | The study showed that HLA-KIR compound genotypes did not affect risk of HIV-2 acquisition in Gambia. |

## 2.5 Getnet Yimer

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| EDCTP Project Coordinator: | Getnet Yimer (Department of Pharmacology, Medical Faculty, Addis Ababa University, Ethiopia) |
| EDCTP Call Title: | PhD Studentship |
| EDCTP Project Title: | Anti-tuberculosis-antiretroviral drugs induced Hepatotoxicity and interaction of these drugs at the level of CYP 450 metabolism |
| EDCTP Project Code: | TA.2005.40204.005 |
| EDCTP Project Start Date: | 2 August 2006 |
| EDCTP Project End Date: | 2 December 2010 |
| Goal: | To evaluate the prevalence, severity, and outcome of hepatotoxicity associated with intake of anti TB and/or ARV drugs when taken concomitantly and when taken alone; and to determine the pharmacokinetic drug-drug interaction between anti TB and ARV at the level of drug metabolism and thereby assess the distribution of CYP 3A4, 3A5, 2C9/19, 2B6, and NAT2. |
| Objectives: | To assess and compare the prevalence, severity and prognosis of anti-TB and ARV drugs induced hepatotoxicity and evaluate the drug-drug interaction at the level of CYP 450 among Ethiopian patients.<br><br>Specific objectives<br>1. To determine the prevalence of DIH in HIV positive TB patients taking anti-TB alone<br>2. To determine the prevalence of DIH in HIV positive TB patients taking anti-TB and ART<br>3. To see the distribution of CYP 3A4, 3A5, 2C9/19, 2B6 polymorphism in our study participants<br>4. To see the effect of CYP 3A4, 3A5, 2C9/19, 2B6 polymorphism on the development of DIH<br>5. To assess the drugdrug interaction between the anti-TB and ARV drugs<br>6. To assess the severity as well as outcome of DIH in our study participants. |
| Status: | Completed |
| Results and outcomes: | The study is reported to have shown that drug induced liver injury (DILI) is common among Ethiopian TB-HIV patients who have a slow acetylation status related to CYP2B6 516TT genotype. This is particularly relevant to patients on efavirenz based regimen. Through these findings close follow up and regular monitoring of plasma efavirenz concentration and liver enzymes during early therapy particularly in patients with, and those with elevated serum amino-transferases, lower haemoglobin, platelet count and albumin at baseline is recommended for early management of efavirenz-based HAART induced liver injury. |

## 2.6 Thuli Mthiyane

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| EDCTP Project Coordinator: | Thuli Mthiyane (Medical Research Council, South Africa |
| EDCTP Call Title: | PhD Studentship |
| EDCTP Project Title: | Safety tolerability and monitoring of combined anti-tuberculosis and antiretroviral therapy (Reconstitution of TB antigen specific IFN-γ responses in TB-HIV co-infected participants) |
| EDCTP Project Code: | TA.2005.40204.025 |
| EDCTP Project Start Date: | 10 November 2006 |
| EDCTP Project End Date: | 31 October 2011 |
| Supervisor(s) | • Graham Rook (University College London, UK)<br>• A. W. Sturm (Nelson R Mandela School of Medicine University of KwaZulu Natal, South Africa)<br>• A. Zumla (University College London, UK) |
| Goal: | To evaluate contribution of anti-TB and ART to hepatotoxicity through tests for NAT2 and Cytochrome P450 and to assess quality of life of patients on these drugs |
| Objectives: | 1. To determine if there is a difference in the experience of<br>– adverse events (AEs) and serious adverse events (SAEs)<br>– hepatotoxicity grade 1-4<br>– immune Reconstitution Syndrome in TB/HIV co-infected patients receiving TB treatment and HAART concomitantly and TB/HIV co-infected patients receiving TB treatment then commencing HAART<br>2. To determine if patients starting ARVs early during TB treatment have a better HRQOL than patients starting ARVs after completion of TB treatment in TB/HIV co-infected patients<br>3. To determine polymorphisms in cytochrome P450 and N-acetyltransferase and their relationship to hepatotoxicity<br>4. and efavirenz bioavailability in participants receiving anti-TB treatment and HAART<br>5. To determine the kinetics of mycobacterial cellular immune responses in patients treated with HAART and tuberculosis drugs using an INF-γ release assay. |
| Status: | Completed |
| Results and outcomes: | The first PhD project was entitled “Reconstitution of TB antigen specific IFN-γ responses in TB-HIV co-infected participants”. The hypothesis was that IRIS may be facilitated by the absence of regulatory T-cell (Treg) activity preventing the development of pathogen specific memory T cells. The plan was to measure T-cell responses to immunological profile change during treatment and assess adverse events associated with levels of CD4, IFN-γ and viral load. This was changed mid-way to study “Safety tolerability and monitoring of combined anti-tuberculosis and antiretroviral therapy”. The justification for the change has been given. The second study aimed to assess treatment responses to combined TB and HIV therapy in co-infected patients recruited in a WHO funded study called “Bioavialability of fixed dose formulation Rifafour coantaining isoniazid, rifampicin, pyrazinamide and ethambutol”. The data to be assessed was in terms of adverse events, interferon gamma release assays in response to treatment, quality of life and genetic polymorphisms affecting drug pharmacokinetics. The achievements in the projects are: Registration of PhD moved from University of KwaZulu-Natal to |

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| | University of Cape Town under Professor Keertan Dheda; recruitment of 89 study participants and completed 24 months follow up |

## 2.7 Leah Mwai

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| EDCTP Project Coordinator: | Leah Mwai (Kenya Medical Research Institute (KEMRI)/Wellcome Trust Research Program, Kenya) |
| EDCTP Call Title: | PhD Studentship |
| EDCTP Project Title: | Understanding the mechanism of resistance to lumefantrine by *Plasmodium falciparum* |
| EDCTP Project Code: | TA.2005.40204.011 |
| EDCTP Project Start Date: | 18 July 2006 |
| EDCTP Project End Date: | 1 October 2010 |
| Supervisor(s): | • Alexis Nzila (KEMRI)/Wellcome Trust Research Program, Kenya)<br>• Steve Ward (Liverpool School of Tropical Medicine and Hygiene (LSHTM), UK) |
| Objectives: | To clarify the mechanisms of LM/PQ/DEAQ resistance, and to identify molecular markers that could be used to predict LM-ATM, DHA-PQ and AQ efficacy |
| Status: | Completed |
| Results and outcomes: | This study which was studentship under Dr Alexis Nzila's supervision showed mechanisms of emerging resistance to three artemesinin combination therapies against malaria and the molecular markers linked to the resistance patterns |
| Publications: | 1. Mwai L, Kiara SM, Abdirahman A, Pole L, Rippert A, Diriye A, Bull P, Marsh K, Borrmann S, Nzila A. *In vitro* activities of piperaquine, lumefantrine and dihydroartemisisn in Kenyan *Plasmodium falciparum* isolates and polymorphisms in Pfcrt and pfmdr1, *Antimicrob Agents Chemother*. 2009 Dec;53(12):5069-73. Epub 2009 Sep 21<br>2. Mwai L, Ochong E, Abdirahman A, Kiara SM, Ward S, Kokwaro G, Sasi P, Marsh K, Borrmann S, Mackinnon M, Nzila A. Chloroquine resistance before and after its withdrawal in Kenya, Malar J. 2009 May 18;8:106<br>3. Nzila A, Mwai L. In vitro selection Plasmodium falciparum drug-resistant parasite lines. *J Antimicrob Chemother*. 2009 Dec 18<br>4. Sasi P, Abdulrahaman A, Mwai L, Muriithi S, Straimer J, Schieck E, Rippert A, Bashraheil M, Salim A, Peshu J, Awuondo K, Lowe B, Pirmohamed M, Winstanley P, Ward S, Nzila A, Borrmann S. In vivo and in vitro efficacy of amodiaquine against *Plasmodium falciparum* in an area of contimued use of 4- aminoquinolines in Africa. *J Infect Dis*. 2009 Jun 1;199(11):1575-82<br>5. Gilbert Kokwaro, Leah Mwai and Alexis Nzila. Artemether-lumefantrine in the treatment of uncomplicated *falciparum* malaria. *Expert Opin Pharmacother*. 2007 Jan;8(1):75-94<br>6. Mwai L, Diriye A, Masseno V, Muriithi S, Feltwell T, et al. (2012) Genome Wide Adaptations of *Plasmodium falciparum* in Response to Lumefantrine Selective Drug Pressure. *PLoS ONE* 7(2): e31623. doi:10.1371/journal.pone.0031623 |

## 2.8 Janha Ramatouli

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| EDCTP Project Coordinator: | Janha Ramatouli (Medical Research Council (MRC) Laboratories, The Gambia) |
| EDCTP Call Title: | PhD Studentship |
| EDCTP Project Title: | Investigating the effects of inactive CYP2C19 alleles on chlorproguanil pharmacokinetics in adults and in children with mild malaria following Lapdap® treatment |
| EDCTP Project Code: | TA.2005.40204.018 |
| EDCTP Project Start Date: | 23 August 2006 |
| EDCTP Project End Date: | 1 March 2010 |
| Supervisor(s): | • Munir Pirrmohamed (University of Liverpool, UK)<br>• Robert Walton (MRC Laboratories, The Gambia)<br>• Fatoumatta Sisay-Joof (MRC Laboratories, The Gambia) |
| Goal: | To investigate whether CYP2C9 and its genetic polymorphs participate in the biotransformation of the antimalarial biguanides |
| Objectives: | This project aims to:<br>1. Survey the range of genetic variation present in CYP2C19, an enzyme important in activating antimalarial drugs<br>2. Identify and biochemically characterise new genetic variants of this enzyme<br>3. Determine whether existing and newly defined variants affect response to therapy in large randomised controlled clinical trial. |
| Status: | Completed |
| Results and outcomes: | This project has described the frequency of the gain-of-function polymorphism and the loss-of-function polymorphism that influence variable pharmacokinetics of chlorcycloguanil in Gambian adults. The conclusion is that genetic variations in CYP2C9 and CYP2C19 influence chlorcycloguanil pharmacokinetics and may lead to the accumulation of toxic dapsone. These factors need to be taken into consideration in future clinical trials involving antimalarial biguanides/dapsone to avoid the adverse events of haemolytic anaemia that could be severe and therefore improve on the success of the trials. |

## 2.9 Charles Arama

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| EDCTP Project Coordinator: | Charles Arama (Malaria Research & Training Center, Mali) |
| EDCTP Call Title: | PhD Studentship |
| EDCTP Project Title: | Host immunogenetic factors involved in the susceptibility to malaria in sympatric ethnic groups (Dogon and Fulani) in Mali |
| EDCTP Project Code: | TA.2005.40204.003 |
| EDCTP Project Start Date: | 10 August 2006 |
| EDCTP Project End Date: | 10 December 2010 |
| Supervisor(s): | • Amagana DOLO (Malaria Research & Training Center, Mali)<br>• Ogobara K. Doumbo (Malaria Research & Training Center, Mali)<br>• Troye-Blomberg, Marita (Stockholm University, Sweden) |
| Objectives: | To investigate whether antigen presenting cells (APCs) obtained from Fulani and Dogon children exhibited differences in terms of activation status and toll-like receptor (TLR) responses during malaria infection |
| Status: | Completed |
| Results and outcomes: | The study results showed that Plasmodium falciparum infection impairs the phenotype of blood dendritic cells and alters toll-like receptor responses (TLR) of peripheral blood mononuclear cells (PBMC) from Dogon children. On the other hand, specific dendritic cells subsets are activated in the Fulani children and their PBMC respond normally to TLR stimuli. In particular, malaria infection induces differential innate IFN-$\gamma$ release in the two ethnic groups |