EDCTP Portfolio

Clinical Trials and Integrated Projects

The EDCTP portfolio of funded projects on HIV/AIDS covers drugs, vaccines and microbicides as well as capacity building projects that do not involve testing of investigational products.

1.1 HIV/AIDS treatment clinical trials

Project Acronym (Coordinator)	Phase of trial	Product(s)	Manufacturer / Developer	Study population	Status
CHAPAS-1 (Chintu)	I/II	Pedimune (Triomune Baby/Junior) tablets: stavudine (d4T), lamivudine (3TC) and nevirapine (NVP) in paediatric co-formulated fixed-dose combinations	Cipla Pharmaceuticals	PAEDIATRIC 211 HIV-1 infected children (≥3 months - ≤14 years)	Completed
CHAPAS-3 (Mulenga)	II	Baby and Junior Triomune (d4T+3TC+NVP); Lamivir S (d4T+3TC); 3TC (lamivudine) +ABC (abacavir) baby and junior scored tablets ZDV (zidovudine) +3TC (lamivudine) baby and junior scored tablets ZDV (zidovudine) +3TC (lamivudine) +NVP (nevirapine) scored tablets.	Cipla Pharmaceuticals	PAEDIATRIC Across the full paediatric age-range, in both previously untreated (ART naïve) children and in children with undetectable viral load who have already been receiving d4T+3TC+NVP as first-line ART. 480 children aged 1 month to 13 years have been recruited from three Ugandan and one Zambian paediatric clinical centres and are followed for a minimum of 96 weeks.	Ongoing
MONOD (Leroy)	III	Azidothymidine-Zidovudine (AZT); Zidovudine (ZDV) syrup; Lamivudine (3TC) syrup; Nevirapine (NVP) syrup; Abacavir (ABC) syrup ; Efavirenz (EFV) syrup Ritonavir boosted Lopinavir (LPV/r) ; Cotrimoxazole syrup	National programmes	PAEDIATRIC HIV-infected children (3 months – 12 months) Early diagnosed between age 6 weeks and 24 months of life Initial prospective therapeutic cohort (N=154) for 12 months, then trial phase 2-3 for 12 months (n=[2*73]=146)	Ongoing
EARNEST (Mugyenyi)	III	Aluvia(lopinavir/ritonavir co-formulated) Truvada(co-formulation of tenofovir and emtricitabine) Lamivudine Emtricitabine	Abbott Merck Pfizer GSK Gilead	ADULTS 1277 HIV-infected adults (12 years and older) on first- line therapy with an NNRTI-based regimen for at least 12 months, with evidence of treatment failure defined by WHO 2010 criteria as	Ongoing

		Didanosine Abacavir Tenofovir Raltegravir		one of the following: New WHO Stage 4 event (with CD4 < 200 cells/mm3 and viral load (VL) > 400 copies/ml) CD4 < 100 cells/mm3, or CD4 fall to pre-treatment baseline or below, or CD4 < 200 cells/mm3 X 2 with previous CD4 > 400 cells/mm3 (with VL > 400 copies/ml) VL > 5,000 copies/ml ×2	
2LADY (Delaporte)	III	Emtricitabine-tenofovir-lopinavir/ritonavir; Abacavir-didanosine-lopinavir/ritonavir; Emtricitabine-tenofovir-darunavir/ritonavir	Gilead Sciences, Janssen Pharmaceutica N.V., Matrix laboratory Ltd	ADULTS (≥18 yrs) 450 HIV positive adults with virological failure	Ongoing
NUSTART (Filteau)	III	Vitamin and mineral preparations and lipid-based nutrient supplement (LNS); Ready-to-Use Therapeutic Foods (RUTF)	Nutriset, France	ADULTS (≥18) 1400 Zambian and 900 Tanzanian participants for a total of 2300 or 1150 per treatment arm. ART-naive (except for single-dose nevirapine to prevent maternal-to-child HIV transmission), BMI < 18.5 kg/m2, requiring ART as determined by CD4 count < 350/l or WHO stage 3 or 4.	Ongoing
PROMPT (Lange)	III	ARV: Stavudine (d4T) or zidovudine (AZT)/lamivudine (3TC)/efavirenz (EFV) Anti-Tb: Isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), ethambutol (ETH), pyridoxine (vitamin B6)			Terminated
RAFA (Merle)	III	ARV: nucleoside Reverse Transcriptase Inhibitor (NRTI) + EFV TB: INH, RIF, PZA and Ethambutol (ERHZ) High dose Rifampacin	Available through National Programs	ADULT, 375 patients per treatment arm = 1125, ARV naïve HIV positive, CD4 cell count ≥ 50 and ≤ 300 cells/mm3 and bacteriologically-confirmed TB.	Ongoing

REMSTART (Egwaga)	III	Early commencement of standard ART treatment available through National Programs	Standard treatment available through National Programs	ADULT, 2300 eligible for ART.	Ongoing

1.1.1 CHAPAS-1

EDCTP Project Coordinator:	Chifumbe Chintu (University Teaching Hospital (UTH), Zambia)
EDCTP Call Title:	Trials assessing the effectiveness and safety of simplified anti-retroviral drug regimens and monitoring
EDCTP Project Title:	Children with HIV in Africa - Pharmacokinetics and Adherence of Simple Antiretroviral regimens
EDCTP Project Code:	CT.2004.33011.001
EDCTP Project Start Date:	3 November 2005
EDCTP Project End Date:	28 February 2009
Collaborators:	• Ganapati Bhat (University of Zambia (UNZA), Zambia) • David Marinus Burger (Radboud University Nijmegen, Netherlands) • Carlo Giaquinto (University of Padova, Italy) • Diana Mary Gibb (Medical Research Council, UK) • Veronica Mulenga (University Teaching Hospital, Zambia) • Andrew Nunn (Medical Research Council, UK) • Ann Sarah Walker (Medical Research Council, UK)
Study / Trial 1	**CHAPAS Trial 1**
Site Principal Investigator(s):	Chifumbe Chintu (Zambia)
Clinical Trial/Study Sponsor:	Medical Research Council (MRC), UK
Trial/Study title:	**C**hildren with **H**IV in **A**frica – **P**harmacokinetics and **A**dherence of **S**imple Antiretroviral Regimens (CHAPAS-1 Trial)
Goal:	To study the appropriate dosing of, and adherence to, a fixed-dose combination of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP) in a new formulation specifically developed for children (Pedimune).
Primary Objective(s):	To describe toxicity (e.g. rash, hepatic toxicity) probably or possibly related to NVP when NVP is initiated at full dose versus half-dose, in order to determine the necessity for dose escalation in African HIV-infected children using fixed dose combinations (FDCs)
Secondary Objective(s):	1. To determine the pharmacokinetics (PK) of NVP, d4T and 3TC in two daily paediatric doses co-formulated fixed-dose crushable/dispersible tablet combinations (Pedimune) in African HIV-infected children, with and without malnutrition and in different age groups, from a subset of children enrolled in the CHAPAS-1 trial 2. To determine possible PK interactions between NVP and common concomitant medications, such as rifampicin and fluconazole in children and adolescents enrolled in the CHAPAS-1 trial 3. To evaluate a visual analogue scale for assessing 28-day adherence to antiretroviral therapy (ART), by comparing with 3-day recall, pill and bottle counts (including unannounced checks at home and measures from Medication Event Monitoring System caps [MEMs caps], which records when the pill bottle has been opened). Unannounced pill counts and MEMs caps will be performed on a subset of children enrolled in the CHAPAS-1 trial 4. To describe mortality, disease progression, hospital admission rates and laboratory markers (CD4 percent, haemoglobin, viral load as measured by plasma HIV RNA) after starting effective ART 5. To estimate the budget impact and cost-effectiveness of effective ART in human immunodeficiency virus (HIV) infected children in Zambia.

Clinical Trial/Study site(s):	UTH (Zambia)
Collaborating site(s):	• MRC (UK) • Radboud University Medical Centre Nijmegen (Netherlands) • San Fransisco General Hospital (USA) • St James' Hospital (Ireland)
Study design:	Phase I/II open-label randomised controlled trial
Product(s):	Pedimune (Triomune Baby/Junior) tablets: stavudine (d4T), l amivudine (3TC) and nevirapine (NVP) in paediatric co-formulated fixed-dose combinations
Manufacturer/Developer:	Cipla Pharmaceuticals Ltd
Cofunders:	• Cipla Pharmaceuticals Ltd (India) • UTH (Zambia) • Irish Aid (Ireland)
Trial Registration number(s):	ISRCTN 31084535
Sub-studies:	**The CHAP 2 Cohort** Objective: to provide information on children before, during and after the introduction of ART in a resource limited setting; document the natural history of HIV infected children in Zambia by monitoring mortality and morbidity prior to the introduction of ART; monitor the introduction of ART, and its effects on mortality and morbidity; and provide data on the health service needs of HIV-infected children for economic analyses
	CHAPAS RIFNVP Objective: to study the pharmacokinetics of nevirapine (NVP) in HIV-infected children younger than three years who are being treated with nevirapine-containing ART and rifampin (RIF) for HIV/TB co-infection
	Adherence sub-study Objective: to investigate the best adherence measure for the clinic setting - MEMS data will be used as gold standard and compared with child/carer adherence questionnaire answers, clinic pill counts and unannounced pill counts with the aim of validating one or more simple questions that could be used widely; and to predictors of adherence - to gain an insight into routes for a possible intervention, which could be used widely
Status:	Completed
Results and Outcomes:	The main study "Children with HIV in Africa: Pharmacokinetics and Adherence of Simple Antiretroviral Regimens (CHAPAS Trials)" was successfully completed in February 2009. The findings of this study were published in major journals. The results contributed to the approval of Triomune Baby/Junior for use in HIV infected children by the FDA in August 2007. The results from the study were used by the WHO Formulation and Pharmacology Group to define the optimal weight bands for Antiretrovirals in children worldwide.
Publications:	1. Rafaella F. A. L'homme, Tim Dijkema, Adilia Warris, Andre J. A. M. van der Ven, Diana M. Gibb and David M. Burger. Pharmacokinetics of two generic fixed-dose combinations for HIV-infected children (Pedimune Baby & Pedimune Junior) are similar to the branded products in healthy adults. *Journal of Antimicrobial Chemotherapy*, 2007;59:92-96 2. Rafaella F. A. L'homme, Tim Dijkema, Adilia Warris, Andre J. A. M. van der Ven, Diana M. Gibb and David M. Burger. Pharmacokinetics of two generic fixed-dose combinations

	for HIV-infected children (Pedimune Baby & Pedimune Junior) are similar to the branded products in healthy adults. *Journal of Antimicrobial Chemotherapy*, 2007;59:92-96 3. Rafaella F.A. L'homme, Desire Kabamba, Fiona M. Ewings, Veronica Mulenga, Chipepo Kankasa, Margaret J. Thomason, A. Sarah Walker, Chifumbe Chintu, David M. Burger and Diana M. Gibb. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. *AIDS* 2008;22:557-65 4. Mairin Ryan, Susan Griffin, Bona Chitah, A. Sarah Walker, Veronica Mulenga, Donald Kalolo, Neil Hawkins, Concepta Merry, Michael G. Barry, Chifumbe Chintu, Mark J. Sculpher and Diana M. Gibb. The cost-effectiveness of cotrimoxazole prophylaxis in HIV-infected children in Zambia. *AIDS* 2008;22:749-57 5. Mairin Ryan, Susan Griffin, Bona Chitah, A. Sarah Walker, Veronica Mulenga, Donald Kalolo, Neil Hawkins, Concepta Merry, Michael G. Barry, Chifumbe Chintu, Mark J. Sculpher and Diana M. Gibb. The cost-effectiveness of cotrimoxazole prophylaxis in HIV-infected children in Zambia. *AIDS* 2008;22:749-57 6. Rafaella F.A. L'homme, Desire Kabamba, Fiona M. Ewings, Veronica Mulenga, Chipepo Kankasa, Margaret J. Thomason, A. Sarah Walker, Chifumbe Chintu, David M. Burger and Diana M. Gibb. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. *AIDS* 2008;22:557-65 7. David Burger, Fiona Ewings, Desire Kabamba, Rafaella L'homme, Veronica Mulenga, Chipepo Kankasa, Margaret J. Thomason, Diana M. Gibb, Chifumbe Chintu and A. Sarah Walker. Limited Sampling Models to Predict the Pharmacokinetics of Nevirapine, Stavudine, and Lamivudine in HIV-Infected Children Treated With Pediatric Fixed-Dose Combination Tablets. *Therapeutic Drug Monitoring* 2010;32:369–372. 8. David Burger, Fiona Ewings, Desire Kabamba, Rafaella L'homme, Veronica Mulenga, Chipepo Kankasa, Margaret J. Thomason, Diana M. Gibb, Chifumbe Chintu and A. Sarah Walker. Limited Sampling Models to Predict the Pharmacokinetics of Nevirapine, Stavudine, and Lamivudine in HIV-Infected Children Treated With Pediatric Fixed-Dose Combination Tablets. *Therapeutic Drug Monitoring* 2010;32:369–372. 9. Mulenga, V; Cook, A; Walker, AS; Kabamba, D; Chijoka, C; Ferrier, A; Kalengo, C; Kityo, C; Kankasa, C; Burger, D; Thomason, M; Chintu, C; Gibb, DM.Strategies for Nevirapine Initiation in HIV-Infected Children Taking Pediatric Fixed-Dose Combination ""Baby Pills"" in Zambia: A Randomized Controlled Trial. *Clinical Infectious Diseases* 2010; 51 (9):1081-1089 10. Haberer, JE; Cook, A; Walker, AS; Ngambi, M; Ferrier, A; Mulenga, V; Kityo, C; Thomason, M; Kabamba, D; Chintu, C; Gibb, DM; Bangsberg, DR. Excellent Adherence to Antiretrovirals in HIV plus Zambian Children Is Compromised by Disrupted Routine, HIV Nondisclosure, and Paradoxical Income Effects. *PLOS ONE* 2011; 6(4)

	11. Fillekes, Q; Mulenga, V; Kabamba, D; Kankasa, C; Thomason, MJ; Cook, A; Ferrier, A; Chintu, C; Walker, AS; Gibb, DM; Burger, DM. Pharmacokinetics of nevirapine in HIV-infected infants weighing 3 kg to less than 6 kg taking paediatric fixed dose combination tablets. *AIDS* 2012; 26(14): 1795-1800

1.1.2 CHAPAS-3

EDCTP Project Coordinator:	Veronica Mulenga (University Teaching Hospital, Zambia)
EDCTP Call Title:	Call to support the establishment of regional networks of excellence for conducting clinical trials and provide mentorship programmes in sub-Saharan Africa
EDCTP Project Title:	Expanding the Availability of Fixed Dose Combination Antiretroviral Formulations for First-line Treatment of HIV-infected Children - the Children with HIV in Africa Pharmacokinetics and Acceptability/Adherence of Simple Antiretroviral Regimens (CHAPAS-3 trial)
EDCTP Project Code:	IP.07.33011.006
EDCTP Project Start Date:	9 December 2009
EDCTP Project End Date:	31 July 2013
Collaborators:	• Alice Asiimwe Rwego (Baylor College of Medicine Children's Foundation, Uganda) • David Marinus Burger (Radboud University Nijmegen, Netherlands) • Chifumbe Chintu (University Teaching Hospital, Zambia) • Carlo Giaquinto (University of Padova, Italy) • Diana Mary Gibb (Medical Research Council, UK) • Chipepo Kankasa (University Teaching Hospital, Zambia) • Adeodata Kekitiinwa (Baylor College of Medicine Children's Foundation, Uganda) • Cissy Mutuluuza Kityo (Joint Clinical Research Center, Uganda) • Nigel Klein (University College London, UK) • Gary Maartens (University of Cape Town, South Africa) • Helen McIlleron (University of Cape Town, South Africa) • Concepta Merry (Makerere University, Uganda) • Victor Musiime (Joint Clinical Research Center, Uganda) • Jose Ramos (Hospital Universitario de Getafe, Spain) • Mairin Ryan (Trinity College, Ireland) • Chafye Siuluta (University of Zambia) • Margaret Thomason (Medical Research Council, UK) • Ann Sarah Walker (Medical Research Council, UK)
Site Principal Investigator(s):	• Diana Gibb (UK) • Addy Kekiitinwa (Uganda) • Cissy Kityo (Uganda) • Veronica Mulenga (Zambia)
Clinical Trial/Study Sponsor:	Medical Research Council (UK)
Trial/Study title:	Children with human immunodeficiency virus (HIV) in Africa - pharmacokinetics and acceptability/adherence of simple antiretroviral regimens (CHAPAS-3 trial)
Goal:	The CHAPAS-3 project aims to conduct a paediatric clinical trial and several sub studies (addressing in particular pharmacokinetics (PK) and antiretroviral toxicity) using four new simplified paediatric antiretroviral (ARV) solid-based formulations administered according to WHO dosing tables. Alongside the trial, over four years the project aims to build all aspects of capacity for implementing paediatric clinical trials in the African region. This includes enhancing capacity at African institutions with some research experience and establishing research capacity alongside newly developing paediatric HIV services in a Ugandan satellite site. The infrastructure and expertise from this project will create a network with internationally accepted standards for performing clinical trials and PK studies and a valuable regional collaboration.

Primary Objective(s):	1. To compare toxicity (grade 3 or 4 laboratory or clinical adverse events) of stavudine (d4T) versus abacavir (ABC) or zidovudine (ZDV) in combination with lamivudine (3TC) as fixed dose combination (FDC) backbone dual NRTI in ART-naïve HIV-infected children initiating NNRTI based first-line and in those who have already received d4T+3TC+NNRTI (most frequently, adult/junior/baby triomune FDC) for a minimum of two years and currently have undetectable HIV viral load 2. To determine via nested PK sub studies: – The plasma PK of ZDV, 3TC and ABC taken as twice daily new paediatric-formulated fixed-dose crushable tablet combinations of ZDV+3TC+(nevirapine) NVP, ZDV+3TC and ABC+3TC in African HIV-infected children with and without malnutrition and across different ages according to weight-based dosing tables – The plasma PK of new EFV 200mg scored tablets administered once daily according to weight-based dosing tables – The plasma PK of 3TC and ABC paediatric-formulated fixed-dose crushable-tablet combinations taken with efavirenz (EFV) once versus twice daily (using a crossover design) in African HIV-infected children with and without malnutrition and across different ages according to WHO weight-based dosing tables.
Secondary Objective(s):	1. To compare skinfold thickness as a measure of lipodystophy/lipoatrophy between randomised trial arms 2. To compare acceptability and adherence between randomised trial arms, and also between once and twice daily abacavir, using questionnaires, pill counts and a visual analogue scale (all being used and compared with electronic monitoring devices (MEMscaps) in the CHAPAS-1 trial) 3. In view of recent data on possible cardiovascular toxicity of abacavir4, to compare measures of cardiac and vascular function and markers of immune activation across the three randomised trial arms. This is done using measures of structural and functional vasculature (using newly developed, simple and validated portable techniques to measure intimal thickness and pulse wave velocity). In addition plasma samples will be stored for a later measurement of biomarkers of vascular injury (e.g. D-dimer, interleukin 6, hsCRP and endothelial microparticles) which have been reported to be related to the risk of cardiovascular events in adults and could be involved in the pathogenesis of toxicity 4. To validate methods to quantify NRTI and NNRTI concentrations in whole blood (50µL samples dried onto filter paper which can be stored at room temperature) 5. Population PK modelling will be done using whole blood and plasma PK data generated within the study, and in addition to other data from African children (e.g. from the CHAPAS-1 trial). The models will be used: – To optimise sparse PK sampling strategies (e.g. one or two samples only being taken at an outpatient visit) for future studies evaluating dosing approaches for ARVs in children – To evaluate the association between PK and adverse drug effects as well as immunological and virological responses – To provide reference population PK models which can be used for individual patient management

	– To simulate dosing approaches in different categories of children based on age, weight, gender and other parameters. Study is expected to gain consent for storage of human DNA and test for associations between three known single nucleotide polymorphisms (CYP2B6*6, CYP2B6*18, CYP2B6*26) and PK measurements 6. To compare changes in growth, disease progression, mortality and HIV laboratory markers (CD4 cell count and percent; HIV RNA viral load measured retrospectively on stored plasma samples) between randomised arms 7. To undertake an economic analysis comparing the cost-effectiveness of the three randomised regimens, and to model the cost-effectives of switching from initial d4T to ZDV or ABC-containing regimens in HIV-infected African children. This approach builds on the economic analyses undertaken in the CHAP cotrimoxazole trial (before use of ARVs became available, funded by IrishAID) and the CHAPAS-1 trial (funded by EDCTP, Health Research Board of Ireland and IrishAID).
Clinical Trial/Study site(s):	• University Teaching Hospital (UTH), Lusaka (Zambia) • Baylor College of Medicine Bristol Myers Squibb Children's Clinical Centre of Excellence formerly Paediatric Infectious Diseases Centre (PIDC) Mulago Hospital, Kampala (Uganda) • Joint Clinical Research Centre (JCRC) Kampala (Uganda) • Joint Clinical Research Centre satellite site at Gulu Hospital (Uganda)
Collaborating site(s):	• MRC Clinical Trials Unit (UK) • Radboud University of Nijmegen Medical Centre (Netherlands) • University of Cape Town (South Africa)
Study design:	Phase II/III open-label randomised controlled trial with three arms. 480 HIV-infected children, aged one month to 13 years will be enrolled over 18 months and followed for a minimum of 96 weeks (total trial length 3.5 years) in three clinical centres in Zambia (UTH, Lusaka) and Uganda (PIDC and JCRC, Kampala).
Product(s):	• ARV products in the urgent or high priority list as recommended by WHO • Baby and Junior Triomune (d4T+3TC+NVP); Lamivir S (d4T+3TC) • 3TC (lamivudine) +ABC (abacavir) baby and junior scored tablets • ZDV (zidovudine) +3TC (lamivudine) baby and junior scored tablets • ZDV (zidovudine) +3TC (lamivudine)+NVP (nevirapine) scored tablets.
Manufacturer/Developer:	Cipla Pharmaceuticals Ltd
Cofunders:	• Cipla Pharmaceuticals Ltd (India) • MRC UK (UK) • Instituto de Salud Carlos III (Spain) • Health Research Board Ireland (Ireland) • Instituto Superiore de Sanita (Italy)
Trial Registration number(s):	ISRCTN69078957 PACTR201006000222401
Sub-studies:	**Population/sparse PK study** Purpose: To optimise dosing of ART in young children in Africa Primary objective: to evaluate the impact of pharmacokinetics (PK) on toxicity and efficacy in all randomised children

	Secondary objective: to describe variability of ARV PK across the study population and over time and identify factors affecting PK including pharmacogenetic variants. **The Cardiovascular sub-study** Title: The Impact of HIV and Antiretroviral Therapy on the Cardiovascular System of HIV-infected children. Purpose: To ascertain whether HIV-infected children have evidence of early cardiovascular damage and the impact that different formulations of ART have on any changes seen. Objectives: 1. To determine the influence of HIV infection on vascular phenotype by comparing HIV-infected Antiretroviral Therapy (ART) naïve children with HIV-uninfected African controls 2. To determine the effects of ART on vascular phenotype by comparing children stable on ART to drug naïve about to start treatment and monitor changes in vascular function over time 3. To gain insight into the potential mechanisms operating to mediate vascular dysfunction looking specifically at: – Structural and functional arterial changes – Evidence of ongoing inflammation and immune activation – Vascular and endothelial injury. **The Lipodystrophy sub-study** Title: Lipodystrophy among HIV-infected children in Uganda and Zambia Purpose: To ascertain the optimal use of antiretroviral therapy that minimises the development of lipodystrophy among HIV-infected children Primary objective: To determine the pattern and relative rates of lipodystrophy as well as the associated factors among study participants Secondary objectives: 1. To determine the clinical and biochemical markers of lipodystrophy among the children 2. To relate any changes in lipid distribution or content with direct and indirect measures of cardiac and vascular function and measures of immune activation 3. To compare findings in HIV-infected children with those in HIV-uninfected controls.
Status:	Ongoing
Results and Outcomes:	Recruitment to the main trial was completed on 28 December 2011, with a total of 480 children enrolled, 450 children are actively being followed up, and according to the protocol, and the last recruited child will reach 96 weeks of follow up in November 2013. In addition, 249 uninfected controls were enrolled. Preliminary analysis on the specimens from the full PK sub-study has been done and the findings were presented at the 2012 IAS conference in Washington. Second batch of specimens for the sparse PK sub-study have been

	sent to Cape Town and results from this analysis are being expected. Preliminary findings from measures for toxicity, specifically lipodystrophy, and analysis of scans for cardiovascular function have been analysed and presented at conferences. **Expected trial outcomes** In addition to the licensed baby and junior Triomune (d4T+3TC+NVP), new FDC formulations (scored dispersible baby pills) of zidovudine (ZDV) + lamivudine (3TC) + nevirapine (NVP), ZDV+3TC and 3TC+abacavir (ABC), as well as scored efavirenz (EFV) 600mg tablets provided by Cipla Pharmaceuticals, India, are being evaluated. The FDCs are manufactured in ratios recommended by the WHO Formulation Working Group and are administered according to WHO recommended weight-band tables (updated in September 2009). The overall hypothesis being tested is that new FDC tablets which contain abacavir (ABC) or zidovudine (ZDV) rather than stavudine (d4T) will provide superior toxicity and/or adherence/acceptability profiles in HIV-infected children taking combination ART, both ART naïve and those switching from d4T based regimens, whilst maintaining adequate pharmacokinetics and similar cost-effectiveness and viral load suppression. The primary endpoint for all children is grade 2/3/4 clinical adverse events or grade 3 (confirmed)/4 (any) laboratory adverse event. **Preliminary findings from the CHAPAS-3 sub-studies:** • Evidence of increased arterial stiffness in HIV-infected children compared to controls • In HIV-infected children, no significant effects on Intimal media thickness (IMT) or Pulse Wave Velocity PWV of age of prior ART exposure • Efavirenz pharmacokinetic parameters of African children weighing 10-<20 Kg, on daily efavirenz using current 2010 WHO weight-bands and new generic tablets were lower and highly variable compared to adult data, but similar to previously reported paediatric values • The CHAPAS-3 sub-study demonstrated the challenges of fixed-dosing when therapeutic range is narrow.
Total number of subjects (clinical trials only):	480 infected children 249 uninfected controls
PhD studies:	Title: The management of Paediatric HIV – infection: strategies to improve treatment outcomes in resource limited settings Candidate: Victor Musiime (Uganda) Dates: 2010-2013
	Title: The Impact of HIV and Antiretroviral Therapy on the Cardiovascular System of HIV-infected children Candidate: Julia Kenny (UK) Dates: 2010-2015
MSc studies:	Candidate: Chishala Chabala (UTH, Zambia)
Publications:	

1.1.3 MONOD

EDCTP Project Coordinator:	Valeriane Leroy (Victor Segalen Bordeaux 2 University, France)
EDCTP Call Title:	Call for the support of clinical trials, capacity building and networking for HIV/AIDS treatment
EDCTP Project Title:	International phase 2b-3 randomized clinical trial to assess a once-daily simplified antiretroviral triple therapy among HIV-infected children early treated by a 12-month twice daily triple therapy between 6 weeks and 24 months of age and in virological success in Africa: The MONOD Project
EDCTP Project Code:	IP.07.33011.002
EDCTP Project Start Date:	16 November 2009
EDCTP Project End Date:	30 September 2014
Collaborators:	• Vic Arendt (Public Research Centre for Health, Luxembourg) • Stéphane Blanche (University of Paris V - René Descartes, France) • Michael Kramer (Ministry of Health, Rwanda) • Philippe Lepage (Hôpital Universitaire des Enfants Reine Fabiola, Belgium) • Nicolas Meda (University of Ouagadougou, Burkina Faso) • Philippe Van de Perre (Montpellier University Hospital Centre (CHU), France) • Christine Rouzioux (University of Paris V - René Descartes, France) • Roger Salamon (Victor Segalen Bordeaux 2 University, France) • Marguerite Timite-Konan (Centre Hospitalier Universitaire de Yopougon, Cote d'Ivoire)
Site Principal Investigator(s):	• Marguerite Timite-Konan (Cote d'Ivoire) • Nicolas Meda (Burkina Faso)
Clinical Trial/Study Sponsor:	French National Agency for Research on AIDS and Viral Hepatitis (ANRS)
Trial/Study title:	International phase IIb-III randomized clinical trial to assess a once-daily simplified antiretroviral triple therapy among HIV-infected children early treated by a 12-month twice daily triple therapy between 6 weeks and 24 months of age and in virological success in Africa: The MONOD Project
Goal:	This trial aims at identifying simplified antiretroviral treatments strategies to be given once daily in children infected with HIV from the age of 15 months (from 6 kg) in real field conditions of use in Africa. It will improve the antiretroviral roll-out in children, with a specific focus on long-term strategies adapted to resource-limited settings. The overall project is aimed at study the feasibility of early HIV diagnosis and antiretroviral access of HIV-infected infants in field conditions of low-income countries to improve their long-term-survival.
Primary Objective(s):	To study the proportion of treatment success (alive, under follow-up and without virologic failure) of a once daily simplified triple therapy ABC-3TC-EFV in a phase IIb-III randomised controlled-trial among HIV-infected children above the age of 15 months old and in virologic success after a 12-month initial phase with a twice daily triple therapy using AZT-3TC-LPV/r in Burkina Faso and Côte d'Ivoire.
Secondary Objective(s):	1. To study the tolerance, the pharmacokinetic properties, treatment observation, the profiles of viro-immunological responses and the cost/efficiency aspects during the randomised phase

	2. To study the survival without virological failure, the kinetics of virological success, the tolerance, the pharmacokinetic properties, the clinical response and the co-morbidities, the adherence of children treated initially with a twice-daily triple therapy 3. To study the compliance over time in children treated initially twice-daily, then once-daily 4. To study the clinical evolution of the children treated initially twice-daily, then once-daily 5. To describe the resistance profiles in children who would develop virological failure 6. To study the cost/efficiency aspects of these combinations 7. To study the social acceptance of these early antiretrovirals regimens.
Clinical Trial/Study site(s):	• Abidjan: within the PACCI programmes, FSU Abobo-Avocatier, CEPREF-Yopougon, Yopougon and Cocody Teaching hospitals (Ivory Coast) • Ouagadougou: Yalgado Ouédraogo Teaching Hospital and Charles de Gaulle Teaching Hospital (Burkina Faso)
Collaborating site(s):	• Inserm U897, Institut de Santé Publique, Epidémiologie et Développement (ISPED), Université Victor Segalen Bordeaux 2 (France) • Centre Hospitalier de Luxembourg (CHU) (Luxembourd) • Hôpital Universitaire des Enfants Reine Fabiola (Belgium) • EA 3620, Faculté de Médecine Necker Enfants Malades and Université Paris-Descartes (France) • University Montpellier 1, Research Team “EA 4205: Transmission, pathogenesis and prevention of HIV and associated infections” (France)
Study design:	Open phase IIb-III randomised, international, multicentre clinical trial, of non-inferiority, conducted in two consecutive steps: **Initial therapeutic cohort of 12 months**: prospective treatment cohort of all HIV-infected children (confirmed with PCR) from six weeks to 24 months of life under triple therapy starting at 10-12 weeks with 2 NRTIs ([AZT, ABC, or 3TC] + LPV/r) twice-daily together with prophylaxis of opportunistic infections with Cotrimoxazole and education regarding treatment. All these children will also receive an anti-pneumococcal vaccine (3 doses of Prevenar13), on the top of the child national immunisation programme schedule. **Simplified randomised phase from 13 to 25 months:** those children in virological success at the end of phase 1 (on two consecutive samples at three months interval) will be randomised in two arms: • Combination with a treatment class change sparing the PIs in one daily dose (ABC- 3TC-EFV) • A control arm: continuation of the twice-daily regimen of the initial phase (AZT, ABC, or 3TC-LPV/r). **Sample size:** initial cohort (N=154) for 12 months, then trial phase 2-3 for 12 months (n=[2*73]=146)
Product(s):	• Azidothymidine-Zidovudine (AZT) • Zidovudine (ZDV) syrup • Lamivudine (3TC) syrup • Nevirapine (NVP) syrup • Abacavir (ABC) syrup

	• Efavirenz (EFV) syrup • Ritonavir boosted Lopinavir (LPV/r) • Cotrimoxazole syrup
Manufacturer/Developer:	National Programs, local Pharmacies, IDA foundation
Cofunders:	• ANRS (France) • INSERM (France) • HUDERF (Belgium) • CRP Luxembourg • Cooperation Luxembourg, • CHU Abidjan • CHU Ouagadougou
Trial Registration number(s):	NCT01127204
Status:	Ongoing
Results and Outcomes:	**Burkina Faso** Actual start and end of recruitment: 16/05/2012 to 21/01/2013 Number of patients enrolled:69 **Ivory coast** Actual start and end of recruitment: 24/08/2011 to 31/01/2013 Number of patients enrolled:114 **Expected results:** Identify an early, simplified antiretroviral strategy that can be used on a long-term basis for HIV-1 infected children, to reduce problems of treatment adherence, to spare a therapeutic class (i.e. PIs), and usable in various contexts in Africa.
Total number of subjects (clinical trials only):	Target: initial cohort (N=154) for 12 months, then trial phase 2-3 for 12 months (n=[2*73]=146) Actual enrolled for the initial cohort, N=183
Total number of subjects (cohort/epidemiological/ other studies):	Target N=154 Actual N=162
PhD study:	Title: Challenges of comprehensive and early antiretroviral care of HIV-infected children in Africa: access, tolerance, adherence, clinical and immunovirological response to long-term antiretroviral treatment Candidate: Malik Coulibaly (Burkina Faso) Dates: 2011-2014
MSc studies:	Title: Early infant diagnosis and access to pediatric HIV care before inclusion in the MONOD trial: barriers and challenges in Abidjan, Côte d'Ivoire in 2011-2012 Candidate: Nizie Pelagie Edith Divine Avit Edi (Cote d'Ívoire) Study period: October 2012-October 2013
	Title: Clinical presentation of children in an early ARV treatment program in three African countries with specific interest to scoring systems: diagnosis of HIV, diagnosis of TB, IRIS, efficacy and tolerance of treatment Candidate: Clarisse Amani-Bosse (Affiliation, Cote d'Ivoire) Dates: 2012-2013
	Candidate: Désiré Dahourou (Burkina Faso) Dates: October 2012-October 2013
Publications:	

1.1.4 EARNEST

EDCTP Project Coordinator:	Peter Mugyenyi (Joint Clinical Research Center, Uganda)
EDCTP Call Title:	Call for the support of clinical trials, capacity building and networking for HIV/AIDS treatment
EDCTP Project Title:	The Europe - Africa Research Network for Evaluation of Second Line Therapy: The EARNEST Trial
EDCTP Project Code:	IP.07.33011.003
EDCTP Project Start Date:	15 September 2009
EDCTP Project End Date:	30 September 2013
Collaborators:	• Jose Arribas (La Paz Hospital, Spain) • Abdel Babiker (Medical Research Council, UK) • Robert Colebunders (Prince Leopold Institute of Tropical Medicine, Belgium) • Graham Stephen Cooke (Imperial College London, UK) • Marisa De Rosa (CINECA - Interuniversity Consortium, Italy) • Philippa Easterbrook (Makerere University, Uganda) • Charles Gilks (World Health Organisation, Switzerland) • Marina Giuliano (Istituto Superiore di Sanità (ISS), Italy) • James Gita Hakim (University of Zimbabwe) • William Hall (University of Dublin, Ireland) • Andrew Kambugu (Makerere University, Uganda) • Cissy Mutuluuza Kityo (Joint Clinical Research Center, Uganda) • Francis Kiweewa (Joint Clinical Research Center, Uganda) • Joseph Marie Albert Lange (ICRH-International Centre of Reproductive Health, The Netherlands) • Patrick William Mallon (University of Dublin, Ireland) • Christine Nabiryo (Makerere University, Uganda) • Marie Louise Newell (Africa Centre for Health and Population Studies, South Africa) • Pius Okong (San Raphael of St. Francis Hospital Nsambya, Uganda) • Joep van Oosterhout (University of Malawi) • Nick Paton (Medical Research Council, UK) • William Powderly (University of Dublin, Ireland) • Andrew Reid (University of Zimbabwe) • Ann Sarah Walker (Medical Research Council, UK) • Patrick Paul Walsh (University of Dublin, Ireland)
Site Principal Investigator(s):	Nick Paton (UK)
Clinical Trial/Study Sponsor:	Medical Research Council (MRC, UK)
Trial/Study title:	EARNEST – A randomised controlled Phase III trial to evaluate options for second-line therapy in patients failing first-line 2NRTI + NNRTI regimen in Africa
Goal:	The EARNEST trial aims to determine the best treatment regimen for patients failing first-line therapy in resource limited settings. The EARNEST trial also aims to strengthen capacity at the selected sites for conducting clinical trials through establishing a network with complementary expertise in different aspects of the study.
Primary Objective(s):	The overall objective of this trial is to find out what, if anything, needs to be combined with a boosted protease inhibitor (PI) in second-line therapy, in order to maximise the chance of a good long-term clinical and immunological outcome following late immunological/clinical failure on a first-line nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse

	transcriptase inhibitor (NNRTI)-containing regimen. More specifically the EARNEST trial aims to determine whether, in patients failing a first-line NRTI and NNRTI-containing regimen • The use of bPI plus raltegravir (an integrase inhibitor) is superior to standard of care (bPI plus 2 new NRTIs) in achieving good HIV disease control at 96 weeks after randomisation • The use of bPI monotherapy is non-inferior to standard of care in achieving good HIV disease control at 96 weeks after randomisation.
Secondary Objective(s):	1. To answer the two aforementioned questions in a way that is relevant to large scale ART rollout programs now and that will remain relevant for many years to come (i.e. that applies to patients who fail relatively late on first- line therapy after low CD4 and/or new WHO stage 4 events and likely with multiple resistance mutations, that can be generalized to situations where viral load (VL) monitoring is performed infrequently or not at all and where resistance testing is generally not performed, and that uses standardised treatment regimens with drugs that can be made available at an affordable cost to roll-out programs 2. To ensure that the evidence obtained through the trial is widely disseminated, and leads promptly to change in public health policy (if appropriate) 3. To expand capacity for conducting clinical trials to new sites and also build new cadres of young researchers to lead future clinical trials 4. To build a well-functioning group of research sites and institutes that will become internationally-recognised as a network of excellence for addressing second-line therapy 5. To extend the network beyond established collaborations to new institutions and sites.
Clinical Trial/Study site(s):	• Academic Model for the Prevention and Treatment of HIV/Aids (AMPATH) Centre, Eldoret (Kenya) • Infectious Disease Institute (IDI), Kampala (Uganda) • JCRC Fort Portal Regional Centre of Excellence, Fort Portal (Uganda) • JCRC Gulu (Uganda) • JCRC Kabale (Uganda) • JCRC Kakira (Uganda) • JCRC Mbale (Uganda) • JCRC Mbarara Regional Centre of Excellence, Mbarara (Uganda) • Joint Clinical Research Centre (JCRC), Kampala (Uganda) • Mzuzu Central Hospital, Mzuzu (Malawi) • St Francis Nsambya Hospital, Kampala (Uganda) • University of Malawi, Queen Elizabeth Hospital, Blantyre • University of Zimbabwe Clinical Research Centre (UZCRC), Harare (Zimbabwe) • University Teaching Hospital (UTH), Lusaka (Zambia)
Collaborating site(s):	• MRC Clinical Trials Unit (UK) • University College Dublin (Ireland) • Istituto Superiore di Sanita (Italy) • CINECA (Italy) • Institute of Tropical Medicine (Belgium) • Hospital La Paz (Spain)
Study design:	Phase III open-label randomised controlled trial with three arms. Patients will be randomised in a ratio of 1:1:1 to one of the

	following three treatment arms. Arm A: bPI + 2 NRTIs chosen by clinician according to local standard of care and availability Arm B: bPI + raltegravir 400 mg twice daily Arm C: bPI alone (after an initial 12-week induction phase with raltegravir) The bPI will be standardised to Aluvia (lopinavir/ritonavir 400 mg/100 mg b.d.). Follow up will be for a minimum of 96 weeks. The primary outcome parameter for the trial is "good HIV disease control" defined as a composite endpoint consisting of all of: No new WHO Stage 4 events between randomisation and week 96 AND CD4 count > 250 cells/mm3 at week 96 AND VL < 10,000 copies/ml or > 10,000 copies/ml with no PI resistance mutations at week 96
Product(s):	• Aluvia (lopinavir/ritonavir co-formulated) • Truvada (co-formulation of tenofovir 300mg and emtricitabine 200mg) • Lamivudine • Raltegravir • Abacavir • Tenofovir
Manufacturer/Developer:	• Merck • Abbott • GSK • Gilead
Cofunders:	• MRC (UK) • Istituto Superiore di Sanità (Italy) • Instituto de Salud Carlos III (Spain)
Trial Registration number(s):	ISRCTN37737787 NCT00988039
Sub-studies:	• EARNEST Virology Substudy • EARNEST Resistance Substudy • EARNEST Immunophenotyping Substudy • EARNEST Quantiferon Substudy • EARNEST Bone Mineral Density Substudy • EARNEST Socioeconomic Substudy • EARNEST PK Rifabutin Substudy • EARNEST Genital Secretions Substudy
Status:	Ongoing
Results and Outcomes:	Recruitment target reached in 4 August 2011. The 1277 enrolled participants are being followed up.
Total number of subjects (clinical trials only):	200 HIV-infected adults failing first-line therapy
PhD studies:	Bone Mineral Density Sub study Candidate: Bonnie Wandera (IDI, Uganda)
	Socioeconomic Sub study Candidate: Jupiter Simbeye (University of Malawi)
	Public Health Candidate: Willard Tinago (University of Zimbabwe)
	Health Economics Candidate: Gibson Mandozana (University of Zimbabwe)
MSc studies:	MSc in clinical trials at the London School of Hygiene and Tropical Medicine (LSHTM) Candidate: Ennie Chidziva (UZCRC, Zimbabwe)
	MSc in clinical trials at the London School of Hygiene and Tropical Medicine (LSHTM)

	Candidate: Michael Katwere (IDI, Uganda).
	MSc in clinical trials at the London School of Hygiene and Tropical Medicine (LSHTM) Candidate: Abbas Lugemwa (Uganda).
Publications:	

1.1.5 2LADY

EDCTP Project Coordinator:	Eric Delaporte (University of Montpellier 1, France)
EDCTP Call Title:	Call for support of integrated projects on clinical trials, capacity building and networking
EDCTP Project Title:	A multicentre phase III trial of second-line antiretroviral treatment in African adults
EDCTP Project Code:	IP.07.33011.004
EDCTP Project Start Date:	13 July 2009
EDCTP Project End Date:	30 September 2014
Collaborators:	• Alexandra Calmy (Médecins Sans Frontières (MSF), Switzerland) • Robert Colebunders (Prince Leopold Institute of Tropical Medicine, Belgium) • Josef Eberle (Ludwig-Maximilians Universitat Munchen, Germany) • Pierre-Marie Girard (University Hospital Sain-Antoine, France) • Michael Hoelscher (Ludwig-Maximilians Universitat Munchen, Germany) • Sinata Koulla-Shiro (National Agency for AIDS Research (ANRS), France) • Arne Kroidl (Mbeya Medical Research Programme, Tanzania) • Vincent Lemoing (University of Montpellier 1, Fance) • Benjamin Longo-Mbenza (University of Limpopo, South Africa) • Leonard Maboko (Mbeya Medical Research Programme, Tanzania) • Zinhle Makatini (University of Limpopo, South Africa) • Nchabeleng Maphoshane (University of Limpopo, South Africa) • Olga Mogiyana Mzileni (University of Limpopo, South Africa) • Papa Salif Sow (University Cheikh Anta DIOP de Dakar (UCAD), Senegal) • Kyaw Thanda (University of Limpopo, South Africa)
Site Principal Investigator(s):	• Sinata Koulla Shiro (Cameroon) • Papa Salif Sow (Senegal) • Adrien Sawadogo (Burkina Faso)
Clinical Trial/Study Sponsor:	French National Agency for Research on AIDS and Viral Hepatitis (ANRS)
Trial/Study title:	A multicentre phase III trial of second-line antiretroviral treatment in African adults
Goal:	This trial aims at evaluating the efficacy and tolerance of 3 different second line treatment strategies: two recommended by WHO combine two non-nucleoside reverse transcriptase inhibitor associated with a ritonavir boosted protease inhibitor (emtricitabine-tenofovir-lopinavir/ritonavir and abacavir-didanosine-lopinavir/ritonavir); the third strategy combines emtricitabine-tenofovir-darunavir/ritonavir and is not yet evaluated in Sub-Saharan Africa. Darunavir has a potentially superior antiviral efficacy, a better tolerance and its single daily administration may facilitate treatment adherence.
Primary Objective(s):	To compare, in an African setting, in patients with virological failure after first-line antiretroviral treatment including a non-nucleoside reverse transcriptase inhibitor, the virological response (plasma HIV RNA < 50 copies/ml) at 48 weeks, in

	three groups of patients receiving three different antiretroviral combinations: the combination of emtricitabine-tenofovir-lopinavir/ritonavir in arm A, the combination of abacavir-didanosine-lopinavir/ritonavir in arm B, and the combination of emtricitabine-tenofovir-darunavir/ritonavir in a single daily dose in arm C.
Secondary Objective(s):	Patients will be followed up for secondary endpoints during the all duration of the trial. To compare the following parameters of response to antiretroviral treatment across the three arms: • Clinical outcome (AIDS events, non-AIDS events, death, adverse events) • Virological response (plasma HIV RNA < 200 and 50 copies/ml) at 24 weeks and after 48 weeks until the end of the trial • Virological response (plasma HIV RNA < 200 copies/ml) at 48 weeks • Immune response: variation in CD4 lymphocytes • Treatment discontinuation • Tolerance, particularly the occurrence of, hypersensitivity syndromes, renal impairment, gastrointestinal disorders and changes in lipids profile • Changes in anthropometric measures • Adherence (measured by pill count and questionnaire).
Clinical Trial/Study site(s):	• The Central Hospital of Yaounde (YCH, Cameroon) • The military hospital in Yaounde (Cameroon) • The University Hospital of Fann (Senegal)
Collaborating site(s):	• Institute of Tropical Medicine, Antwerp (Belgium) • MSF Access Campaign and University of Geneva, (Switzerland) • University of Munich, Munich (Germany) • University of Montpellier/IRD (France)
Study design:	Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment It's a multicentre, non-inferiority, randomised, open label phase III trial comparing the virological efficacy and tolerance of three antiretroviral treatment regimens: the combination of emtricitabine-tenofovir-lopinavir/ritonavir in arm A, the combination of abacavir-didanosine-lopinavir/ritonavir in arm B, and the combination of emtricitabine-tenofovir-darunavir/ritonavir in arm C for 48 weeks in HIV-1-infected patients with treatment failure after first-line antiretroviral treatment in Cameroon, Senegal, and Burkina Faso.
Product(s):	• Emtricitabine-tenofovir and lopinavir/ritonavir • Abacavir-didanosine- lopinavir/ritonavir • Emtricitabine-tenofovir-darunavir/ritonavir
Manufacturer/Developer:	• Gilead Sciences • Janssen Pharmaceutica N.V.
Cofunders:	• Swiss National Science Foundation (Switzerland) • Hôpitaux Universitaire de Genève (Switzerland) • Deutsches Zentrum fuer Luft und Raumfahrt DLR (Germany) • l'Institut de Recherche pour le Dévelopment-IRD (France) • French National Agency for Research on AIDS and Viral Hepatitis (ANRS, France)

	• Prins Leopold Instituut voor Tropische Geneeskunde (Belgium)
Trial Registration number(s):	NCT00928187
Sub-studies:	**The Metabody sub-study** The Metabody sub-study in conducted in Senegal, Cameroun and Burkina Faso with the primary objective of describing morphological changes and metabolic disorders (metabolic syndrome, cardiovascular and fracture risks) in HIV positive patients failing first line antiretroviral treatment and beginning second line ART. **The OSTEOVIH sub-study** This is a complementary study to the Metabody study. This is a cross sectional study conducted in Senegal with the purpose of estimating the prevalence of osteoporosis and osteopenia in aging population living with HIV, receiving antiretroviral treatment.
Status:	Ongoing
Results and Outcomes:	**Recruitment and follow up:** 2LADY trial recruitment was completed at the end of 2012. Follow up is continuing for each patient for 48 weeks, and the last visit for the last patient is expected by end of October 2013. **Expected results:** First results of the trial are expected in the fourth quarter of 2013. A simplified strategy by using boosted protease inhibitor for patients who will have suppressed their viral load is planned for the future. **Training:** GCP, protocol and study specific procedures trainings in Cameroon and Senegal in 2009 and 2010 Associative members involved in research: workshop for staff in Yaoundé facilitated by the GTIA (association network on research)- 3, 10 and 17th of February 2010 in Cameroon Exchange programmes and mentorship for 1 Lab technologist from Senegal to Cameroon (Viral load assay by Biocentric technique) – March-April 2011.
Total number of subjects (clinical trials only):	N=450
PhD studies:	Study topic: Hepatitis B co-infection. In his PhD trainin Candidate: Lucas Maganga (Tanzania)
	Candidate: Bahati Kaluwa (Tanzania)
	Study topic: HIV and other retrovirus genetic diversity in Cameroon Candidate: Julius Chia (Cameroun)
Other/Sub-studies:	ALISA Cohort: Following termination of the ALISA trial, the consortium proposed to establish a second line cohort that will serve as a mock trial to increase the knowledge on adherence, failure and tolerability of standard 2nd line treatment in Mbeya and prepare for future trials that will evaluate novel strategies to keep patients on sustained ARV treatment.
Publications:	

1.1.6 NUSTART

EDCTP Project Coordinator:	Suzanne Filteau (London School of Hygiene and Tropical Medicine, UK)
EDCTP Call Title:	Call for the support of clinical trials, capacity building and networking on treatment of HIV/AIDS
EDCTP Project Title:	Nutritional support for African adults starting antiretroviral therapy (NUSTART)
EDCTP Project Code:	IP.2009.33011.004
EDCTP Project Start Date:	15 November 2010
EDCTP Project End Date:	14 November 2013
Collaborators:	• Aase Bengaard Andersen (Copenhagen University Hospital, Denmark) • Kathy Baisley (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Muhammad Bakari (Muhimbili University College of Health Sciences, Tanzania) • Sekelani S. Banda (University of Zambia) • John Changalucha (National Institute for Medical Research, Tanzania) • Molly Chisenga (University Teaching Hospital, Zambia) • Yolanda Fernandez (LSHTM, UK) • Henrik Friis (Copenhagen University Hospital, Denmark) • Tsinuel Girma (Jimma University, Ethiopia) • Douglas Heimburger (Vanderbilt University, USA) • Samuel Kalluvya (Bugando Medical Centre, Tanzania) • Saidi Kapiga (LSHTM, UK) • Lackson Kasonka (University Teaching Hospital, Zambia) • Paul Kelly (Barts and The London School of Medicine and Dentistry, UK) • John Robert Koethe (Vanderbilt University, USA) • Natasha Larke (LSHTM, UK) • Hildah Banda Mabuda (University Teaching Hospital, Zambia) • Clemens Masesa (National Institute for Medical Research, Mwanza Centre, Tanzania) • Nick Paton (Medical Research Council, UK) • George Praygod (National Institute for Medical Research, Tanzania) • Joshua Siame (University Teaching Hospital, Zambia) • David Thurnham (University of Ulster, UK) • Andrew Tomkins (University College London, UK) • G Wandore (National Institute for Medical Research, Tanzania) • Suzanna Woodd (London School of Hygiene and Tropical Medicine, UK) • Daniel Yilma (Jimma University, Ethiopia)
Site Principal Investigator(s):	• Suzanne Filteau (UK) • Lackson Kasonka (Zambia) • John Changalucha (Tanzania)
Clinical Trial/Study Sponsor:	LSHTM (UK)
Trial/Study title:	Nutritional support for African adults starting antiretroviral therapy (NUSTART)
Goal:	The overall goal of the project is to improve health and survival of HIV-infected Africans by improving African clinicians' ability to research and manage nutritional problems. It will help African clinicians and government health managers integrate nutritional

	support into management of patients with HIV and improve understanding of: • How nutritional metabolism and status interact with HIV and associated infectious diseases • How to interpret research findings and bring them into policy and practice.
Primary Objective(s):	To decrease mortality between referral for ART and 12 weeks after starting ART by using a two-stage intervention to stabilize nutritional metabolism and initiate the return of appetite and weight recovery during the preparatory phase before starting ART and during the first 6 weeks of ART
Secondary Objective(s):	• By stabilising nutritional metabolism during the preparatory phase before starting ART and during the first 6 weeks of ART to: – decrease admission to hospital during the study period – increase BMI and lean body mass by 12 weeks – increase functional lean body mass as measured by grip strength – cause appetite to return more rapidly, enabling nutritional recovery – increase adherence to ART • To compare serum electrolyte shifts early in ART in patients given the vitamin-mineral supplements compared to those given placebo • To compare markers of iron status at 12 weeks in patients given the vitamin-mineral supplements compared to those given placebo.
Clinical Trial/Study site(s):	• University Teaching Hospital (Zambia) • National Institute for Medical Research (Tanzania)
Collaborating site(s):	• Barts & The London School of Medicine, London (UK) • Jimma University Specialised Hospital, Jimma (Ethiopia) • Mwanza Medical Research Centre, Mwanza City (Tanzania) • Odense University Hospital, Odense (Denmark) • University of Copenhagen, Copenhagen (Denmark) • University Teaching Hospital, Lusaka (Zambia) • Vanderbilt University, Nashville (USA)
Study design:	Phase III randomised controlled trial comparing in a two-stage protocol of vitamin and mineral supplements with placebo given from referral to ART until 6 weeks after starting ART. In the first stage the vitamins and minerals will be given with minimal calories, only as the lipid-based carrier, from referral to 2 weeks of ART and then the same nutrients or placebo will be given in a calorie-rich supplement, ready-to-use therapeutic lipid-based food (RUTF), from 2-6 weeks of ART. Although control paste and RUTF will be used, it may be hard to completely blind the taste of the micronutrients in the active preparations; however, our use of the hard primary endpoint of mortality limits potential bias.
Product(s):	Vitamin and mineral fortified lipid nutritional supplements (LNS) developed and produced by Nutriset, France
Manufacturer/Developer:	Nutriset, France
Cofunders:	• MRC (UK) • Nutriset (France) • London School of Hygiene and Tropical Medicine (LSHTM, UK) • Danish International Development Assistance (Danida, Denmark) • University Teaching Hospital (Zambia) • Vanderbuilt School of Medicine (USA)

	• Queen Mary & Westfield College, University of London (UK) • University of Copenhagen (Denmark)
Trial Registration number(s):	PACTR201106000300631
Status:	Ongoing
Results and Outcomes:	Recruitment is currently ongoing.
Total number of subjects (clinical trials only):	1400 Zambian and 900 Tanzanian participants for a total of 2300 or 1150 per treatment arm.
PhD studies:	Title: Pharmacokinetic studies of first line anti-tuberculosis drugs, treatment outcome and associated factors among sputum smear positive pulmonary tuberculosis patients in Mwanza, Tanzania Candidate: Jeremiah Kidola
	Candidate: Tsinuel Girma
	Title: Serum Phosphate, Vitamin D and renal function in HIV infected patients initiating ART in southwest Ethiopia Candidate: Daniel Yilma
	Candidate: Markos Tesfaye
MSc studies:	MSc in Infectious Diseases – LSHTM Candidate: Joshua Siame (Zambia)
	MSc in Infectious Diseases – LSHTM Candidate: Mutinta Muchimba (Zambia)
Postdoctoral fellow:	Title: Body composition following nutritional supplementation of malnourished patients starting ART Candidate: George Praygod
Publications:	

1.1.7 PROMPT

EDCTP Project Coordinator:	Joep Lange (University of Amsterdam, Netherlands)
EDCTP Call Title:	Call for the support of clinical trials, capacity building and networking on treatment of HIV/AIDS
EDCTP Project Title:	Prevention of early mortality by presumptive tuberculosis treatment in HIV-infected patients initiating antiretroviral therapy
EDCTP Project Code:	IP.2009.33011.007
EDCTP Project Start Date:	17 September 2010
EDCTP Project End Date:	1 July 2013
Collaborators:	• Jantje C. Bos (University of Amsterdam, Netherlands) • Frank Cobelens (University of Amsterdam, Netherlands) • Robert Colebunders (Prince Leopold Institute of Tropical Medicine, Belgium) • Josefo Joao Ferro (Catholic University of Mozambique) • Matthias Frank (University of Tübingen, Germany) • Martin Peter Grobusch (University of Amsterdam, Netherlands) • Moses Lutaakome Joloba (Ministry of Health, Uganda) • Ulrich Davy Kombila (Albert Schweitzer Hospital, Gabon) • Frank van Leth (KNCV Tuberculosis Foundation, The Netherlands) • Yukari C Manabe (Makerere University, Uganda) • Harriet Mayanja-Kizza (Makerere University, Uganda) • Roy Mugerwa (Makerere University, Uganda) • Olga Mogiyana Mzileni (University of Limpopo, South Africa) • Nadine Pakker (IATEC, Netherlands) • Jan Marinus Prins (University of Amsterdam, Netherlands) • Afsatou Ndama Traoré (Albert Schweitzer Hospital, Gabon) • William Ofuti Worodria (Makerere University, Uganda)
Site Principal Investigator(s):	• Yuka Manabe (Uganda) • William Ofuti Worodria (Uganda) • Josefo J. Ferro (Mozambique) • Mahomed Riaz Mobaracaly (Mozambique) • Afsatou Traore (Gabon) • Zinhle Makatini (South Africa)
Clinical Trial/Study Sponsor:	Academic Medical Center (AMC), University of Amsterdam (Netherlands)
Trial/Study title:	Prevention of early mortality by presumptive tuberculosis treatment in HIV infected patients initiating antiretroviral therapy
Goal:	The overall goal of the project is to evaluate a strategy for reducing early mortality during antiretroviral treatment in settings with high incidence of TB and limited facilities for diagnosing TB in symptomatic, severely immunosuppressed HIV-infected patients. The project also aims to identify the patients who would most benefit from this intervention.
Primary Objective(s):	1. To determine in a randomised-controlled trial whether TB treatment in HIV-infected patients with CD4<50 cells/µl and BMI<18 who do not have verifiable or suspected pulmonary TB at the time of ART initiation prevents early mortality, by comparing the death rate during the first 6 months among patients started on ART only with that among patients started on anti-TB treatment followed after 1-2 weeks by ART 2. To determine, by sputum culture, the prevalence of pulmonary TB disease at the time of ART initiation among

	HIV infected patients with CD4<50 cells/µl and BMI<18 and cough, and to assess sensitivity and specificity of clinical predictors (symptoms, signs, laboratory parameters) for prevalent TB in this patient population 3. To assess the incidence of unmasking TB in the first 6 months of ART among HIV-infected patients with CD4<50 cells/µl and BMI<18 who do not have verifiable or suspected smear-negative TB at the time of ART initiation 4. To determine the sensitivity and specificity of clinical predictors (symptoms, signs, laboratory parameters) for incident unmasking TB, and the association in this patient population between unmasking TB and prevalent TB at the time of ART initiation 5. To assess, by post-mortem investigations, the causes of death among HIV-infected patients with CD4<50 cells/µl and BMI<18 who do not have verifiable or suspected smear-negative TB at the time of ART initiation in the two groups in the first 6 months after ART 6. To build or strengthen capacity in 4 sites in sub-Saharan Africa for clinical trials of therapeutic interventions of HIV and/or TB disease by infrastructural adjustments, training and supervised engagement in trial procedures with focus on ICH-GCP, data monitoring and management, and good (clinical) laboratory practice.
Secondary Objective(s):	1. CD4 T cell absolute increase 2. Causes of death 3. Safety and tolerability of anti-tuberculous medications 4. HIV viral suppression 5. TB incidence rates after ART initiation
Clinical Trial/Study site(s):	• Infectious Diseases Institute, Makerere University (Uganda) • Mulago National Referral Hospital, Kampala (Uganda) • Tshepang clinic Pretoria, Limpopo (South Africa) • George Mukhari Hospital, Pretoria, Limpopo (South Africa) • Catholic University of Mozambique • Research Center for Infectious Diseases (Mozambique) • Medical Research Unit, Albert Schweitzer Hospital (MRU-HAS, Gabon) • Satellite site - Lambarene General Hospital – HG (Gabon)
Collaborating site(s):	• Academic Medical Center, University of Amsterdam (Netherlands) • Amsterdam Institute for Global Health and Development, (Netherlands) • Catholic University of Mozambique • Infectious Diseases Institute, University Makarere (Uganda) Universitätsklinikum Institut für Tropenmedizin (Germany) • Institute of Tropical Medicine (Belgium) • Medical Research Unit, Albert Schweitzer Hospital (Gabon) • Ministry of Health (Mozambique) • University of Limpopo (South Africa)
Study design:	Phase III open-label randomised controlled trial. Consenting HIV-infected patients with CD4 T cell counts<50 cells/µl and with a body mass index (BMI)<18 will be randomised to: 1. Initiation of 4 drug TB treatment followed by ART (efavirenz-based) within 2 weeks (completion of 6 month full-course TB treatment) 2. ART (efavirenz-based) only (+ pyridoxine 50mg) given

	within 2 weeks after enrolment
Product(s):	• Antiretroviral treatment: Stavudine (d4T) or zidovudine (AZT)/lamivudine (3TC)/efavirenz (EFV) generic fixed dose combination will be administered according to country specific local guidelines. • Anti-tuberculosis treatment: Isoniazid (INH) 5 mg/kg, rifampin (RIF) 10 mg/kg, pyrazinamide (PZA) 10 mg/kg, and ethambutol (ETH) orally for 8 weeks (intensive phase) followed by INH and RIF (plus pyridoxine 50 mg) for an additional 4 months (continuation phase). Sites are given fixed drug combinations if they are available at the site. Although directly observed therapy would be optimal, other measures of drug adherence are used.
Manufacturer/Developer:	No specific manufacturer information is provided, but all drugs utilised in the study are available through national programmes.
Cofunders:	• Health Foundation (Netherlands) • Prins Leopold Instituut voor Tropische Geneeskunde (Belgium) • German Aerospace Center (PT-DLR, Germany) • German Ministry of Education (BMBF, Germany) • Academic Medical Center at the University of Amsterdam (Netherlands) • University of Antwerp (Belgium)
Trial Registration number(s):	NCT01417988
Status:	Terminated
Results and Outcomes:	Trial terminated
Total number of subjects (clinical trials only):	334 patients
PhD study:	Title: Prophylaxis and treatment of patients with Cryptococcal antigenemia and a CD4 count <100 cells/µL Candidate: Ndivhuho Makhado (University of Limpopo, South Africa)
MSc study:	Master's in Public Health, Orientation Disease Control Candidate: Ndagire Gloria Kisake
Publications:	1. Manabe Y, Worodria W, Cobelens F. Empirical tuberculosis treatment or improved diagnostics? *Int J Tuberc Lung Dis* 2012;16:280.

1.1.8 RAFA

EDCTP Project Coordinator:	Corinne Merle (London School of Hygiene and Tropical Medicine, UK)
EDCTP Call Title:	Call for the support of clinical trials, capacity building and networking on treatment of HIV/AIDS
EDCTP Project Title:	A randomised controlled trial of 3 strategies for the treatment of ARV naive HIV infected patients with tuberculosis – RAFA project
EDCTP Project Code:	IP.2009.33011.009
EDCTP Project Start Date:	21 January 2011
EDCTP Project End Date:	20 January 2014
Collaborators:	• Dissou Affolabi (Centre National Hospitalier de Pneumo-Phtisiologie, Benin) • Evelyne Akinocho (Programme National de Lutte contre le SIDA, Benin) • Severin Anagonou (Centre National Hospitalier de Pneumo-Phtisiologie, Benin) • Boubacar Bah (Hôpital National Ignace Deen, Guinea) • Bouke de Jong (Institute of Tropical Medicine, Belgium) • Mouctar Dialo (Hôpital National Ignace Deen, Guinea) • Awa Helene Diop (National Tuberculosis Control Program, Senegal) • Sian Floyd (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Andre Furco (University College London, UK) • Katerina Tatiana Galperine (Tenon University Hospital, France) • Judith Glynn (LSHTM, UK) • Martin Gninafon (Centre National Hospitalier de Pneumo-Phtisiologie, Benin) • Anandi Martin (Institute of Tropical Medicine, Belgium) • Helen McIlleron (University of Cape Town, South Africa) • Alimatou N'Diaye (National Tuberculosis Control Program, Senegal) • N'Dira Sanoussi (Centre National Hospitalier de Pneumo-Phtisiologie, Benin) • Marie Sarr (National Tuberculosis Control Program, Senegal) • Oumou Younoussa Sow (Hôpital National Ignace Deen, Guinea) • Abdoulaye Sidibe Wade (Ministere de la sante et de la prevention medicale, Senegal)
Site Principal Investigator(s):	• Marie Saar (Senegal) • Oumou Bah-Sow (Guinea) • Martin Gninafon (Benin)
Clinical Trial/Study Sponsor:	LSHTM (UK)
Trial/Study title:	A randomised controlled trial of 3 strategies for the treatment of ARV naive HIV infected patients with tuberculosis – RAFA project
Goal:	To assess, using a three-arm approach, whether aggressive management of TB in HIV-infected patients during the 2 first months of TB treatment with a high dose of rifampicin might result in a decrease in the early HIV/TB mortality, without the negative effects of the early severe complications that can arise from the use of early ARV treatment.
Primary Objective(s):	1. To conduct a phase III randomised controlled trial to assess in ARV-naïve TB/HIV patients with CD4 counts more than 50 cells/mm3 and less than 350 cells/mm3 the efficacy in terms of morbidly and mortality of 3 treatment

	strategies: – Early ARV initiation (week 2) with a standard TB treatment – Delayed ARV treatment (week 8) with a standard TB treatment – Delayed ARV treatment (week 8) with high dose rifampicin during the intensive phase of TB treatment (15mg/Kg instead of 10 mg/Kg) and standard TB treatment in the continuation phase 2. To characterise anti-tuberculosis drug pharmacokinetics among HIV-TB co-infected patients, to assess treatment strategy-related sources of pharmacokinetic variation, and to evaluate differences in pharmacokinetics between patients with different treatment outcomes 3. To strengthen the research capacities of 3 well-established Tuberculosis Control Programmes to conduct clinical trials, through providing appropriate technology transfer and training (including 1 PhD program and 3 MSc programs), and guidance and mentoring from experienced researchers, in order to create sustainable research capacities 4. To reinforce the structures and to develop a West African clinical trial TB and TB/HIV network based around sites of excellence for field research in order that in the near future these sites are in a position to initiate, as well as to participate in, further international multicentre trials of new drugs or vaccines.
Clinical Trial/Study site(s):	• TB centres of MBAO and FAN hospital, Dakar (Senegal) • Pulmonary department of Igance Deen hospital and TB centre of Mattam, Conakry (Guinea) • National TB centre of Cotonou and the TB centre of Porto Novo (Benin)
Collaborating site(s):	• LSHTM, London (UK) • UCL, London (UK) • UCT, Rondebosch (South Africa) • Centre Hôspitalier de Pneumo-Phtisiologie, Cotonou (Benin) • CHU Ignace Deen, Service de Pneumo Phtisiologie, Conakry (Guinea) • National TB control Program (NTCP), Dakar (Senegal) • Hôpital Tenon, Paris (France) • Prince Leopold Tropical Institute of Medicine of Antwerp (Belgium)
Study design:	Phase III open-label multicentre randomised controlled trial with three arms. This trial includes as well a nested pharmacokinetic (PK) study in a sub-sample of patients. Subjects will be randomised to receive either arm A, B or C treatment regimen. The treatment schedule is as follows: • Early ARV initiation (after week 2 of TB treatment) combined with standard TB treatment • Delayed ARV treatment (after 8 weeks of TB treatment) combined with standard TB treatment • Delayed ARV treatment (after 8 weeks of TB treatment) combined with a high dose of rifampicin during the intensive phase of TB treatment (15mg/Kg instead of 10 mg/Kg) and standard TB treatment in the continuation phase 375 adult male or female patients in each arm will be recruited

	(1125 patients in total). Among these, 300 patients will be selected to contribute to the population PK study.
Product(s):	**Early ARV:** TB: Isoniazid, Rifampicin (10 mg/kg), Pyrazinamide and Ethambutol during 2 months / followed by Rifampicin (10 mg/kg) andIsoniazid treatment in the continuation treatment phase HIV: 2 nucleoside Reverse Transcriptase Inhibitor (NRTI) + Efavirenz (600mg) initiated 2 weeks after initiating TB treatment **Delayed ARV:** TB: Isoniazid, Rifampicin (10 mg/kg), Pyrazinamide and Ethambutol during 2 months / followed by Rifampicin (10 mg/kg) and Isoniazid treatment in the continuation treatment phase HIV: 2 NRTI + Efavirenz (b) (600 mg) initiated 2 months after initiating TB treatment **High dose Rifampicin:** TB: Isoniazid, Rifampicin (15 mg/kg), Pyrazinamide and Ethambutol during 2 months / followed by Rifampicin (10 mg/kg) and Isoniazid treatment in the continuation treatment phase HIV: 2 NRTI + Efavirenz (b) (600 mg) initiated 2 months after initiating TB treatment
Manufacturer/Developer:	All drugs utilised in the study are available through national programmes.
Cofunders:	• Prince Leopold Institute of Tropical Medicine (Belgium) • MRC (UK) • Centre Hôspitalier de Pneumo-Phtisiologie (Benin) • National TB Control Program (Senegal)
Trial Registration number(s):	PACTR201105000291300
Status:	Ongoing
Results and Outcomes:	The trial is recruiting.
Total number of subjects (clinical trials only):	1125 patients
PhD study:	Title: Anti-tuberculosis drug pharmacokinetics and treatment outcomes among HIV co-infected adult patients with tuberculosis. Candidate: Brice Guendehou
MSc studies:	LSHTM MSc Clinical Trial by Distance learning Candidate: N'Dira
	LSHTM MSc Clinical Trial by Distance learning Candidate: Moubacar Bah
	LSHTM MSc Clinical Trial by Distance learning Candidate: Alimatou Ndiqye
Publications:	

1.1.9 REMSTART

EDCTP Project Coordinator:	Saidi Egwaga (Tanzanian Ministry of Health and Social Welfare, Tanzania)
EDCTP Call Title:	Call for the support of clinical trials, capacity building and networking on treatment of HIV/AIDS
EDCTP Project Title:	Reduction of early mortality among HIV-infected subjects starting antiretroviral therapy: a randomised trial (The REMSTART trial)
EDCTP Project Code:	IP.2009.33011.009
EDCTP Project Start Date:	7 March 2011
EDCTP Project End Date:	6 March 2014
Collaborators:	• Shabir Banoo (Management Sciences for Health, South Africa) • Christian Bottomley (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Jeremiah Chakaya (Kenya Medical Research Institute, Kenya) • Lorna Guinness (LSHTM, UK) • Thomas Harrison (St. George's University of London, UK) • Jaffar, Shabbar (LSHTM, UK) • Moses Joloba Lutaakome (Ministry of Health, Uganda) • Lars Lindqvist (Karolinska Institute, Sweden) • Sayoki Mfinanga (National Institute for Medical Research, Tanzania) • Peter Mwaba (University of Zambia) • Philip C. Onyebujoh (WHO, Switzerland) • Alex Pym (Medical Research Council, South Africa) • Giorgio Roscigno (Foundation for Innovative New Diagnostics (FIND), Switzerland) • Mahnaz Vahedi (WHO, Switzerland) • Alimuddin Zumla (University College London, UK)
Site Principal Investigator(s):	• Peter Mwaba (Zambia) • Sayoki G Mfinanga (Tanzania)
Clinical Trial/Study Sponsor:	LSHTM (UK)
Trial/Study title:	Reduction of early mortality among HIV-infected subjects starting antiretroviral therapy: a randomised trial (The REMSTART trial)
Goal:	To evaluate a health service strategy for reducing the high early mortality associated with antiretroviral therapy in Africa. The strategy involves: accelerated initiation of ART when patients with very advanced disease present to clinic; increased involvement of lay-workers in adherence; increased frequency of diagnostic testing for cryptococcal meningitis and tuberculosis. A simple and large trial – "lean and mean" will be conducted.
Primary Objective(s):	The primary objective of the trial are to determine the effects of the intervention, accelerated initiation of ART and enhanced monitoring, support and diagnostics just before and during the first 4-6 weeks of therapy, as compared with standard care. The primary endpoint will be all-cause mortality up to 12 months after enrolment into the study. Other objectives are: 1. To develop capacity in population-based research, with a special focus on training PhD students in epidemiology and health economics. The overall goal is to train population-based research leaders of the future 2. To strengthen the capacity of the health hospital centres

	in clinical care and diagnostics through the conduct of research 3. To increase linkages between the different partners such that this consortium can bid for funding in clinical and health services research.
Secondary Objective(s):	1. To determine the costs incurred by the health service with this intervention strategy (in relation to standard care) and to relate these to the survival. To determine also the costs associated with accessing care for patients in the two arms of the trial 2. To determine the effects of the intervention on patient retention, hospital admissions, outpatient attendance as compared to standard care 3. To determine the uptake of voluntary counselling and testing services and simple tuberculosis screening among family members of patients on antiretroviral therapy.
Clinical Trial/Study site(s):	• Temeke, Amana and Mwanayamala sites, Dar es Salaam (Tanzania) • Kayama, Matero, Chipata, George, Chelstone sites, Lusaka (Zambia)
Collaborating site(s):	• Karolinska University Hospital, Huddinge (Sweden) • LSHTM (UK) • Ministry of Health (Zambia) • Ministry of Health and Social Welfare (Tanzania) • Special Programme for Research and Training in Tropical Disease (TDR, Switzerland) • St Georges Medical School (UK) • Unit for Tuberculosis Research, South African Medical Research Council (South Africa) • University of Zambia
Study design:	Phase III open-label randomised controlled trial. An estimated 2500 HIV-infected adults with CD4 count<100 cells per microlitre will be randomised to the intervention or the standard of care and followed up for 12 months.
Product(s):	Standard treatments for HIV, TB, cryptococcal meningitis will be used in this study. These are approved by WHO and are available through national programmes.
Manufacturer/Developer:	All drugs used in the study are available through national programmes as essential drugs.
Cofunders:	• Karolinska University Hospital (Sweden) • LSHTM (UK) • Ministry of Health (Zambia) • Ministry of Health and Social Welfare (Tanzania) • MRC (UK) • WHO Tropical Diseases Research (Switzerland)
Trial Registration number(s):	ISRCTN20410413 PACTR201112000327297
Status:	Ongoing
Results and Outcomes:	Currently recruiting.
Total number of subjects (clinical trials only):	2300 patients
Publications:	

1.2 HIV/AIDS prevention and treatment clinical trials

Table 1-2: HIV/AIDS prevention and treatment clinical trials supported by EDCTP

Project Acronym (Coordinator)	Phase of trial	Product(s)	Manufacturer / Developer	Study population	Status
Kesho Bora (Newell)	IV	Zidovudine (ZDV) Nevirapine (NVP) Lamivudine (3TC) Lopinavir/Ritonavir (LPV/r)	Cipla Pharm. Ltd Abbot Lab.	Pregnant women + infants HIV-positive (32 to 36 weeks gestation and their newborns from birth up to 1 year old (mother-infant pairs) N=845	Completed
ComTru Study (Katzenstein)	III	Combivir (ZDV & 3TC) Truvada (Emtricitabine &Tenofovir)	GlaxoSmithKline Gilead	Pregnant women + infants HIV-positive 18-55 years old) and their newborns (mother-infant pairs) N=450 planned, 288 mother-infant pairs evaluated	Completed
VITA-1 Study (Kisanga)	II	Viramune® (NVP) Taver® (Carbamazepine) Epanutin (Phenytoin)	Boeringer Ingelheim Medochemie Pfizer	Pregnant women + infants HIV-positive (>18 years old) & their newborns (mother-infant pairs) N=144	Completed
VITA-2 Study (Kisanga)	II	Viramune® (NVP) Taver® (Carbamazepine) Epanutin (Phenytoin)	Boeringer Ingelheim Medochemie Pfizer	Pregnant women + infants HIV-positive, ARV naive (>18 years old) and their newborns (mother-infant pairs) N=67 (40 complete datasets)	Completed (Pilot Study)
PROMISE-PEP Studies (Van de Perre)	III	Lamivudine (3TC) Lopinavir/Ritonavir (LPV/r)	Generic/GlaxoSmithKline Abbot Lab.	Infants HIV-uninfected infants (7 days old, to be breastfeed by their HIV-positive mothers) N=1,273 infants	Ongoing (Follow-up stage)

1.2.1 Kesho Bora study

EDCTP Project Coordinator:	Marie Louise Newell (Africa Centre for Health and Population Studies, South Africa)
EDCTP Call Title:	Support of studies for the Prevention of Mother to Child Transmission of HIV, including prevention of transmission during breast feeding
EDCTP Project Title:	Impact of HAART during Pregnancy and Breastfeeding on MTCT and Mother's Health: The Kesho Bora Study
EDCTP Project Code:	CT.2006.33020.007
EDCTP Project Start Date:	12 June 2007
EDCTP Project End Date:	30 November 2010
Collaborators:	• Siva Danaviah (University of KwaZulu-Natal, South Africa) • Stanley Luchters (University of Ghent, Belgium) • Stephen Mepham (Africa Centre for Health and Population Studies, South Africa) • Kevi Naidu (University of KwaZulu-Natal, South Africa) • Marcel Reyners (ICRH-International Centre of Reproductive Health, Netherlands) • Nigel Campbell Rollins (Africa Centre for Health and Population Studies, South Africa)
Site Principal Investigator(s):	• Marie Louise Newell (South Africa) • Nigel Rollins (South Africa) • Stanley Luchters (Kenya) • Marcel Reyners (Kenya) • Ruth Nduati (Kenya) • Nicolas Meda (Burkina Faso)
Clinical Trial/Study Sponsor:	World Health Organization (WHO, Switzerland)
Trial/Study title:	Impact of Highly Active Anti-Retroviral Therapy (HAART) during Pregnancy and Breastfeeding on Mother-To-Child-Transmission of HIV and Mother's Health: The Kesho Bora Study
Goal:	The overall goal of the study was to optimise the use of Anti-Retroviral (ARV) drugs during the antepartum, intrapartum and postpartum periods to prevent Mother-To-Child Transmission (MTCT) of Human Immunodeficiency Virus (HIV) type-1 and preserve the health of the mother in settings where the majority of HIV-positive women breastfeed.
Primary Objective(s):	The primary objectives of the prospective cohort study are to describe the rates and correlates of acquired immune deficiency syndrome (AIDS)-free maternal survival and HIV-free child survival among HIV-positive pregnant women and their children receiving care at participating clinical centres, and to assess the acceptability and safety of ARVs offered to these women and children according to World Health Organization (WHO) guidelines. The primary objectives of the randomised controlled trial among women with CD4+ cell counts in the range 200-500 cells/mm3 are to compare the efficacy and safety of the triple-ARV MTCT-prophylaxis regimen with that of the short-course MTCT-prophylaxis regimen with regard to: • HIV-free infant survival at 6 weeks (in utero/intrapartum/early postpartum) and 12 months among all infants, irrespective of mode of infant feeding (intent-to-treat analysis) • AIDS-free survival of mothers at 12 months following delivery • HIV-free infant survival at 12 months among infants who received any breast milk

	• Incidence of serious adverse events in mothers.
Secondary Objective(s):	1. Assess HIV-free survival at birth, 2 weeks, 6 weeks, 6 months, 9 months (a point when all breast feeding is likely to have ceased) and 12 months of age among all enrolled children 2. Estimate the rates of early and late postpartum transmission in ever breastfed infants, according to maternal HIV status and treatment received 3. Describe the correlates of infant HIV-free survival including stage of maternal HIV disease (clinical, immunological and virological factors), ARV prophylaxis and/or therapy given to the mother, and mode of infant feeding 4. Describe the correlates of mother's HIV disease progression and survival including socio-demographic characteristics, disease and nutritional status at enrolment, ARV prophylaxis and/or therapy given to the mother, and mode of infant feeding 5. Identify immunological and virological determinants of residual HIV-1 transmission during breastfeeding 6. Describe and compare the feasibility, acceptability, safety, tolerability of and adherence to the maternal ARV prophylaxis 7. Describe the feasibility and acceptability of current UNAIDS/UNICEF/WHO recommendations on HIV and infant feeding 8. Assess the feasibility and safety of rapid weaning over a two week period with complete cessation of breastfeeding by 6 months of age, and assess nutritional status and growth of children up to two years of age 9. Describe changes in viral load and emergence of viral resistance in blood and breast milk according to the maternal ARV prophylaxis and therapy regimens and immunological and virological status at enrolment 10. Describe the extent of partner involvement, family planning practices, condom use and sexual activity of couples 11. Describe and analyse the social and cultural factors that may increase or reduce HIV rates of transmission through breastfeeding 12. Describe family HIV-care needs and accessibility of HIV-care services 13. Assess the cost-effectiveness of the ARV prophylaxis and therapy regimens in preventing MTC.
Clinical Trial/Study site(s):	• KwaZulu-Natal University Health (Pty) Ltd (South Africa) • Durban and University of KwaZulu-Natal Mtubatuba (South Africa), University of Nairobi, Nairobi (Kenya) • International Centre for Reproductive Health (ICRH), Mombasa (Kenya) • Centre MURAZ, Bobo Dioulasso (Burkina Faso)
Collaborating site(s):	• Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Mtubatuba (South Africa) • KwaDabeka site, University of KwaZulu-Natal University Health (Pty) Ltd., Durban (South Africa) • International Centre for Reproductive Health, ICRH, Mombasa (Kenya) • University of Nairobi, Nairobi (Kenya), Centre MURAZ, Bobo Dioulasso (Burkina Faso) • Centre de Recherche Cultures, Santé, Sociétés, Aix-en-Provence (France), CHR Montpellier (France)

	• Institut de Recherche pour le Développement (IRD) Montpellier (France) • International Centre for Reproductive Health, Ghent (Belgium)
Study design:	Phase IV randomised controlled trial. Eligible women with CD4+ cell count between 200 and 500 cells/mm3 with no contraindication and willing to be randomised will receive one of two different regimens for MTCT prevention: • A triple-ARV regimen (ZDV, 3TC and LPV/r) beginning at 34-36 weeks gestation, through delivery, until six months postpartum; or • A short-course regimen consisting of ZDV beginning at 34-36 weeks gestation until the onset of labour, plus one dose of ZDV and one dose of NVP at the onset of labour All infants born to women enrolled in either part of the study will receive one dose of NVP within 72 hours of birth. All enrolled women and their HIV-infected children whose HIV disease progresses to the point of meeting WHO criteria for treatment will be offered HAART provided they do not have any contraindications to initiating HAART.
Product(s):	• Zidovudine (ZDV) • Lamivudine (3TC) • Lopinavir/ritonavir (LPV/r) • Nevirapine (NVP)
Manufacturer/Developer:	• Cipla Pharmaceuticals Ltd • Abbot Laboratories
Cofunders:	• Belgium Cooperation (Belgium) • Centre for Disease Control (CDC, USA) • Department for International Development [DFID] (UK) • French National Agency for Research on AIDS and Viral Hepatitis [ANRS] (France) • GlaxoSmithKline Foundation • National Institutes of Health (NIH, USA) • Thrasher Research Foundation (USA) • World Health Organization [WHO] (Switzerland)
Trial Registration number(s):	ISRCTN 71468401
Status:	Completed
Results and Outcomes:	The findings of this study, known as the Kesho Bora Study, showed that triple ART during pregnancy and breastfeeding is safe and reduces the risk of HIV transmission to infants. These results led to the revision of the WHO guidelines on prevention of HIV infection in pregnant women, mothers and their infants. WHO now recommends ART for all pregnant women infected with HIV who have CD4 counts of 350 cells per µL or less, and antiretroviral prophylaxis during breastfeeding either to the women not on ART or to the infant.
Total number of subjects (clinical trials only):	845
PhD study	Title: Primary HIV in Pregnancy and its impact on mother-to-child transmission Candidate: Stephen Mepham (Africa Center, South Africa and Aberdeen University, UK) Dates: 2 January 2008 – 30 September 2011
Other/Sub-studies:	Primary HIV in pregnancy and its impact on mother-to-child transmission
Publications:	• Arrivé E, Kyabayinze DJ, Marquis B, Tumwesigye N, Kieffer MP, Azondekon A, Wemin L, Fassinou P, Newell ML, Leroy V, Abrams EJ, Cotton M, Boulle A, Mbori-Ngacha D and

	Dabis F; KIDS-ART-LINC Collaboration. Cohort profile: the paediatric antiretroviral treatment programmes in lower-income countries (KIDS-ART-LINC) collaboration. *Int J Epidemiol*. 2008 Jun;37(3):474-480. Epub 2007 Nov 12 • Rouet F, Foulongne V, Viljoenc J, Steegen K, Becquart P, Valéa D, Danaviah S, Segondy M, Verhofstede C, Van de Perre P, & the WHO/ANRS 1289 Kesho Bora Study Group (Newell ML). Comparison of the Generic HIV Viral Load® assay with the Amplicor™ HIV-1Monitor v1.5™ and Nuclisens HIV-1 EasyQ® v1.2 techniques for plasma HIV-1 RNA quantitation of non-B subtypes: The Kesho Bora preparatory study. *J. Virol. Methods* 2010 Feb;163(2):253-7. Epub 2009 Oct 27 • Mepham SO, Bland RM & Newell ML. Prevention of mother-to-child transmission of HIV in resource-rich and -poor settings. International Journal of Obstetrics and Gynaecology, 2010; 118(2), 201-218.[DOI: 10.1111/j.1471-0528.2010.02733.x] • Kesho Bora Study Group (Newell ML). Eighteen-Month Follow-Up of HIV-1–Infected Mothers and Their Children Enrolled in the Kesho Bora Study Observational Cohorts. *J Acquir Immune Defic Syndr*. 2010, 54(5) 533-541 • The Kesho Bora Study Group (authors include Mepham S, Naidu K & Newell ML). Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. *Lancet Infectious Diseases* 11(3) (2011) 171-180. [doi:10.1016/S1473-3099(10)70288-7] • The Kesho Bora Study Group (authors include Mepham S, Naidu K & Newell ML. Safety and effectiveness of antiretroviral drugs during pregnancy, delivery and breastfeeding for prevention of mother-to-child transmission of HIV-1: The Kesho Bora Multicentre Collaborative Study rationale, design, and implementation challenges.*). Contemporary Clinical Trials* 32 (2011) 74–85 • Mepham S, Zondia Z, Mbuyazia A, Mkhwanazi N & Newell ML. Challenges in PMTCT antiretroviral adherence in northern KwaZulu-Natal, South Africa. *AIDS Care*, 2011; 23(6), 741-747 • James Ndirangu, Marie-Louise Newell, Ruth M. Bland, and Claire Thorne. Maternal HIV infection associated with small-for-gestational age infants but not preterm births: evidence from rural South Africa. *Human Reproduction* 2012, 27(6), 1846–1856 • Fao, P; Fao, P; Ky-Zerbo, O; Gouem, C; Somda, P; Hien, H; Ouedraogo, PE; Kania, D; Sanou, A; Kossiwavi, IA; Sanogo, B; Ouedraogo, M; Siribie, I; Valea, D; Ouedraogo, S; Some, R; Rouet, F; Rollins, N; McFetridge, L; Naidu, K; Luchters, S; Reyners, M; Irung for the Kesho Bora Study Group. Maternal HIV-1 Disease Progression 18-24 Months Postdelivery According to Antiretroviral Prophylaxis Regimen (Triple-Antiretroviral Prophylaxis During Pregnancy and Breastfeeding vs Zidovudine/Single-Dose Nevirapine Prophylaxis): The Kesho Bora Randomised. *Clinical Infectious Diseases* 2012, 55, 449-460 • Kirsten Bork, Cécile Cames, Amandine Cournil, Faith Musyoka, Kossiwavi Ayassou, Kevindra Naidu, Stephen

	Mepham, Christine Gichuhi, Jennifer S. Read, Philippe Gaillard, and Isabelle de Vincenzi, for the Kesho Bora Study Group. Infant Feeding Modes and Determinants Among HIV-1–Infected African Women in the Kesho Bora Study. *JAIDS* 2013, 62(1), 109–118

1.2.2 ComTru Study

EDCTP Project Coordinator:	Terese Lea Katzenstein (University Hospital Copenhagen, Denmark)
EDCTP Call Title:	Support of studies for the Prevention of Mother to Child Transmission of HIV, including prevention of transmission during breast feeding
EDCTP Project Title:	Backup with Combivir (AZT/3TC) or single dose Truvada (FTC/TDF) in order to avoid Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) resistance after single dose Nevirapine for the prevention of mother-to-child transmission (MTCT)
EDCTP Project Code:	CT.2006.33020.001
EDCTP Project Start Date:	29 October 2007
EDCTP Project End Date:	31 January 2012
Collaborators:	• Mercy Chiduo (National Institute for Medical Research (NIMR), Tanzania) • Leo Flamholc (University Hospital of Malmoe, Sweden) • Jan Gerstoft (University Hospital Copenhagen, Denmark) • Martha Lemnge (National Institute for Medical Research (NIMR), Tanzania) • Godfrey Mgaya (Makorora Health Centre, Tanzania) • Margareth Mhando (Bombo Regional Hospital, Tanzania) • Alice Mliga (Ngamiani Health Centre, Tanzania) • Frederick Mtatifikolo (Bombo Regional Hospital, Tanzania) • Tine Strand (University Hospital Copenhagen, Denmark) • Zahra Theilgaard (Copenhagen University Hospital, Denmark)
Site Principal Investigator(s):	• Terese Lea Katzenstein (Denmark) • Tine Strand/Zahra Theilgaard (Denmark) • Celine Mandara (Tanzania) • Mercy G Chiduo (Tanzania) • Martha Lemnge (Tanzania)
Clinical Trial/Study Sponsor:	Rigshospitalet (Denmark)
Trial/Study title:	Backup with Combivir (AZT/3TC) or single dose Truvada (FTC/TDF) in order to avoid Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) resistance after single dose Nevirapine for the prevention of mother-to-child transmission (MTCT)
Goal:	The aim of the study is to find short course alternatives to single dose (sd) nevirapine for the prevention of mother-to-child HIV-transmission with the same or better degree of transmission protection than single dose nevirapine but with less NNRTI resistance development.
Primary Objective(s):	1. To assess the efficacy of zidovudine (ZDV) from week 28 with single dose Nevirapine plus 7 days Combivir and Zidovudine from week 28 with single dose Nevirapine plus single dose Truvada for the prevention of vertical transmission of HIV-1 from pregnant women to neonates in Tanzania 2. To assess Truvada to the same extent as Combivir reduces the risk of NNRTI resistance after single dose Nevirapine given during delivery compared to historical controls. Main study end points will be differences between the study groups in: • HIV-1 infection of neonates at age 6-8 weeks measured by HIV-RNA

	• NNRTI-associated resistance mutations K103N and Y181C in mothers and children at 6-8 weeks postpartum detected by sensitive assays.
Secondary Objective(s):	1. Monitor acceptance of VCT and participation among pregnant women in Tanga, Tanzania 2. Monitor ZDV adherence from initiation at 28 weeks or as soon as possible thereafter, until delivery, through measurement of MCV, self-reported adherence questioning and comparison with pharmacy records 3. Evaluate heat dissociation-boosted (HDB) p24-antigen ultra-sensitive assay for diagnosis of HIV-1 infection and quantification of viral load for infants by birth, week six-eight and month nine and for women at enrolment, delivery, day seven, week six-eight and month nine, using HIV-RNA as reference 4. Determine side effects of the medications 5. Assessment of compliance between the two treatment groups 6. Determine HIV-1 subtypes and correlation to risk of MTCT and NNRTI resistance at birth, week six-eight and month nine for each of the subtypes A, C and D, which are expected to account for one third each 7. Determine blood and breast milk drug levels of Nevirapine in the woman at day one, day seven and week 6-8 and relations to development of NVP resistance among the subtypes A, C and D 8. Measure breast milk HIV-RNA day seven, week six-eight and month nine and correlated to postpartum MTCT at week six-eight and month nine 9. Compare HIV-1 RNA levels in vaginal secretion and the risk of HIV-1 MTCT at birth among subtypes A, C and D 10. Investigate successful referral and retention rates at CTC through close collaboration with the staff at CTC examination of the patient database at CTC.
Clinical Trial/Study site(s):	• Ngamiani and Makorora Health Centres (Tanzania) • Bombo Regional Hospital (Tanzania) • National Institute of Medical Research (Tanzania)
Collaborating site(s):	• University of Copenhagen (Denmark) • University Hospital of Malmoe (Sweden) • National Institute of Medical Research (Tanzania) • Bombo Hospital (Tanzania) • Kilimanjaro Christian Medical College [KCMC] (Tanzania)
Study design:	Phase III open-label randomised controlled trial with two arms. Women are 1:1 randomly assigned to National guideline pre/intra/postpartum including sd-Nevirapine and Combivir or to National guideline prepartum followed by sd-Nevirapine and Truvada. Thus all women will receive Zidovudine from week 28 of pregnancy or as soon as possible thereafter. **Arm 1: National guideline pre/intra/postpartum:** AZT 300 mg BD from 28 weeks. Intrapartum: sdNVP 200 mg at the onset of labour. AZT 300mg and 3TC 150 mg at the onset of labour. Continue AZT every 3 hours and 3TC every 12 hours until delivery. During the postpartum period: Combivir (AZT 300 mg and 3TC 150 mg) BD for 7 days. **Arm 2: National guidelines prepartum:** AZT 300 mg BD from 28 weeks.

	Intrapartum: sdNVP 200 mg and sdTruvada (300 mg Tenofovir and 200 mg Emtricitabine). Children will receive sd NVP syrup (2 mg/kg) and AZT syrup (4 mg/kg BD) according to the national guidelines.
Product(s):	• Zidovudine and Lamivudine (Combivir) • Emtricitabine and Tenofovir (Truvada)
Manufacturer/Developer:	• GlaxoSmithKline • Gilead
Cofunders:	• University Hospital Copenhagen (Denmark) • Statens Serum Institute and Novo Nordisk (Denmark) • University Hospital Malmo and Swedish Orphan (Sweden) • Bjorn Astrups Foundation (Denmark) • Jens Christensen and Wife Korna Christensen Foundation (Denmark)
Trial Registration number(s):	NCT 00346567
Status:	Completed
Results and Outcomes:	A summary of the major findings are given below: • Mother-to-child transmission rates at 6-8 weeks: Combivir arm = 5.8%, Truvada arm = 5.6% (RR =1.0 95%CI = 0.4 – 2.4.) • Mother-to-child transmission rates at 9 months: Combivir arm= 9.5%, Truvada arm = 11.7% (RR = 1.2, 95% CI = 0.6 – 2.6) • NNRTI resistance data are being finalized. We expect these analyses to be completed by August 2012 • P24 antigen for early infant diagnosis compared to HIV RNA PCR: the sensitivity of the p24 antigen analysis was found to be 33% at birth, 80% at week SEW and 100% at month nine (Table 3). The specificity was found to be 94%, 99% and 97% at birth, SEW weeks and nine months respectively (Table 3). The overall sensitivity and specificity was found to be 79% and 97%, respectively • STIsHIV-infected women had significantly higher prevalence of trichomoniasis (18.8% versus 5.0%; P, 0.003) and candidiasis (16.5% versus 2.0%; P, 0.001) while the higher rate of gonorrhoea (3.5% versus 0%; P ¼ 0.095) was not statistically significant when compared with HIV-uninfected women. There were no statistically significant differences in prevalence of chlamydial infection (0% versus 3.0%; P ¼ 0.156) or syphilis (2.4% versus 3.0%; P ¼ 1) between HIV-infected and uninfected women. Other STIs were common in both HIV-infected and uninfected pregnant women • Stigma is highly prevalent in Tanga, and a major contributing factor to attrition from ART for women.
Total number of subjects (clinical trials only):	Mother-infant pairs 450 planned, 288 mother-infant pairs evaluated
PhD studies:	Title: Antiretroviral Therapy for Women in a resource-limited setting – success, efficacy and challenges Candidate: Zahra Theilgaard (University of Copenhagen, Denmark) Date: 1 January 2009 – 28 February 2013
	Title: Levels of Zidovudine in Cervico-vaginal secretions and Sexual Transmitted Infections in relation to Mother-to-child transmission of HIV among pregnant women in Tanga north-eastern Tanzania Candidate: Mercy Chiduo (University of Copenhagen, Denmark and NIMR, Tanzania) Dates: 1 January 2009 – expected December 2013

MSc study:	Title: Exploring how community leaders perceive the effects of antiretroviral treatment: A grounded theory study in Tanga, Tanzania Candidate: Christiane Pahl (MSc in Public Health at the Lund University, Sweden) Dates: 1 January 2008 – 1 December 2010
Publications:	1. Arreskov A, Minja E, Theilgaard Z, Mandara C, Gerstoft J, Lemnge M, Katzenstein TL. Referral success among HIV-infected women and HIV-exposed children referred for monitoring and treatment in Tanga, Tanzania. *International Health* 2010; 2 (1): 36-41. Doi: 10.1016/j.inhe.2009.12.010 2. Salado-Rasmussen K, Theilgaard ZP, Chiduo M, Pedersen C, Gerstoft J, Katzenstein TL. Good performance of an immunoassay based method for nevirapine measurements in human breast milk. *Clin Chem Lab Med* 2011; 49(7) 1171-5. Doi: 10.1515/CCLM.2011.184. 3. Chiduo M, Theilgaard ZP, Bakari V, Mtatifikolo F, Bygbjerg I, Flanholc L, Gerstoft J, Christiansen CB, Lemnge M, Katzenstein TL. Prevalence of Sexually Transmitted Infections among women attending antenatal clinics in Tanga, north eastern Tanzania. *International Journal of STD & AIDS* 2012; 23: 325-329.

1.2.3 VITA Studies

EDCTP Project Coordinator:	Elton R. Kisanga (Kilimanjaro Christian Medical Centre (KCMC), Tanzania)
EDCTP Call Title:	Support of studies for the Prevention of Mother to Child Transmission of HIV, including prevention of transmission during breast feeding
EDCTP Project Title:	The effect of single dose carbamazepine on the pharmacokinetics of single dose nevirapine (VIramune®, NVP) and development of NVP resistance for the prevention of mother-to-child transmission in Tanzania & Zambia (VITA studies)
EDCTP Project Code:	CT.2006.33020.006
EDCTP Project Start Date:	15 October 2007
EDCTP Project End Date:	30 September 2012
Collaborators:	• David Marinus Burger (Radboud University Nijmegen, Netherlands) • Catherine Chunda (University Teaching Hospital, Zambia) • Quirine Fillekes (Radboud University Nijmegen, Netherlands) • Diana Mary Gibb (Medical Research Council, UK) • Chipepo Kankasa (University Teaching Hospital, Zambia) • Eva P Muro (Kilimanjaro Christian Medical Centre (KCMC), Tanzania) • Werner Schimana (Kilimanjaro Christian Medical Centre (KCMC), Tanzania) • Margaret Thomason (Medical Research Council, UK) • Andreas van der Ven (Radboud University Nijmegen, Netherlands) • Ann Sarah Walker (Medical Research Council, UK) • Leszek Wojnowski (The Johannes Gutenberg University Mainz, Germany)
Study / Trial 1	**VITA 1 study**
Site Principal Investigator(s):	• Elton R. Kisanga (Tanzania) • David Burger (Netherlands) • Chipepo Kankasa (Zambia) • Diana Gibb (UK)
Clinical Trial/Study Sponsor:	Radboud University Nijmegen Medical Centre (RUNMC, Netherlands)
Trial/Study title:	The effect of single dose carbamazepine on the pharmacokinetics of single dose nevirapine (VIramune®, NVP) and development of NVP resistance, PMTCT program of Moshi, TAnzania (VITA1)
Goal:	Test the hypothesis that single dose carbamazepine decreases development of resistance to nevirapine (NVP) in HIV-positive pregnant Tanzanian women by decreasing NVP half-life.
Primary Objective(s):	1. To determine the pharmacokinetics of single dose nevirapine in HIV seroconverted pregnant women and their newborns 2. To determine the effect of single dose carbamazepine on the pharmacokinetics of single dose nevirapine in HIV seroconverted pregnant women and their newborns 3. To determine resistance against nevirapine in women before and after a single dose of nevirapine or a single dose of nevirapine/carbamazepine 4. Follow-up of newborns with focus on the HIV status, resistance and toxicity 5. To examine the possible relation between nevirapine levels in cord blood and plasma (of both mother and child) just after delivery and the HIV status of the newborn.
Secondary Objective(s):	1. To determine the safety of single dose nevirapine and single

	dose nevirapine/carbamazepine.
Clinical Trial/Study site(s):	Majengo Antenatal Clinic and Kilimanjaro Christian Medical Centre (Tanzania)
Collaborating site(s):	• Kilimanjaro Christian Medical Centre (Tanzania) • University Teaching Hospital (Zambia) • Radboud University Nijmegen Medical Centre (Netherlands) • Medical Research Council (UK)
Study design:	Phase IIa open-label randomised pharmacokinetic trial with two arms. **Arm 1 (Active Comparator):** An oral dose of 400 mg carbamazepine is added to the 200 mg oral dose nevirapine intake prior delivery. **Arm 2 (Placebo Comparator):** Standard therapy of 200 mg nevirapine oral prior to delivery.
Product(s):	• Taver® (Carbamazepine) • Viramune ® (Nevirapine, NVP) tablets & oral suspension
Manufacturer/Developer:	• Medochemie Ltd. • Boeringer Ingelheim
Cofunders:	• NACCAP (Netherlands) • Medical Research Council (MRC, UK)
Trial Registration number(s):	NCT 00294892
Total number of subjects (clinical trials only):	144 mother-infant pairs
Status:	Completed
Results and Outcomes:	The results of the VITA1 shows that addition of single-dose carbamazepine to single-dose nevirapine at labour onset in HIV-infected, pregnant women did not affect nevirapine plasma concentration at delivery, but significantly reduced it one week postpartum, with a trend towards fewer nevirapine resistance mutations, although missing samples reduced power to reach statistical significance.
Study/Trial 2	**VITA 2 study**
Site Principal Investigator(s):	• Elton R. Kisanga (Tanzania) • Werner Schimana (Tanzania) • David Burger (Netherlands) • Andreas J. van der Ven (Netherlands)
Clinical Trial/Study Sponsor:	Radboud University Nijmegen Medical Centre (Netherlands)
Trial/Study title:	The effect of phenytoin on the pharmacokinetics of nevirapine and the development of nevirapine resistance after a single dose nevirapine (VIramune®), which is part of ARV prophylaxis for PMTCT in Moshi, TAnzania, and in Lusaka, Zambia (VITA2 Trial)
Goal:	To test the hypothesis that phenytoin reduces the elimination half-life of SD NVP and thereby decreases development of resistance to NVP in HIV positive pregnant Tanzanian and Zambian women
Primary Objective(s):	1. To determine the elimination half-life of NVP in HIV positive pregnant women receiving it as a single dose in labour in addition to the ZDV and 3TC with or without seven days phenytoin (pilot PK phase) 2. To determine NVP resistance in HIV positive pregnant women receiving it as a single dose in labour in addition to ZDV and 3TC with or without seven days phenytoin (main trial phase).
Secondary Objective(s):	1. To determine the safety of single dose nevirapine with seven days phenytoin as a part of ARV prophylaxis for

	PMTCT vs. single dose of nevirapine without phenytoin as a part of ARV prophylaxis for PMTCT 2. To determine the HIV status of the infant 3. To determine the safety of the ARV prophylaxis for PMTCT with seven days of phenytoin on the newborn.
Clinical Trial/Study site(s):	Majengo Antenatal Clinic, Mawenzi ANC, Pasua ANC and Kilimanjaro Christian Medical Centre (Tanzania)
Collaborating site(s):	• Kilimanjaro Christian Medical Centre (Tanzania) • University Teaching Hospital (Zambia) • Radboud University Nijmegen Medical Centre (Netherlands) • Medical Research Council (UK)
Study design:	Phase IIa/IIb open-label multi-centre randomised pharmacokinetic trial. ARV prophylaxis for PMTCT follows national guidelines (which differ slightly): **Mother:** • Antepartum: start zidovudine 300 mg BID from 28 weeks of gestation or as soon as feasible thereafter, at least four weeks before delivery. • Intrapartum (Tanzania): single dose NVP 200 mg at onset of labour, continue zidovudine 300 mg at onset of labour every three hours until delivery and start lamivudine 150 mg every 12 hours at onset of labour. • Intrapartum (Zambia): single dose NVP 200 mg at onset of labour, start zidovudine 600 mg and lamivudine 300 mg at onset of labour every 12 hours until delivery. • Postpartum: continue zidovudine 300 mg BID and lamivudine 150 mg BID for seven days. • If randomised to phenytoin intrapartum: start phenytoin 184 mg (2 tablets of 92mg) OD at onset of labour and continue for seven days. **Child:** • Postpartum (within 24-72 hours): Single dose nevirapine 2mg/kg and zidovudine 4 mg/kg BID for seven days.
Product(s):	• Taver® (Carbamazepine) • Viramune ® (Nevirapine) tablets & oral suspension • Epanutin® (Phenytoin)
Manufacturer/Developer:	• Medochemie Ltd • Boeringer Ingelheim • Pfizer
Cofunders:	• NACCAP (Netherlands) • Medical Research Council (MRC, UK)
Trial Registration number(s):	NCT 01187719
Status:	Completed
Results and Outcomes:	VITA 1 study: the results shows that addition of single-dose carbamazepine to single-dose NVP at labour onset in HIV-infected, pregnant women did not affect NVP plasma concentration at delivery, but significantly reduced it one week postpartum, with a trend towards fewer NVP resistance mutations, although missing samples reduced power to reach statistical significance. These results were published by Muro EP, et al. in J. Acquir. Immune Defic. Syndr. (2012), 1;59(3):266-73. (PMID:22134145). Enzyme inducers, such as carbamazepine, may show new possibilities for pMTCT programs to reduce the development of NVP resistance in settings where other ART regimens are limited. VITA 2 pilot study: recruited 67 participants instead of 50 as per

	the protocol. This was discussed with the external monitors and DSMB members. The aim was to get 40 complete datasets (analysable) to have enough power to address the primary objectives of the pilot trial, i.e. pharmacokinetics studies. The investigators have submitted the findings to the Clinical Infectious Diseases Journal and presented the data at CROI, March 2013. In brief, it is observed that addition of an enzyme inducer (i.e. phenytoin) for 7 days to sdNVP for the prevention of MTCT reduced the presence of sub-therapeutic NVP levels by shortening the NVP elimination half-life; no NVP resistance was observed. As prolonged sub-therapeutic NVP exposure is known to lead to resistance emergence, in the absence of a larger phase III trial, sdNVP could be used with phenytoin if other ARV drugs are unavailable, since it is safely and widely used in pregnancy. VITA 2 main study: was not conducted as it was considered unethical to begin the study which could not be completed for various reasons, i.e. slow recruitment, expected high loss to follow-up (as per experienced in VITA 1 and VITA 2 pilot studies), unrealistic timelines, etc. Other accomplishments: 1. Capacity building & infrastructure upgrade: significant short training coursed in GCP/GCLP and ethics were accomplished during the grant. In addition, it took place the construction of the two upper floors of Kilimanjaro Clinical Research Institute (KCRI) with NACCAP funding 2. Dissemination: One scientific article published in March 2012 (VITA 1 results). VITA 2 pilot study results submitted to Clinical Infectious Diseases Journal. Possibly, a manuscript in preparation from the MSc dissertation of Lutengano George. 3. Training: 2 PhD students and 2 MSc students have been trained. An additional PhD student was included after establishing the collaboration with the University of Mainz, Germany) (Mrs Dorothea Baranyai). The 2 MSc students graduated but the PhDs defences are still ongoing.
Total number of subjects (clinical trials only):	VITA 2 pilot study: 50 HIV-positive, ARV naive, African, pregnant women (18 years or older) and their newborns - ongoing VITA 2 main study: 150 HIV-positive, ARV naive, African, pregnant women (18 years or older) and their newborns – main study cancelled
PhD studies:	Title: Clinical Pharmacology of ARV agents in resource limited settings Candidate: Quirine Fillekes (Radboud University, Netherlands) Dates: October 2007-September 2012
	Title: Clinical Pharmacology of pMTCT Candidate: Eva Muro (Radboud University, Nijmegen, Netherlands) Dates: October 2007-September 2012
MSc studies:	Title: Age standardization in relative survival Candidate: Humphrey Mkali (MSc in Biostatistics at the Leicester University, United Kingdom) Date: October 2007-September 2011
	Title: MSc in Clinical research Candidate: Lutengano George (KCM College, Tanzania) Completion date: October 2007-September 2012
Publications:	1. Muro EP, Fillekes Q, Kisanga ER, L'homme R, Aitken SC, Mariki G, Van der Ven, AJAM, Dolmans W, Schuurman R, Walker AS, Gibb DM, Burger DM. Intrapartum single-dose carbamazepine shortens nevirapine elimination half-life and

	may reduce resistance after a single dose of nevirapine for perinatal HIV prevention. *J Acquir Immune Defic Syndr* 2012; 59 (3), 266-273

1.2.4 PROMISE-PEP Studies

EDCTP Project Coordinator:	Philippe Van de Perre (Montpellier University Hospital Centre (CHU), France)
EDCTP Call Title:	Support of studies for the Prevention of Mother to Child Transmission of HIV, including prevention of transmission during breast feeding
EDCTP Project Title:	A randomised controlled trial comparing the efficacy of infant peri-exposure prophylaxis with Lopinavir/Ritonavir (LPV/r) versus Lamivudine to prevent HIV-1 transmission by breastfeeding
EDCTP Project Code:	CT.2006.33020.004
EDCTP Project Start Date:	21 March 2008
EDCTP Project End Date:	30 June 2013
Collaborators:	• Stéphane Blanche (University of Paris V - René Descartes, France) • Tanya Doherty (Medical Research Council South Africa (MRC), South Africa) • Pierre Dujols (University of Montpellier 1, France) • Eva-Charlotte Ekström (Uppsala University, Sweden) • Vincent Foulongne (University of Montpellier 1, France) • Knut Fylkesnes (University of Bergen, Norway) • Harry Hausler (University of the Western Cape, South Africa) • Debra Jackson (University of the Western Cape, South Africa) • Chipepo Kankasa (University of Zambia (UNZA), Zambia) • Nicolas Meda (Centre Muraz, Burkina Faso) • Philippa Musoke (Makerere University, Uganda) • Nicolas Nagot (University of Montpellier 1, France) • Dorine Neveu (University of Montpellier 1, France) • Vernice Cheryl Nikodem (University of the Western Cape, South Africa) • Marie-Christine Picot (University of Montpellier 1, France) • Francois Rouet (Centre Muraz, Burkina Faso) • David Sanders (University of the Western Cape, South Africa) • Michel Segondy (University of Montpellier 1, France) • Seter Siziya (University of Zambia) • Halvor Sommerfelt (University of Bergen, Norway) • Jean-Marc Tréluyer (University of Paris V - René Descartes, France) • James K Tumwine (Makerere University, Uganda) • Thorkild Tylleskar (University of Bergen, Norway)
Site Principal Investigator(s):	• Thorkild Tylleskar (Norway) • Nicolas Meda (Burkina Faso) • James K Tumwine (Uganda) • Chipepo Kankasa (Zambia) • Justus Hofmeyr (South Africa) • Eva-Charlotte Ekström (Sweden) • Stephane Blanche (France)
Clinical Trial/Study Sponsor:	France National Agency for Research on AIDS & Hepatitis (ANRS)
Trial/Study title:	A randomised controlled trial comparing the efficacy of infant peri-exposure prophylaxis (PEP) with Lopinavir/Ritonavir (LPV/r) versus Lamivudine to prevent HIV-1 transmission by breastfeeding (ANRS 12174 trial)
Goal:	To assess, in a multi-centre randomised clinical trial, the efficacy and safety of prolonged peri-exposure prophylaxis (PEP) on

	postnatal transmission of HIV-1 from infected breastfeeding (BF) mothers not eligible for HAART to their infants, after perinatal antiretroviral prophylaxis.
Primary Objective(s):	1. To compare the efficacy of infant Lopinavir/Ritonavir (LPV/r, 80/20mg twice a day) vs lamivudine (3TC, 12 mg twice daily if <6 kg, 24 mg per day if 6.0 to 9.0 kg, and 36 mg per day if ≥ 9.0 kg) from day 7 until one week after cessation of BF (maximum duration of prophylaxis: 50 weeks for a maximum duration of breastfeeding of 49 weeks) to prevent postnatal HIV-1 acquisition between 7 days and 50 weeks of age.
Secondary Objective(s):	1. To assess the safety of long-term infant prophylaxis with LPV/r versus lamivudine (including resistance, adverse events and growth) at 50 weeks 2. To assess HIV-1-free survival until 50 weeks 3. To build clinical trials capacity at the four study sites.
Clinical Trial/Study site(s):	• University of Ouagadougou (Burkina Faso) • University of the Western Cape (South Africa) • Makerere University (Uganda) • University Teaching Hospital (Zambia)
Collaborating site(s):	• University of Montpellier and University of Paris V (France) • University of Bergen (Norway) • University of Uppsala (Sweden) • South African Medical Research Council (South Africa)
Study design:	Phase III double-blinded randomised controlled trial with two arms. **Arm 1 (Experimental):** infant peri-exposure prophylaxis with lopinavir/ritonavir (LPV/r) Oral liquid formulation lopinavir/ritonavir(80 mg lopinavir + 20 mg ritonavir/mL). Dosing: 40/10mg twice daily if infant weight is between 2 to 4 kg and 80/20mg twice daily if infant weight is above 4kg. The lopinavir/ritonavir will be given to the baby from Day 7 postnatal until one week after the cessation of breastfeeding. **Arm 2 (Active Comparator):** infant peri-exposure prophylaxis with lamivudine (3TC) Oral liquid solution lamivudine (10 mg/mL). Dosing: 7.5 mg twice daily if infant weight is between 2 to 4 kg; 25 mg twice daily if infant weight is between 4 to 8 kg; 50 mg twice daily if infant weight is above 8kg. The lamivudine will be given to the baby from Day 7 postnatal until 4 weeks after the cessation of breastfeeding.
Product(s):	• Lopinavir/ritonavir (LPV/r) • Lamivudine (3TC)
Manufacturer/Developer:	• GlaxoSmithKline/Generic supplier (for lamivudine) • Abbott (for lopinavir/ritonavir)
Cofunders:	• French National Agency for Research on AIDS and Viral Hepatitis (ANRS, France) • The Research Council of Norway (Norway) • Swedish International Development Cooperation Agency (SIDA, Sweden)
Trial Registration number(s):	NCT 00640263
Status:	Ongoing
Results & Outcomes:	The participant recruitment took place from November 2009 to October 2010 (in Burkina Faso, Zambia, Uganda, and South Africa and was considered completed in May 2012. The trial has enrolled 1,273 infants (84.8% of the original sample size, i.e.

	above the set power of 80% as per the study protocol) and follow-up of the last participant is expected to be in May 2013. The team had to extended the enrolment period until May 2012 because the recruitment rate was lower than expected, mainly due to lower than anticipated HIV prevalence in pregnant women in Burkina Faso (1.5% vs. 4%) and in Uganda (5% vs. 8%). In South Africa, the regulatory approval process delayed the recruitment initiation, and the recruitment was much impacted by both a history of formula feeding for HIV-infected mothers, and the implementation of a national policy to administer nevirapine to infants during the breastfeeding period. Furthermore, the increase threshold for HAART initiation to 350 cell/µL in all countries also influenced substantially on the recruitment potential of each site. In contrast, the Zambian study site recruits more infants than expected, which partly compensates for the low number in the other study sites. Preliminary results show that the transmission rate of the disease from mother to child is of 1.1% at 12 months, the lowest rate ever reported during breastfeeding. Moreover, the survival rate was 96% among infants who remained uninfected for a period of 50 weeks, which is the highest rate ever reported, corroborating the health benefits of ART prophylactic treatment during breastfeeding. Data analyses for the comparative efficacy and tolerance of the two regimens are expected to be available in September 2013. The final report will be submitted by end of 2013. The major infrastructure upgrades took placed in: • Burkina Faso, two empty rooms split and upgraded for recruitment and follow-up; new house rented for other staff; upgrade of some antenatal clinics as needed. • Zambia, the study site moved to a new 'Paediatric Centre of HIV Excellence' at the University Teaching Hospital in Lusaka in November 2011. • Uganda, a building has been rehabilitated within the local hospital to host the study team. • South Africa, four research rooms rehabilitated for the study within the Cecilia Makewane Hospital. Networking activities: • This project has led to the consolidation of the PROMISE EBF/PEP Research Consortium Group • Several Poster Presentations were made at the 6th EDCTP Forum in Addis Ababa.
Total number of subjects (clinical trials only):	1,500
PhD studies:	Title: Male involvement in the PMTCT programme in Uganda Candidate: Robert Byamugisha (University of Bergen, Norway) Completion date: December 2007 - September 2013
	Title: The social context of prevention of mother-to child transmission of HIV in Mbale District Eastern Uganda Candidate: Joseph Rujumba (University of Bergen, Norway) Completion date: April 2008 - 27 November 2012
	Title: Anthropometry in the PROMSE-PEP study Candidate: Amwe Sunday Aku (University of Bergen, Norway) Completion date: January 2013 - June 2015
MSc study:	Title: Assessment of the PMTCT programme in Ouagadougou and impact of the implementation of PROMISE-PEP on this

	programme Candidate: Hugues Traore (University of Nancy, France) Completion date: September 2011 - 21 September 2012
Other/Sub-studies:	Sub-studies are planned based on the biological sample storage, but no protocol has been discussed and approved by the trial scientific committee yet.
Publications:	1. Tylleskar T. Making it happen, level 2. *Glob Health Action*. 2010, 1;3. doi: 10.3402/gha.v3i0.5370 2. Byamugisha R, Tumwine JK, Semiyaga N, Tylleskar T. Determinants of male involvement in the prevention of mother-to-child transmission of HIV programme in Eastern Uganda: a cross-sectional survey. *Reprod Health*. 2010 Jun 23; 7:12 3. Byamugisha R, Tumwine JK, Ndeezi G, Karamagi CA, Tylleskar T. Attitudes to routine HIV counselling and testing, and knowledge about prevention of mother to child transmission of HIV in eastern Uganda: a cross-sectional survey among antenatal attendees. *J Int AIDS Soc*. 2010;13:52 4. Engebretsen IM, Tylleskar T. HIV, breast feeding and antiretroviral agents. *Norwegian Tidsskr Nor Laegeforen*. 2010 Mar 11;130(5):520-2 5. Byamugisha R, Tylleskar T, Kagawa MN, Onyango S, Karamagi CA, Tumwine JK. Dramatic and sustained increase in HIV-testing rates among antenatal attendees in Eastern Uganda after a policy change from voluntary counselling and testing to routine counselling and testing for HIV: a retrospective analysis of hospital records, 2002-2009. *BMC Health Serv Res*. 2010;10:290 6. Nicolas Nagot, Chipepo Kankasa, Nicolas Meda, Cheryl Nikodem, James K. Tumwine, Charles Karamagi, Halvor Sommerfelt, Dorine Neveu, Thorkild Tylleskar and Philippe Van de Perre for the PROMISE-PEP group. Lopinavir/Ritonavir (LPV/r) versus Lamivudine peri-exposure prophylaxis to prevent HIV-1 transmission by breastfeeding: the PROMISE-PEP trial Protocol - ANRS 12174. *BMC Infectious Diseases* 2012, 12:246.

1.3 HIV/AIDS microbicides capacity building and clinical trials

Table 1-3a: HIV/AIDS microbicides capacity building projects supported by EDCTP

Project Acronym	Capacity Building Goal	Study population	Status
Van de Wijgert	Preparing for Phase III vaginal microbicide trials in Rwanda and Kenya: Preparedness studies, capacity building, and strengthening of medical referral systems	Cohort of high-risk women N= 800	Completed
TVMTU (Hayes)	To strengthen and expand the capacity for phase I, II and III clinical trials of candidate vaginal microbicides in Tanzania and Uganda, in order to facilitate the rapid evaluation of new products that, if shown to be effective, would provide a valuable tool for women to protect themselves against heterosexually-acquired HIV infection.	Cohort of high-risk women N=2000 (1970)	Completed
MRC CTU (McCormack)	MDP301: To build additional infrastructure at the RHRU Orange Farm site, Johannesburg; training on ethics, GCP/GCLP training for collaboarators, personnel, etc.; database training; in order to conduct the clinical trial to evaluate the efficacy and safety of 0.5% and 2% PRO 2000/5 gels for the prevention of vaginally acquired HIV infection compared to placebo in preventing vaginally acquired HIV infection	N=9673	Completed
	TopUp Pilot Study: To determine the feasibility of conducting a microbicide trial of daily vaginal gel and to inform the way adherence should be assessed and to investigate the acceptability and adherence to daily intravaginal universal placebo gel over 12 weeks.	N=270	Completed
	Mozambique Feasibility Study: A Feasibility Study to evaluate the population and study site in the Healthcare centres of Mavalane and Manhiça in preparation for a phase III randomised controlled trial of a vaginal microbicide for the prevention of HIV (FS Microbicides)	N=505	Completed
Mandaliya-Biomarkers – HIV microbicide	Establish baseline ranges of biomarkers related to the vaginal environment in groups of women targeted for microbicide trials in Kenya, Rwanda, and South Africa	Cohort of women N=430	Completed

Table 1-3b: HIV/AIDS microbicides clinical trials supported by EDCTP

Project Acronym	Phase of trial	Product(s)	Manufacturer / Developer	Study population	Status
MDP301/Pro 2000 (McCormack)	III	PRO 2000 vaginal gel / HEC Placebo gel	Indevus Pharmaceuticals (ENDO Pharma)/ CONRAD	Adult women Sexually active, HIV-uninfected women from communities with access to primary health care N=9673	Completed
TopUp Pilot study (McCormack)	Prospective cohort study	Hydroxyethyl cellulose (HEC)	CONRAD	Adult women Women from existing MDP301 trial sites and MDP feasibility study site (min 45 per site over 6 sites). Male partners who agree for interview. N=270	Completed

Both the MDP301 phase III trial and the TopUp Pilot study were conducted under the MRC CTU project coordinated by Dr Sheena McCormack. The studies were supported under a call on capacity building for the conduct of clinical trials of vaginal microbicides against sexual transmission of HIV.

1.3.1 Van de Wijgert

EDCTP Project Coordinator:	Janneke van de Wijgert (University of Amsterdam, Netherlands)
EDCTP Call Title:	Capacity building for the conduct of phase I/II and Phase III trials of vaginal microbicides against sexual transmission of HIV
EDCTP Project Title:	Preparing for Phase III vaginal microbicide trials in Rwanda and Kenya: Preparedness studies, capacity building, and strengthening of medical referral systems
EDCTP Project Code:	CT.2005.33070.001
EDCTP Project Start Date:	10 April 2007
EDCTP Project End Date:	9 April 2011
Collaborators:	• Anne Buvé (Prince Leopold Institute of Tropical Medicine, Belgium) • Patricia Claeys (University of Ghent, Belgium) • Tania Crucitti (Prince Leopold Institute of Tropical Medicine, Belgium) • Eveline Geubbels (Projet Ubuzima, Rwanda) • Peter Gichangi (International Centre for Reproductive Health (ICRH), Kenya) • Vicky Jespers (Prince Leopold Institute of Tropical Medicine, Belgium) • Kishor Mandaliya (International Centre for Reproductive Health (ICRH), Kenya) • Justin Ntirushwa (Projet Ubuzima, Rwanda) • Marcel Reyners (International Centre for Reproductive Health (ICRH), Kenya) • Barbara Suligoi (Istituto Superiore di Sanità (ISS), Italy) • Marleen Temmerman (University of Ghent, Belgium) • Joseph Vyankandondera (Projet Ubuzima, Rwanda)
Study / Trial 1	
Site Principal Investigator(s):	• Janneke van de Wijgert (Netherlands) • Anne Buve (Belgium) • Marleen Temmerman (Belgium) • Kishor Mandalayi (Kenya) • Joseph Vyankandondera (Rwanda)
Trial/Study titles:	• Kigali HIV Incidence Study • Mombasa HIV Incidence Study • Reproductive Health Study • SEARCH study
Goal:	Preparing for phase III vaginal microbicide trials in Rwanda and Kenya. Preparedness studies, strengthening of medical referral systems, and capacity building
Primary Objective(s):	1. Conduct cross-sectional HIV surveys in Kigali and Mombasa using BED capture enzyme immunoassay (BED-CEIA) measures and Avidity Index (AI) testing, to estimate HIV prevalence in potential microbicide trial target populations, and to validate BED/AI testing in African settings 2. Establish cohorts of high-risk women in Kigali and Mombasa, after expanding community outreach into high-risk populations, to measure incidence of HIV, reproductive tract infections (RTIs) and pregnancy, and to evaluate recruitment and retention strategies 3. Improve microbicide trial capacity in Kigali and Mombasa by strengthening the clinical, laboratory, and data management infrastructure, local ethics committees, and reproductive health referral systems and by staff development at the sites as well as the wider research

	communities.
Clinical Trial/Study site(s):	• Projet Ubuzima (PU, Rwanda) • ICRHK (Kenya)
Collaborating site(s):	• AMC-CPCD (Netherlands) • ITM (Belgium) • Gent University (Belgium)
Study design:	Cross-sectional studies; and establishment of cohort of high-risk women
Cofunders:	• AMC-CPCD (Netherlands) • ITM (Belgium) • Gent University (Belgium) • ICRH (Kenya) • Projet Ubuzima (Rwanda) • NACCAP (Netherlands)
Status:	Completed
Results and Outcomes:	Both the HIV prevalence and incidence studies in Kigali and Mombasa have been completed successfully. Additionally, PU has conducted two IPM-sponsored microbicide safety studies and was selected as trial site for the upcoming Phase III microbicide trial of IPM. The PU team has generated seventeen papers thus far using data from the Kigali HIV Incidence Study (KHIS) and the Reproductive Health Study (RHS); nine papers have been published (see publications list) and the others are in various stages of the submission and review process. The ICRH-Kenya team has published two papers. The Rwanda government is currently planning interventions for sex workers, and is leaning heavily on PU's experience. The Rwanda government is furthermore implementing an integrated HPV screening and vaccination program and the KHIS, RHS and SEARCH HPV results will be valuable in monitoring HVP type-specific distribution post-vaccination. The reproductive health clinic established at the Kigali Teaching Hospital is still up and running, increasing treatment options for cervical cancer and infertility. The successful Rwanda-Kenya-Belgium-Netherlands collaboration that was established in this project will continue in the next few years under the EDCTP funded Biomarkers project led by Dr Kishor Mandaliya entitled "Characterisation of novel microbicide safety biomarkers in East and South Africa".
Total number of subjects (cohort/epidemiological/ other studies):	Kigali: • Cross-sectional survey VCT clients: 1,250 • Cross-sectional survey high-risk women: 800 • Prospective cohort study HIV-negative high-risk women: 400 • Reproductive Health Study: 312 infertile women – 254 infertile male partners / 312 fertile women – 189 fertile male partners • SEARCH study: 300 HIV positive women + 100 HIV positive men. Mombasa: • Cross-sectional survey female sex workers: 800 • Cross-sectional survey post-partum women: 800 • Prospective cohort study HIV-negative female sex workers: 400

PhD studies:	Title: The Epidemiological Utility of antibody-based assays for estimating HIV incidence in Kigali, Rwanda Candidate: Sarah Braunstein (Columbia University, USA) Dates: 2005 - September 2009
	Title: The epidemiology of HIV and HPV among high-risk women and steady couples in Kigali, Rwanda Candidate: Nienke Veldhuijzen (University of Amsterdam, the Netherlands) Dates: 2006 -9 June 2011
	Title: Clinical, epidemiological and socio-cultural aspects of infertility in resource-poor settings. Evidence from Rwanda Candidate: Nathalie Dhont (Ghent University, Belgium) Dates: 2007 - 15 April 2011
MSc studies:	Title: Both health and life matter becoming a sex worker: the experiences of women living in Kigali, Rwanda Candidate: Chantal Ingabire (University of Amsterdam, Netherlands) Dates: September 2009 -17 August 2010
	Title: MSc Public Health Candidate: Sanbola Fulgencio (ITM, Belgium [Kenya]) Dates: 2007 – 2008
	Title: MSc Public Health Candidate: Jean Paul Balinda (National University of Rwanda, Rwanda) Dates: January 2011 – December 2011
	Title: MSc Public Health Candidate: Aline Umutoni (National University of Rwanda, Rwanda) Dates: January 2011 – December 2012
BSc studies:	Title: BSc Administration Candidate: Clair Bukuru (Free University Kigali, Rwanda) Dates: January 2011 – December 2013
Other/Sub-studies:	The “Reproductive Health Study” (RHS): an observational study on infertility, and the links between HIV, sexually transmitted infections (STIs), and infertility, in the new CHUK clinic, as part of Dr Dhont’s PhD fellowship. RHS is a case-control study in which the cases are infertile and the controls fertile Rwandan women. Their male partners are also invited to participate. All female study participants are interviewed, counselled, physically examined (including a pelvic examination), and tested for HIV, pregnancy, and a variety of reproductive tract infections (RTI) at study visits. They are screened for cervical precancerous lesions and treated if necessary. Infertile women also receive hysterosalpingography. The SEARCH Kigali: this study aims to evaluate reproductive health outcomes in HIV-positive women who are or are not yet taking HAART treatment. The study is being conducted in the TracPlus HIV clinic in Kigali. Most of the study is funded by the INTERACT program in Kigali (which is funded by the Dutch Government via the NACCAP mechanism and by EuropeAID).
Publications:	1. Veldhuijzen NJ, Braunstein SL, Vyankandondera J, Ingabire C, Ntirushwa J, Kestelyn E, Tuijn C, Wit FW, Umutoni A, Uwineza M, Crucitti T, van de Wijgert JH. The epidemiology of human papillomavirus infection in HIV-positive and HIV-negative high-risk women in Kigali, Rwanda. *BMC Infect Dis.* 2011 Dec 2;11:333. doi: 10.1186/1471-2334-11-333 2. Veldhuijzen NJ, Dhont N, Vyankandondera J, Gasarabwe A,

	Busasa R, Crucitti T, van de Wijgert JH. Prevalence and concordance of HPV, HIV, and HSV-2 in heterosexual couples in Kigali, Rwanda. *Sex Transm Dis*. 2012 Feb;39(2):128-35. doi: 10.1097/OLQ.0b013e3182367c4c.

1.3.2 TVMTU

EDCTP Project Coordinator:	Richard Hayes (London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom)
EDCTP Call Title:	Capacity building for the conduct of phase I/II and phase III trials of vaginal microbicides against sexual transmission of HIV
EDCTP Project Title:	Site preparation and capacity strengthening for trials of vaginal microbicides in Tanzania and Uganda
EDCTP Project Code:	CT.2005.33070.002
EDCTP Project Start Date:	5 May 2007
EDCTP Project End Date:	27 February 2011
Collaborators:	• John Changalucha (National Institute for Medical Research (NIMR), Tanzania) • Anatoli Kamali (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda) • Sheena McCormack (Medical Research Council, UK) • Janneke van de Wijgert (ICRH-International Centre of Reproductive Health, Netherlands)
Study / Trial 1	
Site Principal Investigator(s):	• Richard Hayes (UK) • Saidi Kapiga • Judith Vandepitte • Janneke van de Wijgert (Netherlands) • Sheena McCormack (UK)
Trial/Study title:	1. A feasibility study to assess potential cohort suitability for future microbicide trials in North West Tanzania 2. Studies on the epidemiology and prevention of HIV and other sexually transmitted infections in a cohort of women involved in high risk sexual behaviour in Kampala
Goal:	To strengthen and expand the capacity for phase I, II and III clinical trials of candidate vaginal microbicides in Tanzania and Uganda, in order to facilitate the rapid evaluation of new products that, if shown to be effective, would provide a valuable tool for women to protect themselves against heterosexually-acquired HIV infection.
Primary Objective(s):	1. To strengthen clinical trial resources at research units in Mwanza and Entebbe to provide additional capacity to carry out future microbicide trials to ICH/GCP standards. This will include strengthening of laboratory and clinical resources to support safety studies in phase I, II and III trials, strengthening of ethical review, work to ensure access of trial participants to appropriate HIV care, and staff development and training for Tanzanian and Ugandan scientists in the skills required to carry out clinical trials and to develop future scientific leaders 2. To establish new study cohorts in towns and roadside settlements near Mwanza (Tanzania) and in Kampala (Uganda). In each site, women at high-risk of HIV infection will be recruited to a feasibility study and followed up for 12 months to record retention rates and the prevalence and incidence of HIV, STIs and pregnancy, to develop and test study procedures and to establish effective community liaison.
Secondary Objective(s):	1. Capacity strengthening activities in both study sites to make an optimal contribution to current and future microbicide research in cooperating with the multi-centre collaboration coordinated by the Microbicide Development

	Programme (MDP).
Clinical Trial/Study site(s):	• Mwanza: Geita, Shinyanga, and Kahama (Tanzania) • Entebbe: Kibuye (Uganda)
Collaborating site(s):	• Mwanza Intervention Trials Unit (MITU, Tanzania) • National Institute for Medical Research (NIMR, Tanzania) • Medical Research Council/Uganda Virus Research Institute (MRC/UVRI, Uganda) • Academic Medical Center - Center for Proverty-related Communicable Diseases (AMC-CPCD, Netherlands) • Medical Research Council Clinical Trials Unit (MRC CTU, UK) • London School of Hygiene & Tropical Medicine (LSHTM, UK)
Study design:	Mwanza: prospective cohort study The study will recruit 1,000 women who work in recreational facilities in the northwest region of Tanzania. This is a cohort study with objectives including determining prevalence and incidence of HIV and other sexually transmitted infections; determining retention and pregnancy rates identifying key factors associated with retention; and establishing capacity to conduct a clinical trial. Kampala: A similar protocol was developed to recruit a cohort of 1,000 women involved in high risk sexual behaviour in Kampala, of which 500 HIV-negative women contributed to this study.
Status:	Completed
Results and Outcomes:	**Mwanza:** Enrolled 970 women (Geita 377, Shinyanga 286, Kahama 307). In 2010 follow-up activities continued until August 2010 with mop-up activities continuing until September 2010. During this time the baseline dataset for analysis was being worked on and from September to December 2010 the follow-up dataset was finalised. Preliminary results indicate that among 1,775 women who attended screening at all sites, 21.8% were already HIV positive (prevalence). The HIV incidence rate over 12 month period was 4.1/100 person-years. The pregnancy incidence rate was 30.3/100 person-years. Also observed high prevalence and incidence of other sexually transmitted infections, low condom usage, and substantial self report of risky sexual behaviours. Overall retention rate at 12 months was 84.0%, with some variation among the three sites (80.9% Geita, 87.7% Shinyanga, 84.4% Kahama). The capacity building activities involved establishing systems and routines in order to conduct a clinical trial following ICH/GCP standards. Three dedicated, functioning research clinics which can be used for future research were set up. Numerous staff trainings were conducted in main areas of clinical trial: laboratory, clinical management, data management, ethical review and research ethics, as well as financial and management training and system improvement. Further, project colleagues were supported in pursuing post-graduate learning within the Unit. In terms of overall achievements, the project successfully developed the research infrastructure required for future research activities to test new interventions, including

	microbicide trials. Project staffs were trained to conduct research according to the highest ethical and scientific standards and a system to recruit and follow-up women working in these settings and retain them in active follow-up for a period of up to one year was developed. A strong community liaison system was established to ensure effective communication between researchers, the participants, and other local stakeholders. **Uganda:** Outcomes show it is feasible to enrol and keep a cohort of female sex workers (high attendance rates achieved). Offering general care for them and their children under five is a major asset to motivate them to join and stay in the project. Results indicate: High HIV prevalence (37%) and incidence (16 HIV seroconverters over 374 person years, HIV incidence rate = 4.28 per 100 person years (95% CI 2.62-6.99)) • HIV seroconversion is not associated with any of the investigated behavioural factors in this high risk population, but is strongly associated with STIs (NG, HSV2, high titre active syphilis) • High prevalence of other STIs at baseline (NG 8%, CT 9%, high titer active syphilis 2%, TV 11% and BV48%); only CT and TV infection rates significantly decreased over the one year follow up period • High pregnancy rate: 59 new pregnancies; Pregnancy incidence rate = 16.78 per 100 person year (95% CI 13.00-21.66) • Relatively low uptake of hormonal contraceptives (oral pill 13%, injectable 31%), which did not significantly improve over one year of follow up despite continued promotion of family planning. Overall, the first female high risk cohort has been set up in Uganda providing important information for policy makers and scientists. Further, the project succeeded to build up a well performing new study site that has the capacity to carry out future microbicide trials to ICH/GCP standards. The site has all the facilities to run the research activities and to provide general care and includes office space for social science and administrative staff. The dedicated research team is well trained. An appropriate referral system for HIV care is established. Senior staff have improved their skills required to carry out clinical trials. The project has demonstrated that the study populations of women in both Tanzania and Uganda at high risk of HIV are suitable for the implementation of future trials of microbicides or other HIV prevention tools, with high HIV incidence and high retention rates. The high pregnancy rate and low use of effective contraceptive methods in the study point to the need for more intensive measures in any future trial to promote contraceptive use and reduce the rate of pregnancy. As a result of the studies, the MRC funded a project titled “Intravaginal practices in Tanzania and Uganda: Relationships with the vaginal microenvironment, HIV and other STIs” which was carried out in close collaboration with the EDCTP project.

	This research was to better understand potential risk factors for HIV infection among women. Intravaginal practices (IVP) are common in Africa and have been shown to be associated with HIV in some cross-sectional studies. The only two prospective studies investigating these behaviours in Africa have shown conflicting results. More prospective studies are needed to investigate the effects of IVP on HIV incidence. In addition, the MRC also funded a Population Health Sciences fellowship based on secondary analyses of data from three observational cohorts and the testing and analysis of stored specimens to do in-depth analyses of the correlates of BV and recurrence, description and correlates of BV-specific bacteria, and description of immune responses associated with BV or BV-specific bacteria.
Cofunders:	• UK MRC (UK) • AMC-CPCD/NACCAP (NL) • MITU NIMR (Tanzania) • MRC UVRI (Uganda) • MRC CTU (UK) • LSHTM (UK)
Total number of subjects (cohort/epidemiological/ other studies):	1,970
MSc studies:	Title: Distance Learning MSc programme at LSHTM Candidate: Joseph Masanja (MRC NIMR, Tanzania) Dates: 2009 – 2011
	Title: Distance Learning MSc programme at LSHTM Candidate: Erick Mgina (MRC NIMR, Tanzania) Dates: 2009 - 2011
Other/Sub-studies:	MITU/NIMR: Investigation of intravaginal practices among the study cohort by way of two sub studies – social science diary sub study and the inflammation sub-study.
Publications:	1. Vandepitte J, Bukenya J. Weiss H et al. HIV and Other Sexually Transmitted Infections in a Cohort of Women Involved in High-Risk Sexual Behavior in Kampala, Uganda. *Sexually Transmitted Diseases* 2011 - Volume 38 - Issue 4 - pp 316-323 2. Kamali a, Byomire H, Muwonge C, Bakobaki J, Rutterford C, Okong P, Profy A, Byaruhanga R, Namukwaya S, McComarck S, Grosskurth H, Nunn AJ, Lacey CJ. A randomised placebo-controllled safety and acceptability trial of PRO 2000 vaginal microbicide gel in sexually active women in Uganda. *Sex. Transm. Infcet* 2010;86(3):222 3. Nunn A, McComarck S, Crook AM, Pool R, Rutteford C, Hayes R. Microbicides Development Programme: design of a phase III trial to measure the efficacy of the vaginal microbicide PRO 2000/5 for HIV prevention. *Trials*. 2009;10:99 4. Vandepitte J, Bukenya J, Hughes P, Muller E, Buvé A, Hayes R, Weiss HA, Grosskurth H. Clinical characteristics associated with Mycoplasma genitalium infection among women at high risk of HIV and other STI in Uganda. *Sex Transm Dis.* 2012 Jun;39(6):487-91. doi: 10.1097/OLQ.0b013e31824b1cf3 5. Vandepitte J, Muller E, Bukenya J, Nakubulwa S, Kyakuwa N, Buvé A, Weiss H, Hayes R, Grosskurth H Prevalence and correlates of Mycoplasma genitalium infection among female sex workers in Kampala, Uganda. *J Infect Dis*. 2012 Jan 15;205(2):289-96. doi: 10.1093/infdis/jir733. Epub 2011 Nov 18

	6. Vandepitte J, Weiss HA, Bukenya J, Nakubulwa S, Mayanja Y, Matovu G, Kyakuwa N, Hughes P, Hayes R, Grosskurth H. Alcohol use, mycoplasma genitalium, and other STIs associated With HIV incidence among women at high risk in Kampala, Uganda. *J Acquir Immune Defic Syndr*. 2013 Jan 1;62(1):119-26. doi: 10.1097/QAI.0b013e3182777167.

1.3.3 MRC CTU / MDP 301

EDCTP Project Coordinator:	Sheena McCormack (Medical Research Council, UK)
EDCTP Call Title:	Capacity building for the conduct of phase I/II and phase III trials of vaginal microbicides against sexual transmission of HIV
EDCTP Project Title:	Establishing HIV microbicide clinical trial capacity in Mozambique and expanding an existing site in South Africa
EDCTP Project Code:	CT.2005.33070.003
EDCTP Project Start Date:	3 May 2007
EDCTP Project End Date:	31 December 2010
Collaborators:	• Pedro Alonso (University of Barcelona, Spain) • Sibone Mocumbi (Instituto Nacional de Saúde (INS), Mozambique) • Paula Monjane (Community Develoment Foundation (FDC), Mozambique) • Helen Rees (University of the Witwatersrand, South Africa) • Jonathan Weber (Imperial College London, UK)
Study / Trial 1	**MDP 301**
Site Principal Investigator(s):	Gita Ramjee (RHRU)
Clinical Trial/Study Sponsor:	Medical Research Council (MRC, UK)
Trial/Study title:	An international multi-centre, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of 0.5% and 2% PRO 2000/5 gels for the prevention of vaginally acquired HIV infection Microbicides Development Programme (MDP) 301 (version 2.1)
Goal:	To evaluate the efficacy and safety of 0.5% and 2% PRO 2000/5 gels for the prevention of vaginally acquired HIV infection
Primary Objective(s):	To determine the efficacy and safety of 0.5% and 2% PRO 2000/5 Gel (P) compared to placebo in preventing vaginally acquired HIV infection
Secondary Objective(s):	To collect qualitative data via multi-method data collection strategy, involving triangulation of sexual behaviour data from case record forms (which will be collected in all participants), in-depth interviews and coital diaries
Clinical Trial/Study site(s):	• Reproductive Health & HIV Research Unit [RHRU] Orange Farm (South Africa) • NIMR Mwanza (Tanzania) • UVRI MRC (Uganda) • UTH Mazabuka (Zambia) • HPRU Durban (South Africa) • Africa Centre for Health and Population Studies Kwazulu Natal (South Africa)
Collaborating site(s):	• University of Barcelona (Spain) • RHRU (South Africa) • Imperial College of Science • Technology and Medicine (UK) • LSHTM (UK) • University Teaching Hospital Lusaka (Zambia) • UVRI MRC (Uganda) • NIMR Mwanza (Tanzania) • Africa Centre for Health and Population Studies Kwazulu Natal (South Africa) • South Africa African Medical and Research Foundation (AMREF, South Africa) • St George's Hospital Medical School (UK)

Study design:	Phase III multi-centre double-blinded randomised placebo-controlled trial
Product(s):	• PRO 2000 vaginal gel • HEC Placebo gel
Manufacturer/Developer:	• Indevus Pharmaceuticals (ENDO Pharma) • CONRAD (USA)
Cofunders:	• MRC (UK) • University of Barcelona (Spain) • RHRU (South Africa) • Imperial College of Science • Technology and Medicine (UK) • DfID (UK) • IPM (USA) • Indevus Pharmaceuticals (USA)
Trial Registration number(s):	ISRCTN 64716212
Status:	Completed
Results and Outcomes:	The study screened 15,818 of which 9,385 were enrolled into three arms; 2% PRO 2000 (n=2734), 0.5% PRO 2000 (N=3326) and the Placebo (n=3325). The RHRU centre successfully enrolled 2508 women, which was the largest contribution to the overall accrual of 9385, although lower than the original target agreed for this centre of 2800. The following HIV and STIs rates were found at enrolment: • HIV positive at screening: 26% • Chlamydia trachomatis: 8% • Neisseria gonorrhoea: 3% • Herpes (serology): 60% • Syphilis: 4% • Trichomonas vaginalis: 10% This study provided negative results which revealed that PRO 2000 (0.5 % concentration) was safe as tested but did not provide protection against HIV as compared to a placebo. Albeit negative, MDP301 did demonstrate that microbicides are highly acceptable to women and their partners, and that adherence was high at 92%. The key messages of the trial were: • Women and their partners liked the gel and used it • The study teams made supreme efforts to remind women about their appointments and the women came • Therefore the participants and staff gave PRO 2000 the best chance, and it is disappointing that the gel did not add benefit to the HIV prevention package • The study benefited women: regular exams, STI testing and treatment, risk reduction and supportive counselling Capacity for microbicide trials has been built in Mozambique as demonstrated by the successful completion of the Top Up study in two clinics, Manhica and Maputo. Further, the Mozambique team became a partner in the MDP network, and subsequently MDP has completed the Top Up study in 5 sub-Saharan African countries, and is actively engaged in raising funds (grant applications, advocacy) for the MDP302 trial to assess a single pre-sex dose of tenofovir 1% vaginal gel. Two Mozambican clinical research centres (Manhica and Maputo 1 de Junho) now have capacity for HIV prevention

	trials using unlicensed products. Because staff also have experience of the service sector, including ARV provision for therapy, they are well positioned to inform and support implementation of tenofovir gel should it become licensed in future. Laboratory capacity has been boosted for HIV, HSV-2 and syphilis testing **Challenges and setbacks** With the original funding of this EDCTP application, it was intended for Wits Health Consortium (Pty) Ltd) (the legal entity for Reproductive Health and HIV Research Unit (RHRU), Johannesburg Orange Farm site to expand so that 1,500 MDP301 participants could be enrolled. The RHRU was unable to purchase the plot for expansion within the timeframe of enrolment to the clinical trial. This did not impact on the overall power of the trial as the estimate for HIV incidence (4/100 person years) used in the sample size calculation was conservative and a smaller number than the target 9673 was needed to achieve 90% power. The original plan for Mozambique to become the seventh MDP301 recruiting trial site was ambitious and could only have been achieved with an earlier start to the award. A rogue blogger in Zambia caused reputational damage to MDP, which proved difficult to contain and ultimately led to a halt in microbicide research being approved in Zambia, notably VOICE which NIH had to withdraw. In February 2010 a meeting was organised by Dr Chisembele with MoH and Zambian researchers to set the record straight, and finally after several months approval for the Top Up study was obtained and the successful implementation of this in Zambia demonstrated that microbicide research was still viable. This was an important achievement for the MDP network with their partner CONRAD.
PhD study:	Title: PhD Social Anthropology Candidate: Jonathan Stadler (University of Pretoria, South Africa) Dates:2007-2011
MSc studies:	Title: MSc Epidemiology & Biostatistics Candidate: Jocelyn Moyes (University of the Witwatersrand (Wits), South Africa) Dates: 2009 – 2010
	Title: MSc Epidemiology & Biostatistics Candidate: Ananta Nanoo (University of the Witwatersrand (Wits), South Africa) Dates: 2009- 2010
	Title: MSc Epidemiology & Biostatistics Candidate: Sibongile Walaza (University of the Witwatersrand (Wits), South Africa) Dates: 2009-2010
	Title: Masters in Public Health Candidate: Mdu Mntambo Dates: 2008-2010
Study/Trial 2	**TopUp pilot study**
Site Principal Investigator(s):	• Robert Pool (Spain) • Khátia Munguambe (Mozambique)
Clinical Trial/Study Sponsor:	MRC UK
Trial/Study title:	A study to determine the feasibility of conducting a microbicide

	trial of daily vaginal gel and to inform the way adherence should be assessed: Top-Up Study
Goal:	To determine the feasibility of conducting a microbicide trial of daily vaginal gel and to inform the way adherence should be assessed
Primary Objective(s):	To investigate the acceptability and adherence to daily intravaginal universal placebo gel over 12 weeks.
Secondary Objective(s):	1. To inform the way adherence is assessed in a future clinical trial by comparing the following outcomes across three methods for monitoring adherence: – Adherence to daily use of gel – Consistency of the adherence measure – Retention of participants.
Clinical Trial/Study site(s):	Manhica and Maputo (CISM, Mozambique)
Collaborating site(s):	• CRESIB (Spain) • LSHTM (UK) • MRC CTU (UK) • MDP Programme Muzabuka (Zambia) • CISM (Mozambique) • HPRU MRC, Durban (South Africa) • NIMR (Tanzania) • UVRI MRC (Uganda)
Study design:	A multi-centre open-label randomised study, in which participants are randomised to one of three methods for monitoring adherence.
Product(s):	Hydroxyethyl cellulose (HEC) [placebo vaginal gel]
Manufacturer/Developer:	CONRAD (USA)
Cofunders:	• MRC (UK) • CRESIB (Spain)
Trial Registration number(s):	PACTR 2010060002133418
Status:	Completed
Results and Outcomes:	The trial started June 2010 and finished follow up November 2010. There were 75 (40 in Manhica, 35 in Maputo) women screened of which 63 (31 in Manhica, 32 in Maputo) were enrolled. With respect to the daily placebo gel, women also found this acceptable, and reported adherence was higher than expected at 79% overall, albeit lower than reported in MDP301 when women were instructed to use a single dose of gel prior to sex. The TopUp study provided the first experience of microbicides in Mozambique and an opportunity to widely disseminate the CAPRISA 004 results raising hope for the future.
Publications:	1. Montgomery CM, Lees S, Stadler J, Morar NS, Ssali A, Mwanza B, Mntambo M, Phillip J, Watts C and Pool R. The role of partnership dynamics in determining the acceptability of condoms and microbicides. *AIDS Care*. 2008 Jul;20(6):733-40. 2. Sayles JN, Macphail CL, Newman PA and Cunningham WE. Future HIV Vaccine Acceptability Among Young Adults in South Africa. *Health Educ Behav*. 2009 Jun 9.
Study/Trial 3	**Mozambique feasibility study**
Site Principal Investigator(s):	Sibone Mocumbi (Mozambique)
Clinical Trial/Study Sponsor:	MRC (UK)
Trial/Study title:	A Feasibility Study to evaluate the population and study site in the Healthcare centres of Mavalane and Manhiça in preparation for a phase III randomised controlled trial of a vaginal microbicide for the prevention of HIV (FS Microbicides)

Goal:	A Feasibility Study to evaluate the population and study site in the Healthcare centres of Mavalane and Manhiça in preparation for a phase III randomised controlled trial of a vaginal microbicide for the prevention of HIV (FS Microbicides)
Primary Objective(s):	The primary objectives are to measure the prevalence and incidence of HIV and HSV2 infections, the prevalence of NG and CT; the maximal achievable rate of recruitment and retention in follow-up at 40 weeks, the frequency of vaginal intercourse and other sexual practices and the impact of safe sex counselling on the rate of condom use.
Secondary Objective(s):	1. Assess the level of HIV/AIDS awareness in the general community and within the target population 2. Assess the willingness of women to participate in a microbicide trial
Clinical Trial/Study site(s):	Manhiça Health Research Centre (Mozambique)
Collaborating site(s):	• MRC (UK) • Foundation for the Development of the Community (FDC) • Mavalane General Hospital (HGM, Mozambique) • Manhiça Health Research Centre (CISM, Mozambique) • Centre for International Health Hospital Clinic Barcelona (Spain)
Study design:	Prospective cohort study
Cofunders:	• MRC (UK) • University of Barcelona (Spain) • Reproductive Health and Research Unit • University of the Witwatersrand (South Africa)
Status:	Completed
Results and Outcomes:	Incidence in the Feasibility confirmed that women enrolled through these two clinics were a suitable target population, and indeed was higher than expected at 5/100 person years (95% CI 3.1-8.0). Recruitment was slow in Mozambique at both centres, but particularly in Manhica where there was no reimbursement according to the centre policy. In contrast to participation in the Demographic survey, women have to give up considerable time to take part in the Feasibility and Top Up studies. However, through a variety of community mobilisation exercises, this challenge was overcome, and the target number of 500 was exceeded. There were also challenges due to the language differences in the provision of training to the larger body of staff, and for data entry staff, for who English was not familiar. The database was programmed to enable staff to 'flip' between English and Portuguese screens to overcome this, and CRFs were developed with both languages on the same page. The skills gained in recruiting the 505 women, achieving 71% (361) retention according to the combined database increasing to 79% if the 35 pregnancies and 13 seroconvertors are subtracted from the denominator, and regular genital examinations and laboratory testing of adults have been a valuable addition to the existing capacity in Manhica which was predominantly demographic surveillance and vaccine trials in infants. Moreover, the Feasibility Study provided the first incidence data in Mozambique, complementing the national ante-natal data and raising awareness amongst government and policy makers that HIV is a major threat to health in Mozambique.

Publications:	1. McCormack S et al. PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double blind, parallel-group trial. The Lancet.2010;376(9749):1329-37 2. Kamali a, Byomire H, Muwonge C, Bakobaki J, Rutterford C, Okong P, Profy A, Byaruhanga R, Namukwaya S, McCormack S, Grosskurth H, Nunn AJ, Lacey CJ. A randomised placebo-controllled safety and acceptability trial of PRO 2000 vaginal microbicide gel in sexually active women in Uganda. Sex. Transm. Infcet 2010;86(3):222-6 3. Nunn A, McCormack S, Crook AM, Pool R, Rutteford C, Hayes R. Microbicides Development Programme: design of a phase III trial to measure the efficacy of the vaginal microbicide PRO 2000/5 for HIV prevention. Trials.2009;10:99 4. Nunn A, McCormack S, Crook AM, Pool R, Rutteford C, Hayes R. Microbicides Development Programme: design of a phase III trial to measure the efficacy of the vaginal microbicide PRO 2000/5 for HIV prevention. Trials.2009;10:99

1.3.4 Mandaliya-Biomarkers HIV Mic

EDCTP Project Coordinator:	Kishor Mandaliya (International Centre for Reproductive Health (ICRH), Kenya)
EDCTP Call Title:	Call for the support of clinical studies, capacity building and networking for HIV/AIDS microbicides
EDCTP Project Title:	Characterisation of novel microbicide safety biomarkers in East and South Africa
EDCTP Project Code:	IP.2007.33070.001
EDCTP Project Start Date:	6 April 2009
EDCTP Project End Date:	4 January 2013
Collaborators:	• Saade Ahmed Abdallah (International Centre for Reproductive Health (ICRH), Kenya) • Bazil Baltazar (National Institute for Medical Research, Mwanza Centre, Tanzania) • Anne Buvé (Prince Leopold Institute of Tropical Medicine, Belgium) • John Changalucha (National Institute for Medical Research (NIMR), Tanzania) • Joseph Chilongani (National Institute for Medical Research (NIMR), Tanzania) • Tania Crucitti (Prince Leopold Institute of Tropical Medicine, Belgium) • Gustavo Doncel (CONRAD, USA) Eechoutte, Mario Van (University of Ghent, Belgium) • Suzanna Francis (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Richard Hayes (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Betsy Herold (Albert Einstein College of Medicine, USA) • Rene Hol (Pantarhei Devices/Pantarhei Biosciences, Netherlands)
Site Principal Investigator(s):	• Mary Mwaura (Kenya) • Sinead Delany-Moretlwe (South Africa) • Gilles Ndayisaba (Rwanda)
Clinical Trial/Study Sponsor:	International Centre for Reproductive Health Kenya (ICRHK)
Trial/Study title:	Characterisation of novel microbicide safety biomarkers in East and South Africa
Goal:	Establish baseline ranges of biomarkers related to the vaginal environment in groups of women targeted for microbicide trials in Kenya, Rwanda, and South Africa
Primary Objective(s):	1. Characterise the vaginal environment with respect to: the vaginal microbial flora; biomarkers of epithelial integrity; and soluble and cellular biomarkers of immune activation, including target cells for HIV, in HIV-negative adult women in good health at low risk for HIV 2. Determine the presence of laboratory-confirmed genital infections, clinical signs of epithelial disruption and inflammation, and any other clinical observations and self-reported symptoms in these women 3. Compare the vaginal environment as described in primary objective 1 in HIV-negative adult women in good health at low risk for HIV with and without bacterial vaginosis.
Secondary Objective(s):	1. Assess the primary parameters (primary objective 1 and 2 in: HIV-negative adolescents; HIV-negative adult women using traditional vaginal practices; HIV-negative adult women at high-risk for HIV; and asymptomatic HIV-

	positive adult women 2. Describe the association between presence/quantity of biomarkers of immune activation/epithelial integrity, visible signs of inflammation/epithelial integrity during pelvic exam/colposcopy, and self-reported symptoms indicative of genital irritation/inflammation
Tertiary Objective(s):	1. Compare cervicovaginal lavage (CVL) by self-sampling with the Pantarhei® screener with CVL clinician sampling and determine the feasibility of these methods 2. Compare the results of this study in African populations with results available in the literature (mostly from non-African populations), with future results of a similar vaginal characterization study by the CONRAD in the US population (study protocol A04-097), and results of similar study in a European population (EMPRO)
Clinical Trial/Study site(s):	• ICRHK (Kenya) • Reproductive Health Research Unit (South Africa) • Project Ubuzima (Rwanda)
Collaborating site(s):	• MITU/NIMR (Tanzania) • AMC-CPCD (Netherlands) • ITM (Belgium) • LSHTM • MRC CTU (UK)
Study design:	Multi-country prospective cohort study in 430 women
Product(s):	Pantarhei® screener
Manufacturer/Developer:	Pantarhei Devices
Cofunders:	• Medical Research Council (MRC, UK) • ITM (Belgium) • Ghent University (Belgium) • Pantarhei Devices (Netherlands) – to be confirmed
Trial Registration:	DOH-27-0910-3223
Status:	Completed
Results and Outcomes:	In Kenya, Rwanda and South Africa, the study characterised the vaginal environment in 430 women at seven time points over eight months, and in Tanzania, the study characterised the vaginal environment in 100 women at 12 time points over 28 days. The vaginal microbiome was assessed by Amsel and Nugent criteria; quantitative PCR (qPCR) of 6 Lactobacillus species known to be related to vaginal health and five bacterial vaginosis associated species; a phylogenetic DNA micro-array containing probes for 251 vaginal bacteria; and Lactobacillus culture. Principal component analysis (PCA) of the qPCR data showed that a score based on levels of L. crispatus, L. jensenii, L. vaginalis, A. vaginae and G. vaginalis can be used as an indicator of a healthy or unhealthy vaginal microbiome. The L jensenii and L. crispatus species will be used in in vitro models to test new molecules for safety in the future. Preliminary micro-array data indicate the presence of 4 to 6 vaginal microbiome clusters dominated by either individual Lactobacillus species or by different levels and combinations of anaerobic bacteria. Both the PCA scores and the clusters correlated well with bacterial vaginosis status by Nugent score but not with bacterial vaginosis status by Amsel criteria (which are currently used for diagnosis in clinical settings). Furthermore, soluble biomarkers of inflammation and immune responses, such as cytokines, chemokines and antimicrobial peptides, were measured. The study identified several biomarkers that correlated with a healthy or unhealthy vaginal

	microbiome.
MSc studies:	Title: MSc in Public Health and Developing Countries Candidate: Bazil Baltazar (MITU-NIMR, Tanzania) Dates: 10 January 2011 – 1 November 2011
	Title: Master in Public Health Candidate: Marie Michelle Umulisa (PU) Dates: August 2011-November 2013
	Title: Master in Business Administration Candidate: Irene Kibara (ICRHK) Dates: 8 May 2010 – 29 June 2013
	Title: Master in Nutrition Candidate: Faith Musyoka (ICRHK) Dates:11 October 2009 – 9 September 2011
	Title: Master in Health Informatics Candidate: Masesa Clemens (MITU/NIMR) Dates: 2011-2012
PhD studies:	Title: Defining the immune vaginal environment and factors affecting HIV transmission Candidate: Jordan Kyongo (Kenya) Dates: July 2010-July 2013
	Title: Epidemiology and medical statistics & Advanced course in epidemiology analysis Candidate: Mary Mwaura (Kenya) (site PI) Dates: 21 June- 9 July 2010 & 5 – 16 September 2011
BSc studies:	Title: BSc in Biomedical Laboratory Sciences Candidate: Lambert Mwambarangwe (PU) Dates: January 2012-June 2014
	Title: BSc Information Systems Candidate: Mary Thiongo (ICRHK) Dates: January 2011- June 2014
Other/Sub-studies:	The 'inflammation Sub-study' in Tanzania was an intensive longitudinal sub-study of 100 women carried out to look at rapid changes in the vaginal environment over one menstrual cycle. This study was also designed to capture changes in the vaginal environment due to previously documented highly prevalent vaginal practices. Participants in the Inflammation Sub-study were followed up every two to three days for 28 days (12 visits) with retention of 97%. Experiences gained from the in the Inflammation Sub-study were shared to allow for optimisation of study procedures, laboratory testing and analysis for the Biomarker Study in Rwanda, Kenya, and South Africa. The data from the Inflammation Sub-study will be analysed in conjunction with the Biomarkers study data.
Publications:	1. Ndayisaba G, Verwijs M, van Eeckhoudt S, Gasarabwe A, Hardy L, Borgdorff H, Kestelyn E, Jespers V, van de Wijgert J. Feasibility and Acceptability of a Novel Cervicovaginal Lavage Self-Sampling Device among Women in Kigali, Rwanda. Sexually Transmitted Diseases.2013;40:7

1.4 HIV/AIDS vaccines capacity building

Table 1-4: HIV/AIDS vaccines capacity building studies supported by EDCTP

Project Acronym (Coordinator)	Study design	Product(s)	Manufacturer / Developer	Study population	Status
SASHA – HPV vaccine study (Bekker)	Prospective cohort study	GARDASIL	Merck Sharp & Dohme (Pty) Ltd	Adolescents (12-17), up to 200 participants at 6 sites N = 835	Completed
SASHA – Community attitudes (Bekker)	prospective cohort	Not applicable	Not applicable	Adolescents (12-17) with parents/guardians and stakeholders. Focus group: N=59 (of 6-10 participants each)	Completed
HIVTAB (Kapiga)	Prospective cohort study	Not applicable	Not applicable	Tanzania: Adult women (18-44) working in bars, guest houses, hotels or other recreational facilities Burkina Faso: Adult women (18-44) sex workers Moshi and Mwanza: 150 prevalent HIV+ve and 70 incident HIV+ve; Burkina Faso: 150 prevalent HIV=ve and 30 incident HIV+ve	Completed
TaMoVac-01 – Feasibility of neonatal vaccination in Maputo (Bakari)	Not applicable	Not applicable	Not applicable	200 mothers in Maputo	Completed
CHIVTUM (Kaleebu)	Qualitative study and prospective cohort study	Not applicable	Not applicable	Malawi: Adult men and women (over 20) and “mature minors” (13-15) who are married or have children working in fishing communities, HIV sero-negative, N = 743 Uganda: Adult men and women (13-49) working in fishing communities, HIV sero-negative, N = 1000	Completed
AfrEVacc – Beira study	Cross-sectional	Not applicable	Not applicable	Adult, women at risk of sexual acquisition of HIV, cross sectional survey,	Completed

(Weber)	study and prospective coshort study			N = 1000; prospective cohort, N= 400; BED false negative, N= 400.	
AfrEVacc – Manhica EVAS (Weber)	Longitudinal F/U	Not applicable	Not applicable	Adults N=70	Completed
AfrEVacc - Manhica Epidemiology (Weber)	Cross sectional study	Not applicable	Not applicable	Adults N= 696	Completed
AfrEVacc – Africa Centre (Weber)	Longitudinal F/U	Not applicable	Not applicable	Adult men N= 200	Completed
AfrEVacc – Joburg (Weber)	RCT	Not applicable	Not applicable	Adult, men sero-negative N= 150	Completed

1.4.1 SASHA

EDCTP Project Coordinator:	Linda-Gail Bekker (University of Cape Town, South Africa)
EDCTP Call Title:	Capacity building in preparation for the conduct of preventive HIV vaccine trials (EDCTP/Gates Foundation/MS joint call)
EDCTP Project Title:	Feasibility of and Capacity Building for Adolescent HIV Vaccine Trials in South Africa
EDCTP Project Code:	CT.2006.33111.004
EDCTP Project Start Date:	21 January 2008
EDCTP Project End Date:	29 July 2011
Collaborators:	• Thola Bennie (Centre for the AIDS Programme of Research in South Africa (CAPRISA), South Africa) • Jimmy Chandia (Walter Sisulu University, South Africa) • Gavin Churchyward (Aurum Institute for Health Research, South Africa) • François Dabis (Victor Segalen Bordeaux 2 University, France) • Matthias Egger (University of Bern, Switzerland) • Glenda Gray (Perinatal HIV Research Unit (PHRU), South Africa) • Mary Latka (Klerksdorp Research Site (KOSH), South Africa) • Surita Roux (Desmond Tutu HIV Centre (DTHF), South Africa) • Maphoshane Nchabeleng (University of Limpopo, South Africa) • Catherine Slack (HIV AIDS Vaccines Ethics Group (HAVEG), South Africa) • Leslie Swartz (Stellenbosch University, South Africa) • Eftyhia Vardas (University of the Witwatersrand, South Africa)
Study / Trial 1	**HPV study**
Site Principal Investigator(s):	• Surita Roux (South Africa) • Glenda Gray (South Africa) • Mary Latka (South Africa) • Thola Bennie (South Africa) • Maphoshane Nchabeleng (South Africa) • Jimmy Chandia (South Africa)
Clinical Trial/Study Sponsor:	Merck Sharp & Dohme (Pty) Ltd
Trial/study title	Preparing for adolescent HIV vaccine trials in South Africa: A multi-centre study to evaluate acceptability of the HPV vaccine in adolescents
Goal:	Identify potential challenges to the inclusion of adolescents in HIV prevention trials by the use of the HPV vaccine as a proxy.
Primary Objective(s):	1. To assess recruitment and retention of adolescents in a vaccine trial for STDs and identify characteristics associated with recruitment, vaccine update and retention.
Secondary Objective(s):	1. Document prevalence and incidence of HIV, other STDs, pregnancies and circumcisions in adolescents 2. Compare methods of assessing understanding of vaccine assent 3. Determine the impact of vaccine receipt on sexual risk behaviour 4. Explore adolescent perceptions of risk and sexual behaviour 5. Investigate adolescent and parental attitudes towards informed consent norms

	6. Assess social harms and benefits associated with adolescent participation in an HIV-related study 7. Document adolescent health service needs.
Clinical Trial/Study site(s):	South African AIDS Vaccine Initiative (SAAVI) sites: • Desmond Tutu HIV Centre (DTHC, South Africa) • Perinatal HIV Research Unit (PHRU, South Africa) • Klerksdorp Research Site (KOSH, South Africa) • Centre for the AIDS Programme of Research in South Africa (CAPRISA), (South Africa) • Medunsa Clinical Research Unit (MeCRU, South Africa) • Walter Sisulu University (South Africa)
Collaborating site(s):	• University of KwaZulu Natal & HIV AIDS Vaccines Ethics Group (HAVEG, South Africa) • Institute of Public Health, Epidemiology & Development (France)
Study design:	Prospective cohort study with self-selecting intervention and control groups
Number of subjects:	Establishing a cohort group, adolescents (12-17), 200 participants are expected to be enrolled at each site
Product(s):	GARDASIL
Manufacturer/ Developer:	Merck Sharp & Dohme (Pty) Ltd
Cofunders:	• Bill & Melinda Gates Foundation (USA) • ANRS (France) • Irish Aid (Ireland) • NACCAP (Netherlands) • SIDA (Sweden) • SNSF (Switzerland) • MRC (UK), Merck Sharp & Dohme (Pty) Ltd (South Africa)
Status:	Completed
Results and Outcomes:	In all, 834 adolescents were enrolled in the HPV vaccine study and 816 of these chose to be vaccinated. Overall, 85% of those screened were enrolled. Out of the total number of recruits, 502 were female and 698 were under 16 years. The SASHA group speculated that it is possible that the requirements for adolescents over 16 years to be sexually active and have their parents' consent to participation may have acted as a barrier to this age group. They concluded that further analysis is needed to establish this. The main reasons for adolescent study participation were: • 'I think the HPV vaccine will help to protect me against HIV infection' • 'I want to learn more about STDs' • 'I want to receive free and regular HIV tests' While the study did not achieve the enrolment numbers they planned for the HPV study, this was not necessary in order to address the primary aim. It has, however, increased the SASHA consortium's awareness of the challenges of recruiting an adolescent cohort and has prepared them for further adolescent studies. SASHA collected incidence data for South African adolescents in HIV, pregnancy, STI and circumcision. In addition, the study gathered key social science data such as sexual risk behaviour, family communication, substance use, social support, and attitudes. By simulating a vaccine trial with a STI related licensed vaccine; the consortium got a handle on the ethical and legal aspects and the interaction with ethics committees.

	Consequently, the study developed ethical-legal guidelines and resources for the conduct of adolescent clinical trials in South Africa, which are currently open source and are rapidly becoming a nationally- and internationally-used reference.
Study/Trial 2	**Community attitudes study**
Site Principal Investigator(s):	• Surita Roux (South Africa) • Glenda Gray (South Africa) • Mary Latka (South Africa) • Thola Bennie (South Africa) • Maphoshane Nchabeleng (South Africa) • Jimmy Chandia (South Africa)
Trial/study title	Community Attitudes towards Adolescent Involvement in HIV Vaccine Trials: a Multi-Centre South African Study
Goal:	Prepare for adolescent involvement in HIV vaccine trials by exploring attitudes towards participation, informed consent, provision of adolescent prevention services and experiences of communication about HIV and sexual issues.
Primary Objective(s):	1. Assess adolescent attitudes towards participation in HIV vaccine trials 2. Explore adolescent attitudes towards disclosure of sexual activity to parent/guardian 3. Assess adolescent attitudes towards appropriate age of informed consent and disclosure of trial information to parent/guardian 4. Assess adolescent, parent/guardian and stakeholder views on the potential impact of HIV vaccine trial participation on sexual disinhibition 5. Examine adolescent, parent/guardian and stakeholder views on requirements for adolescent health services 6. Examine adolescent, parent/guardian and stakeholder attitudes toward male circumcision as a risk reduction method 7. Explore adolescent, parent/guardian and stakeholder perceptions of sexual risk behaviour in adolescents 8. Explore adolescent and parent/guardian attitudes toward and experiences of communicating about HIV and sexual issues.
Clinical Trial/Study site(s):	South African AIDS Vaccine Initiative (SAAVI) sites: Desmond Tutu HIV Centre (DTHC), Nyanga district, Cape Town (South Africa) Perinatal HIV Research Unit (PHRU), Johannesburg (South Africa) Klerksdorp Research Site (KOSH), Matlosana district (South Africa) Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban (South Africa) Medunsa Clinical Research Unit (MeCRU), Limpopo (South Africa) Walter Sisulu University, Mthantha (South Africa)
Collaborating site(s):	• University of KwaZulu Natal & HIV AIDS Vaccines Ethics Group (HAVEG, South Africa) • Institute of Public Health, Epidemiology & Development (France)
Study design:	Cross-sectional qualitative focus group study, with separate focus groups with parents/guardians, adolescents and stakeholders. Three focus groups will be conducted with adolescents, two with parent/guardians and two stakeholders.
Number of subjects:	Adolescents (12-17) from Nyanga Cape Town and their parents/guardians will be recruited.

	For the focus group, approximately 7-9 focus groups will be conducted at each site, with approximately 8 participants in each group (N= ca. 72 per site).
Cofunders:	• Bill & Melinda Gates Foundation (USA) • ANRS (France) • Irish Aid (Ireland) • NACCAP (Netherlands) • SIDA (Sweden) • SNSF (Switzerland) • MRC (UK)
Status:	Completed
Results and Outcomes:	In all, 141 Adolescents, 104 Parents, and 117 Stakeholders took part in the focus group. Preliminary data has shown that communication about sex is difficult between parents and adolescents; there are many misunderstandings and miscommunications between the two; and 3) third parties such as relatives seem to facilitate communication between parents and adolescents.
Total number of subjects (cohort/epidemiological/ other studies):	N = 1178
MPH study:	Title: Predictors of sexual risk behaviour in adolescents Candidate: Agnes Rowan (University of Cape Town, South Africa) Supervisor: Landon Myer (University of Cape Town, South Africa/Columbia University Mailman School of Public Health, USA) Dates: November 2009-June 2012
Publications:	1. Ellen, J., Wallace, M., Sawe, F.K. and Fisher, K. (2010). Community Engagement and Investment in Biomedical HIV Prevention Research for Youth: Rationale, Challenges and Approaches. *JAIDS*, 54 Suppl 1, S7-S11 2. Selected ethical-legal norms in child and adolescent HIV prevention research in south africa: consent, confidentiality and mandatory reporting

1.4.2 HIVTAB

EDCTP Project Coordinator:	Saidi Kapiga (London School of Hygiene and Tropical Medicine (LSHTM), UK)
EDCTP Call Title:	Capacity building in preparation for the conduct of preventive HIV vaccine trials (EDCTP/Bill & Melinda Gates Foundation/MS joint call)
EDCTP Project Title:	Capacity development and strengthening in preparation for HIV vaccine trials in Tanzania and Burkina Faso
EDCTP Project Code:	CT.2006.33111.013
EDCTP Project Start Date:	12 March 2008
EDCTP Project End Date:	11 September 2011
Collaborators:	• Dorothy Bray (ImmunoClin Ltd, UK) • John Changalucha (National Institute for Medical Research, Tanzania) • Mario Clerici (University of Milano–Bicocca, Italy) • Richard Hayes (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Philipe Mayaud (LSHTM, UK) • Nicolas Meda (UFR-SDS University of Ouagadougou & Centre Muraz/site ANRS, Burkina Faso) • Nicolas Nagot (University of Montpellier 1, France) • Balthazar Nyombi (Kilimanjaro Christian Medical Centre (KCMC), Tanzania) • Philippe Van de Perre (Montpellier University Hospital Centre (CHU), France) • John Shao (KCMC, Tanzania) • Deborah Watson-Jones (LSHTM, UK) • Basia Zaba (LSHTM, UK)
Study / Trial 1	**Capacity development and strengthening in preparation for HIV vaccine trials in Tanzania and Burkina Faso**
Site Principal Investigator(s):	• Saidi Kapiga (Tanzania) • John Changalucha (Tanzania) • Balthazar Nyombi (Tanzania) • Nicolas Meda (Burkina Faso)
Trial/Study title:	Capacity development and strengthening in preparation for HIV vaccine trials in Tanzania and Burkina Faso
Goal:	Establish and strengthen research capacity and conduct specific research studies in preparation for clinical trials to assess the protective efficacy of HIV candidate vaccines
Primary Objective(s):	1. To develop and maintain study cohorts among high-risk populations and characterise potential study populations for future phase II/III HIV vaccine trials in Burkina Faso and Tanzania 2. To characterise HIV-1 viral isolates and assess factors associated with viral genotypes among identified target populations 3. To determine immunological and genetic factors that could confer resistance to HIV infections and/or slow down disease progression 4. To establish and strengthen research capacity in the study sites in Burkina Faso and Tanzania and promote South-South and North-South collaboration.
Clinical Trial/Study site(s):	Mwanza Intervention Trials Unit (Tanzania) Kilimanjaro Christian Medical Centre and National Institute for Medical Research (Tanzania) UFR-SDS University of Ouagadougou & Centre Muraz/Site ANRS du Burkina Faso (Burkina Faso)

Collaborating site(s):	• London School of Hygiene & Tropical Medicine and ImmunoClin (UK) • University of Montpellier (France) • Milano University Medical School (Italy)
Study design:	Prospective cohort study **Tanzania:** • Develop and maintain study cohorts with adult women (18-44 years) working in bars, guest houses, hotels or other food and recreational facilities for future phase II/III vaccine trials: – Dataset from well-characterised high-risk populations from previous studies in Mwanza and Moshi will be analysed; – Additional data collected from ongoing cohort study to assess feasibility of future microbicides trials in Geita town, Mwanza region and Kahama and Shinyanga towns in Shinyanga region; – Establish new cohort from Moshi town and surrounding areas. • To characterise HIV-1 viral isolates and assess factors associated with viral genotypes among identified target populations (adult women, 18-44 years, HIV-sero-positive): – From ongoing microbicide feasibility study in Geita, Kahama and Shinyanga; – From serological surveillance system established in Kisesa to assess the feasibility of a future phase III intervention trial, including trials of new microbicide candidates; – From new cohort of high-risk women working in Moshi Town. • To determine immunological and genetic factors that could confer resistance to HIV infection and/or slow down disease progression: – Mainly adult men and women from the Kisesa serological surveillance system in Mwanza. Looking for: – Long-term non-progessors (LTNP); – Exposed sero-negative (repeated exposure, remain HIV-uninfected, ESN); – HIV-sero-positives infected after short exposure; – HIV-sero-positives who are rapid progressors. **Burkina Faso** • Develop and maintain study cohorts with adult women (18-44 years) sex workers and characterise potential study populations for phase II/III vaccine trials: – Datasets from well-characterised Yerelon Cohort population from previous studies in Bobo-Dioulasso will be analysed – Additional datasets to be collected from: – Ongoing Yerelon Cohort assessing the effectiveness of HIV prevention and care interventions among high-risk professional and part-time female sex workers – New cohort of HIV-sero-negative high-risk women (18-25 years) working as professional or part-time sex workers to be established in Ouagadougou. • To characterise HIV-1 viral isolates and assess factors associated with viral genotypes among identified target

	populations (adult women, 18-44 years, HIV-sero-positive): – HIV-sero-positive women from Yerelon cohort; – Newly diagnosed HIV-sero-positive women (18-25 years) from Ouagadougou. • To determine immunological and genetic factors that could confer resistance to HIV infection and/or slow down disease progression: – From Yerelon study, will classify subjects as: HIV-sero-positive before HAART; HIV-sero-postitive taking HAART with undetectable plasma load; LTNP; ESN.
Number of subjects:	Moshi and Mwanza: 150 prevalent HIV+ve and 70 incident HIV+ve; Burkina Faso: 150 prevalent HIV+ve and 30 incident HIV+ve
Cofunders:	• Bill & Melinda Gates Foundation (USA) • ANRS & IRD (France) • Irish Aid (Ireland) • Milano University Medical School (Italy) • MRC (UK) • LSHTM & ImmunoClin (UK)
Status:	Completed
Results and Outcomes	Apart from maintaining existing cohorts in Tanzania (Moshi and Mwanza) and Burkina Faso (Yerelon), two new cohorts of high-risk women were established in Moshi, Tanzania (n = 650) and Ouagadougou, Burkina Faso (n = 300). In Tanzania, the prevalence of HIV in the general population decreased from 7.1% (95% CI 6.7-7.7%) in 2001 to 5.6% in 2009 (USAID, 2010). Although the incidence of HIV among women in the general population is unknown, it is likely to be much less than what was observed in the Moshi cohort [14.7% prevalence, with an incidence of 3.7/100 person-years (PYs) (95% CI: 2.2-6.2)]. This suggests that the Moshi cohort is suitable for future HIV vaccine trials. The prevalence (8%) as well as the incidence (0%) of HIV infection in the Ouagadougou cohort was not significantly different from that in the general population. This low incidence of HIV among these high-risk women may be related to the declining HIV prevalence in the general population in Burkina Faso and the positive impact of the risk reduction intervention delivered to the cohort by the study team. Therefore, this cohort is not suitable for future trials to test the efficacy of HIV candidate vaccines. HIV viral isolates in the two Tanzanian sites were characterised. Preliminary results show that there are multiple HIV subtypes in Moshi and Mwanza, with a substantial proportion of recombinant viruses. The study team suggest that Tanzania may be ideal place to study characteristics of different viruses and also in testing new vaccines against a range of viruses. When looking at the immunological and genetic factors that could confer resistance to HIV infection, the study team reported preliminary results that pointed to the importance of genes located in chromosome 22 in the resistance and control of HIV infection. However, they suggest that there might be differences between Caucasians and Africans.

	Collaborators in Montpellier developed an ELISpot assay which, combined with PCR techniques, examined factors associated with HIV-1 replication and immune responses. Using these techniques, samples from 52 HIV-1 infected women (33 of these were on HAART) from Burkina Faso were investigated. Results suggest that HIV-1 sexual transmission may occur independently of the HIV-1-infected cells located in the genital secretions but mostly involve HIV-1 secreted by cells from genital lymph nodes. This work reinforced the hypothesis that the genital compartment is separated from the vascular system in terms of HIV-1 reservoir and viral replication. In terms of capacity building, the following was achieved in this grant: • Strengthened the Mwanza Intervention Trials Unit (MITU) with administrative and technical support from LSHTM • Developed laboratory capacity to separate plasma and process PBMC, HIV viral genotyping (a genetic sequencer was purchased with the help of this grant and staff received related training), monitoring safety of future trial participants • Developed a GCP-compliant data management system in Tanzanian and Burkina Faso sites. This capacity will be helpful for future vaccine trials • Provided a range of training courses (short courses, ethics training, GCP, GCLP, data management, ethics review) within the consortium and beyond.
MSc study:	Title: Impact of Co-infection of herpes simplex virus (HSV-1) with human immunodeficiency virus (HIV-1) on HIV-1 Progression and HAART efficacy among High Risk women in Burkina Faso Candidate: Isodore Traore (University of Montpellier, France) Dates: September2010-September 2011
Publications:	Pending

1.4.3 TaMoVac-01

EDCTP Project Coordinator:	Muhammad Bakari (Muhimbili University College of Health Sciences, Tanzania)
EDCTP Call Title:	Capacity building in preparation for the conduct of preventive HIV vaccine trials (EDCTP/Gates Foundation/MS joint call)
EDCTP Project Title:	HIV vaccine trial capacity building in Tanzania and Mozambique by continued exploration of optimal DNA priming and MVA boosting strategies
EDCTP Project Code:	CT.2006.33111.007
EDCTP Project Start Date:	4 March 2008
EDCTP Project End Date:	31 December 2012
Collaborators:	• Sören Andersson (Örebro University Hospital, Sweden) • Gunnel Biberfeld (Karolinska Institute, Sweden) • Pontus Blomberg (Karolinska Institute, Sweden) • Frances Gotch (Imperial College, UK) • Bo Hejdeman (Karolinksa Institute, Sweden) • Michael Hoelscher (LMU, Germany) • Nesrina Imami (Imperial College, UK) • Ilesh Jani (Instituto Nacional de Saúde (INS), Mozambique) • Andrew Kitua (WHO/Special Programme for Research and Training in Tropical Diseases, Switzerland) • Leonard Maboko (MMRP, Tanzania) • Sayoki Mfinanga (NIMR, Tanzania) • Fred Mhalu (University of Dar es Salaam, Tanzania) • Charlotta Nilsson (Karolinska Institute, Sweden) • Nafissa Osman (Instituto Nacional de Saúde (INS), Mozambique) • Eric Sandstrom (Karolinska Institute, Sweden) • Willy Urassa (MUHAS, Tanzania) • Paula Vaz (Instituto Nacional de Saúde (INS), Mozambique) • Jonathan Weber (Imperial College, UK)
Study / Trial 1	**Feasibility of Neonatal Vaccination in Maputo**
Site Principal Investigator(s):	Paula Vaz (Mozambique)
Trial/Study title:	Feasibility study for HIV Vaccination Among Children in Maputo City, Mozambique
Goal:	Assess factors involved in the acceptability of a new-born/infant HIV vaccine trial
Primary Objective(s):	Evaluate knowledge and attitudes from mothers and families concerning HIV and vaccines
Clinical Trial/Study site(s):	Maputo Central Hospital, Maputo, Mozambique Polana Caniço Health Centre, Maputo, Mozambique
Study design:	Pilot study including qualitative and quantitative methods
Number of subjects:	200
Status:	Completed
Results and Outcomes:	A pilot acceptability study has been undertaken in November 2011 aimed at preparing IEC interventions for an eventual HIV vaccine trial in neonates. The study took place in Maputo Central Hospital (MCH) and Polana Caniço Health Center (PCHC) whereby 36 respondents filled in questionnaires and underwent interviews. These were women and men sitting in waiting rooms at the maternity and pediatric services, as well as husbands and

	mothers-in-law. After analysis of the data, it has been learnt that husbands and mothers-in-law must be reached by direct invitation to facilitate neonatal vaccination. The conditions have therefore been set to actually implement the study.
Publications:	

1.4.4 CHIVTUM

EDCTP Project Coordinator:	Pontiano Kaleebu (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda)
EDCTP Call Title:	Capacity building in preparation for the conduct of preventive HIV vaccine trials (EDCTP/Gates Foundation/MS joint call)
EDCTP Project Title:	Strengthening of long-term clinical and laboratory research capacity, cohort development, and collection of epidemiological and social science baseline data in Uganda and Malawi to prepare for future HIV vaccine trials
EDCTP Project Code:	CT.2006.33111.011
EDCTP Project Start Date:	20 November 2007
EDCTP Project End Date:	31 December 2011
Collaborators:	• Frans van den Boom (International AIDS Vaccine Initiative (IAVI), Netherlands) • Jill Gilmour (IAVI, Netherlands) • Simon Heck (The WorldFish Center, Malawi) • Robert Heyderman (Malawi-Liverpool-Wellcome Trust Research Programme, Malawi) • David Lalloo (University of Liverpool, UK) • Victor Mwapasa (Malawi-Liverpool-Wellcome Trust Research Programme, Malawi)
Study / Trial 1	**Malawi epidemiological and social science study**
Site Principal Investigator(s):	Victor Mwapasa (Malawi)
Trial/Study title:	HIV and STI in fishing communities in Mangochi: assessing the transmission dynamics and feasibility of conducting future preventative trials
Goal:	Assess the transmission dynamics and feasibility of conducting preventative trials on HIV and STI in fishing communities in Mangochi
Primary Objective(s):	1. Determine and understand the transmission dynamics of STIs, including HIV in fishing communities 2. Determine factors promoting or preventing the participation of these communities in research studies and/or health interventions.
Secondary Objective(s):	1. Explore how different constituents comprising fishing communities shape vulnerability/resilience to STIs including HIV 2. Assess the acceptability of the fishing communities to participate in preventative health research and health interventions, including HIV testing and counselling, anti-retroviral treatment and vaccine trials 3. Determine the prevalence, incidence and type of HIV and STIs in the fishing communities in Mangochi 4. Determine the retention rates of clients from a fishing community participating in a prospective cohort study and explore factors promoting and preventing study participation.
Clinical Trial/Study site(s):	Fishing communities of Namaso, Nkope, Malembo, Msaka, Mvunguti and Chirombo villages. Sample processing and short-term sample storage was done at Mangochi District Hospital. Lab analyses were conducted at the Mangochi District Hospital and Malawi-Liverpool-Wellcome Trust Clinical Research Programme in Blantyre.
Collaborating site(s):	• Division of Community Health and Research on Equity and Access to Community Health (REACH) Trust (Malawi) • Liverpool School of Tropical Medicine (UK) • World Fish Centre (Malawi)

Study design:	**Participatory and qualitative studies:** The participatory methods will provide contextual information from the perspective of the participants on the characteristics of the fishing community: livelihoods, mobility, health service provision and access to health services and views on health research. Whereas the quantitative research (interviews, focus groups and participant observation) will collect information on: how social norms and behaviours can affect vulnerability/resilience to HIV and other STIs, levels of mobility and sexual interactions amongst different groups, health seeking behaviour, level of utilisation of HIV and AIDS services and views and experiences of health research. **Prospective cohort study:** Participants will be screened for HIV and those that are HIV-negative will be followed up at 3 month intervals to obtain data on the incidence of HIV, STIs and pregnancy.
Number of subjects:	**Participatory and qualitative study:** Study population: Adult men and women (over 20yrs) and young women (under 20) from fishing communities of Namaso, Nkope, Malembo, Msaka, Mvunguti and Chirombo villages. N= 382 **Prospective cohort:** Study population: Men and women (15-49yrs) as well as young people classified as “mature minors” (13-15yrs) who are married or have children residing in the fishing communities of Namaso, Nkope, Malembo, Msaka, Mvunguti and Chirombo villages for at least 3 months prior to recruitment and who plan to stay for the following two years, either continuously or intermittently. N=1000
Cofunders:	• Bill & Melinda Gates Foundation (USA) • IAVI (Netherlands) • Irish Aid (Ireland) • Malawi-Liverpool-Wellcome Trust Clinical Research Programme and WorldFish Center (Malawi) • SIDA (Sweden) • UVRI (Uganda) • MRC (UK) • WHO African AIDS Vaccine Programme (Switzerland) • Canadian HIV Trials Network (Canada) • Foundation for the National Institutes of Health (USA)
Status:	Completed
Results and Outcomes	The rates of HIV in the Malawi study population were found to be similar to the general population. This was suspected to be because a significant proportion of study participants (around 44%) knew of their HIV negative status prior to enrolment. Consequently, there was evidence of changes in sexual networking, whereby study participants who tested negative preferred to engage in sexual relations amongst each other. However, high-risk behaviours were identified during the course of the study such as unprotected sex or coerced sex. In addition, high rates of herpes simplex, a surrogate marker of high-risk behaviour, were found, suggesting that this population is still at higher risk for HIV infection than the general population.

Study / Trial 2	**Uganda epidemiological, social science and virology study**
Site Principal Investigator(s):	Pontiano Kaleebu (Uganda)
Trial/Study title:	Prospective cohort study to determine HIV incidence, risk factors for HIV infection, describe the molecular epidemiology and the social and behavioural characteristics in fishing populations of three lakeshore districts in Uganda in preparation for future HIV prevention research
Goal:	Determine HIV incidence, risk factors for HIV infection, describe social and behavioural characteristics and the molecular epidemiology in fishing populations in three lakeshore districts in Uganda in preparation for future HIV prevention research
Primary Objective(s):	Main cohort study: 1. Identify HIV-negative high-risk populations within fishing communities in which preliminary prevalence data indicate that new high incidence cohorts could be established 2. Recruit, counsel and test for HIV infection, determine retention rates and factors that impact loss to follow-up 3. Assess risk factors and understand social and behavioural characteristics for HIV infection in these populations.
Secondary Objective(s):	Virology sub-study: 1. Characterise the circulating HIV-1 subtypes in order to better understand the molecular epidemiology in these populations. Social and behavioural context sub-study: 1. Describe the broader social and behavioural characteristics of the general population in the fishing communities 2. Assess the acceptability to people living in fishing communities of preventative health research and health interventions, including HIV testing and counselling, anti-retroviral therapy and vaccine trials.
Clinical Trial/Study site(s):	Fishing villages in the Wakiso, Masaka and Mukono districts (Uganda)
Collaborating site(s):	• MRC/UVRI Uganda Research Unit on AIDS and UVRI-IAVI HIV Vaccine Program (Uganda)
Study design:	The **main cohort study** is a prospective cohort study, through which a demographic, medical history questionnaire will be administered and volunteers requested to provide blood samples at each visit. The **virology sub-study** will have blood collected to be used to describe the molecular epidemiology of circulating virues. The **social and behavioural context sub-study** will utilise qualitative and quantitative methods, including mapping, semi-structured and in-depth interviews.
Number of subjects:	Main cohort: Male and female volunteers (13-49yrs), n= 1000; Virology sub-study: sub sample (N= 300) of HIV+ volunteers who screen out due to HIV sero-positivity at enrolment from the main cohort and those who enrol and seroconvert during follow-up Social and behavioural context: N= 50
Cofunders:	• Bill & Melinda Gates Foundation (USA) • IAVI (Netherlands) • Irish Aid (Ireland) • Malawi-Liverpool-Wellcome Trust Clinical Research Programme (Malawi)

	• WorldFish Center (Malawi) • SIDA (Sweden) • UVRI (Uganda) • MRC (UK) • WHO African AIDS Vaccine Programme (Switzerland) • Canadian HIV Trials Network (Canada) • Foundation for the National Institutes of Health (USA)
Status:	Completed
Results and Outcomes	A new high-risk population has been identified in Uganda which has great potential for inclusion in future HIV prevention research. This is particularly important given recent findings related to ARV based prevention which may eventually make it difficult to work with cohorts that are comprised solely of discordant couples. Findings from the cohort include an HIV and active syphilis prevalence of about 28.8% and 4.3% respectively while HIV incidence has been reported as 4.9%. High-risk behaviours have been reported in this population as well. When the study team identified HIV-1 sub-types from study participants, the major subtypes identified were subtypes A and D but with a high percentage (21%) of unique recombinant viruses. Results also pointed to a high degree of sexual mixing in this population. Significant capacity has been developed both in Uganda and Malawi: • Increased capacity for immunological research at the UVRI with expanded laboratory space, new equipment enabling new assays to be conducted, training and experience in new techniques such as microarray assay • Increased data management capacity at the UVRI • Clinical teams have built upon their capacity to develop new protocols and studies • Integration of social science into the development of new protocols and studies • Increased capacity in Malawi for the conduct of population based studies, community mobilization and social science • Developed guidelines and training manuals for Community Advisory Groups which have are being used in other research sites • Development of a new south-south network which has been mutually beneficial and which has led to new projects and collaborations • Increased capacity at UVRI for south–south training in laboratory techniques and in GCP and GCLP • Increased the ability of the MLW laboratory to progress towards GCLP compliance • Increased capacity at UVRI and MLW in managing large international grants and in managing activities within a consortium.
Total number of subjects (cohort/epidemiological/ other studies):	N = 1000
Other/Sub-studies (including cohorts/ epidemiology studies):	Yellow Fever DNA Microarray Assay study A study to compare DNA microarray immune response profiles in healthy Ugandan adults against DNA microarray immune response profiles in South and North American populations using the Yellow Fever vaccine. This study will investigate a novel method

	of tracking the immune response to vaccines, the microarray assay, which tracks the expression of genes involved in the innate and adaptive immune responses. Schistosomiasis sub study (among those from main cohort) – pending approval of protocol To determine the odds of worm infections diagnosed using stool samples obtained on three consecutive days for intestinal Schistosoma mansoni infection in stool (Kato Katz method) and using blood samples for Mansonella perstans (Knott's method) in 50 incident cases of HIV infection compared to 150 HIV-negative controls from the fisher folk main cohort. To compare prevalence of S. mansoni infection status from stored blood samples at enrolment and at 18 months among 50 HIV incident cases and 150 HIV-negative controls from the fisher folk cohort. To investigate innate and adaptive immune responses among HIV incident cases with worm infections.
PhD study:	Title: Immunological interactions between helminths and HIV infection Candidate: Andrew Obuku Akii (Makerere University, Uganda) Dates: December 2010-March 2015
MSc studies:	Title: Monoclonal B-cell lymphocytosis in a rural Ugandan population Candidate: Aloysious Ssemaganda (Makerere University, Uganda) Dates: August 2010-January 2013
	Title: Hepatitis C Virus Genotypes and Confirmation of Antibody Reactive Serum Samples from East Africa using Reverse Transcriptase and Real Time PCR Candidate: Paul Kato Kitandwe (Makerere University, Uganda) Dates: November 2007-December 2011
Publications:	1. Asiki, G, Mpendo, J, Abaasa, A, Agaba, C, Nanvubya, A, Nielsen, L, Seeley, J, Kaleebu, P, Grosskurth, H, Kamali, A. (2011) HIV and syphilis prevalence and associated risk factors among fishing communities of Lake Victoria, Uganda. *Sex Transm Infect*. Oct;87 (6):511-5, doi: 10.1136/sti.2010.046805 2. Seeley, J, Nakiyingi-Miiro, J, Kamali, A, Mpendo, J, Asiki, G, Abaasa, A, De Bont, J, Nielsen, L, Kaleebu, P; CHIVTUM Study Team. (2012) High HIV incidence and socio-behavioural risk patterns in fishing communities on the shores of Lake Victoria, Uganda*. Sex Transm Dis*., Jun;39(6):433-9. doi: 10.1097/OLQ.0b013e318251555d 3. Nazziwa, J, Njai, HF, Ndembi, N, Birungi, J, Lyagoba, F, Gershim, A, Nakiyingi-Miiro, J, Nielsen, L, Mpendo, J, Nanvubya, A, Debont, J, Grosskurth, H, Kamali, A, Seeley, J, Kaleebu, P, The Chivtum Study Team. (2013) Transmission clusters and evidence of HIV-1 transmitted drug resistance among recently infected antiretroviral naïve individuals from Ugandan fishing communities of Lake Victoria. *AIDS Res Human Retroviruses*, May;29(5):788-95, doi: 10.1089/AID.2012.0123 4. MacPherson, EE, Sadalaki, J, Njoloma, M, Nyongopa, V, Nkhwazi, L, Mwapasa, V, Lalloo, DG, Desmond, N, Seeley, J, Theobald, S. (2012) Transactional sex and HIV: understanding the gendered structural drivers of HIV in

	fishing communities in southern Malawi. *J Int AIDS Soc*. 15 Suppl 1:1-9, doi: 10.7448/IAS.15.2.17364.

1.4.5 AfrEVacc

EDCTP Project Coordinator:	Jonathan Weber (Imperial College London, UK)
EDCTP Call Title:	Capacity building in preparation for the conduct of preventive HIV vaccine trials (EDCTP/Gates Foundation/MS joint call)
EDCTP Project Title:	African-European HIV Vaccine Development Network (AfrEVacc)
EDCTP Project Code:	CT.2006.33111.001
EDCTP Project Start Date:	28 March 2008
EDCTP Project End Date:	27 May 2012
Collaborators:	• Sinead Delany-Moretlwe (University of the Witwatersrand, South Africa) • Josefo Joao Ferro (Faculty of Medicine of Universidade Católica de Moçambique, Mozambique) • Michael Hoelscher (Ludwig-Maximilians Universitat Munchen, Germany) • John Imrie (Africa Centre for Health and Population Studies, South Africa) • Joep Lange (Academic Medical Center, University of Amsterdam, Netherlands) • Leonard Maboko (Mbeya Medical Research Programme, Tanzania) • Sheena McCormack (MRC, UK) • Khátia Munguambe (Manhiça Health Research Center (Mozambique) • Denise Naniche (Hospital Clinic of Barcelona, Spain) • Marie Louise Newell (Africa Centre for Health and Population Studies, South Africa) • Giuseppe Pantaleo (Centre Hospitalier Universitaire Vaudois-CHUV/EuroVacc Foundation, Switzerland) • Robert Pool (Manhiça Health Research Center, Mozambique) • Gita Ramjee (MRC, South Africa) • Helen Rees (University of the Witwatersrand, South Africa) • Wendy Stevens (University of the Witwatersrand, South Africa) • James Tartaglia (Sanofi-Aventis, France) • Kylie Glasgow (Imperial Colege, UK) • Roger Tatoud (Imperial College, UK) • Hans Wolf (University of Regensburg, Germany) • Arlinda Zango (Faculty of Medicine of Universidade Católica de Moçambique (UCM), Mozambique)
Study / Trial 1	**Beira Study**
Site Principal Investigator(s):	Josefo João Ferro and Arlinda Zango (Mozambique)
Trial/Study title:	Combined cross-sectional and prospective cohort study for measurement of HIV incidence in Beira, Mozambique
Goal:	To estimate HIV incidence within a population at higher risk of HIV in Beira, Mozambique, in preparation for future HIV prevention interventions and intervention studies.
Primary Objective(s):	1. To estimate HIV incidence in women at higher risk in Beira using a cross-sectional methodology, and to compare the results with HIV incidence measured prospectively within a subgroup of initially HIV-negative women from the cross-sectional phase 2. To determine the percentage of known HIV infected individuals (12+ months) that are identified by BED assay as having a recent infection 3. To assess UCM's ability to recruit and retain a cohort of approximately 400 women at higher risk for one year.

Secondary Objective(s):	1. To validate the BED assay for use in HIV incidence estimation in the Beira context; 2. To estimate HIV incidence in sub-groups, for example according to HIV risk behaviours/groups and age, and to describe demographic characteristics and HIV risk behaviours of participants; 3. To determine prevalence and incidence of pregnancy and herpes simplex virus type 2 (HSV-2) in the prospective cohort study.
Clinical Trial/Study site(s):	Universidade Católica de Moçambique, Beira (Mozambique)
Collaborating site(s):	• FHI, Research Triangle Park (USA) • Amsterdam Medical Center (The Netherlands)
Study design:	Cross-sectional survey and prospective cohort study: • Cross-sectional survey: HIV-positive individuals in survey will be tested for recent HIV infection using the Calypte HIV-1 BED Incidence EIA (BED), which estimates the rate of new HIV infections in populations by determining what population of HIV-positive individuals were infected within six months of sample collection • Prospective cohort study: HIV-negative individuals in the cross-sectional survey will be invited to join a prospective cohort study for 12 months. At each monthly visit, cohort participants will be tested for HIV antibodies. Those who seroconvert during the 12 month follow-up period will have previous samples tested by HIV-1 RNA PCR to pinpoint the time of seroconversion • BED false recent calibration: HIV-positive individuals who have been infected for 12+ months and who have not used antiretroviral treatment will be eligible for the BED False Recent phase. The BED assay will be used to determine the percentage of established HIV infections that are falsely labelled as 'recent'. This will be done by Western blot and HIV-1 RNA PCR.
Number of subjects:	• Cross-sectional survey: approximately 1000 women at risk of sexual acquisition of HIV infection • Prospective cohort: approximately 400 women who tested HIV-negative in the cross-sectional survey and who volunteer for follow-up • BED false recent calibration: Approximately 400 HIV-positive individuals (men and women) known to be HIV infected for 12+ months from study start and who have not used ART.
Cofunders:	• Bill & Melinda Gates Foundation (US) • US Agency for International Development (USAID)
Status	Completed
Results and Outcomes	The team successfully established a new clinical research centre at the UCM in Beira – the CIDI. During the course of the study, very high incidence rates of HIV were found in this region. CIDI enrolled 1,020 women with unknown HIV status (18-35 years of age) in a cross-sectional HIV seroprevalence survey, of whom 406 HIV-negative women were subsequently followed in a prospective cohort study for 12 months. In addition, CIDI enrolled 408 women and men with chronic HIV infection (also 18-35 years of age) in the BED false recent survey. This was to determine the local false recent rate to be used for HIV incidence estimation using the BED assay. Data collection will be completed in September 2012.

	Interim analysis results are as follows: The HIV prevalence in the cross-sectional survey was 33% (95% CI 30.1-35.9). The prospective HIV incidence rate was 8.4 per 100 women-years (95% CI: 5.2–12.8), with 21 seroconversions over 251.2 women-years (WY) of follow-up. Prospective HIV incidence was higher among the 18–24 age group (9.1 per 100 WY; 95% CI: 5.4–14.3) than the 25–35 age group (5.7 per 100 WY; 95% CI: 1.2–16.7). The estimated cross-sectional incidence using the BED assay results was 9.6% (95% CI: 6.5–12.6) using the Hargrove correction formula and the locally derived false recent rate of 1.8%.
Study/Trial 2	**Manhica Feasibility Studies (EVAS) (capacity building)**
Site Principal Investigator(s):	• Khátia Munguambe (Mozambique) • Denise Naniche (Spain)
Trial/Study title:	A feasibility and acceptability study in preparation for phase I/II clinical trials of an HIV vaccine candidate in Manhiça, Mozambique (EVAS)
Goal:	To contribute to capacity development and provide information needed for the conduction of HIV vaccine trials in Mozambique
Primary Objective(s):	1. To assess the feasibility and acceptability of future HIV vaccine trials in Manhiça by determining: – The recruitment: screening: enrolment ratio by assessing the proportion of individuals contacted that enrol in the cohort study – The proportion of those enrolled, who complete the follow-up period – Acceptability of study procedures (including blood draws) – Willingness to participate in future HIV vaccine trials – Potential barriers and motivators to participation of adults in vaccine interventions. 2. To develop the Manhiça site in specific procedures related to future HIV vaccine trials by assessing: – The ability to retrieve viable peripheral blood lymphocytes after separation and freezing measured by cell viability – The suitability of different data collection tools to retrieve information regarding risk behaviour – The ability to engage and liaise with the community through the introduction of locally acceptable community advisory boards.
Clinical Trial/Study site(s):	Centro de Investigaçao em Saúde da Manhiça (CISM), Manhiça district (Mozambique)
Collaborating site(s):	National Health Laboratory Services, Johannesburg (South Africa)
Study design:	The feasibility study will adopt the design of a follow-up study, in which a cohort will be clinically followed-up for a period of 16 weeks after enrolment. The study population comprises mostly of subsistence farmers and employees of the sugar estates from Maragra and Xinavane. Manhiça is a source of migrant labour to South Africa, which contributes to a highly mobile population. A significant number of people, mainly women, are engaged in vending activities in markets and on the streets.
Number of subjects:	N = 70 participants (50 men and 20 women)
Cofunders:	• Bill & Melinda Gates Foundation (US) • Fondo de Investigaciones Sanitarias (FIS) – Instituto de Salud Carlos III, (Spain)

Status:	Completed
Results and Outcomes:	A total of 77 potential participants were screened, of which 71 (20 women and 51 men) were enrolled. Nine participants (7 men and 2 women) withdrew from the study and a 12 week follow up was completed for 62 participants. During clinical follow-up, participants underwent two rounds of in-depth interviews (IDI) to assess their level of acceptability and barriers/ enabling factors to enrol and remain under follow-up. Preliminary results suggest that participants had a good understanding of the purpose of the study. Vaccination in adults was mostly welcome as it would help prevent and/or decrease the spread of HIV and other diseases such as malaria. Adults would be willing to participate in HIV vaccine trials as it would provide them with guaranteed treatment and clinical care. The barriers to trial participation included fear of injections, blood draws and being the first recipient of an investigational vaccine.
Study / Trial 3	**Manhiça Epidemiology Study (capacity building)**
Site Principal Investigator(s):	• Khátia Munguambe (Mozambique) • Denise Naniche (Spain)
Trial/Study title:	Establishment of community prevalence of human immunodeficiency virus infection and sexual transmitted infections in Manhiça district, southern Mozambique
Goal:	To develop capacity and provide epidemiological information needed for conducting HIV prevention trials including HIV vaccine trials in Mozambique.
Primary Objective(s):	1. To establish age-specific community HIV prevalence in adults aged 18-27, 28-37 and 38-47 years old 2. To estimate the incidence of HIV in the community in adults aged 18-47 3. To determine community prevalence of STI relevant to HIV transmission.
Clinical Trial/Study site(s):	Centro de Investigaçao em Saúde da Manhiça (CISM), Manhiça district (Mozambique)
Study design:	Two cross sectional studies with an interval of two years between both studies. The HIV incidence will be estimated by randomly recruiting subjects the demographic surveillance (DSS) in Manhica. The prevalence of selected STI will be determined by a single cross sectional study. The first cross-sectional study will determine age-specific HIV prevalence in the Manhiça region. The second cross sectional study will determine age-specific HIV incidence and prevalence of selected STIs in Manhiça community
Number of subjects:	First cross sectional study: Adults (men and women), 18-47, part of the Manhiça DSS area, 232 subjects per age group (18-27; 28-37 and 38-47), N= 696 Second cross sectional study: Adults (men and women), 18-47yrs, part of the Manhiça DSS area, 232 subjects per age group (18-27yrs; 28-37yrs and 38-47yrs), N= 696.
Cofunders:	• Fondo de Investigaciones Sanitarias (FIS) – Instituto de Salud Carlos III (Spain)
Status:	Completed
Results and Outcomes:	HIV community prevalence in the Manhiça Demographic surveillance district was established in two cross sectional surveys conducted in 2010 and 2012.

	In the first cross sectional study, a total of 839 individuals (ages 18-47yrs) were invited to participate in the study, of which 722 were recruited. HIV community prevalence was 39.9% [95% CI 35.9–43.8%]. HIV prevalence increased with increasing age group and was higher among women than men in all age groups. In the second cross sectional study, a total of 896 individuals (aged 18 -50yrs) were invited to participate, of which 792 were recruited. Preliminary results indicate an overall HIV prevalence 37.4%. Prevalence was found to be higher in women in all three age groups. It was also found that HIV prevalence increases with age, in both men and women, with incidence estimated to peak in the 20-24 age group. The team found two limiting factors in the study: participant absence during home visits and the exclusion of teenagers from the study. The high HIV prevalence in this region suggests that the epidemic is in a mature stable phase. Incidence rates estimation combining data from the 2010 and 2012 prevalence studies is on-going. It is noteworthy that a smartphone-based method of data collection was introduced for this epidemiological study.
Study/Trial 4	**Africa Centre Impilo Yamadoda - Men's Health Study (capacity building)**
Site Principal Investigator(s):	John Imrie (South Africa)
Trial/Study title:	An exploratory study of issues in men's health and mechanisms to increase participation and retention of male participants in community-based HIV prevention research
Goal:	To complete an exploratory programme of research investigating key health issues for rural Zulu men and strategies for recruiting and retaining young men in community-based HIV prevention research; making these findings available to the AfrEVacc Network Partners and in so doing, defining a range of generalisable strategies for increasing men's involvement in bio-medical and behavioural HIV prevention research in southern African settings.
Primary Objective(s):	1. Explore and map the main general health and HIV concerns of rural Zulu men with specific attention to issues of understanding of the role and relevance of research and particularly, HIV prevention research 2. Describe, define and test different community engagement strategies to establish a cohort of young Zulu men from the local area surrounding of the Africa Centre (i.e. Hlabisa Health Sub-district) and test mechanisms to increase participants ongoing engagement with the Africa Centre and its programme of behavioural and biomedical HIV prevention research 3. Test the feasibility and efficacy of different follow-up/retention strategies, including monetary and non-monetary incentive packages for use with men recruited to an individually randomised study involving multiple observations and collection of bio-specimens 4. Develop guidance and recommendations for other AfrEVacc Network Partners regarding recruitment and retention for community samples of young adult men for

	biomedical, vaccine and behavioural HIV prevention trials from rural and peri-urban settings in South Africa.
Clinical Trial/Study site(s):	Africa Centre for Health and Population Studies, Hlabisa Health sub-district of the Umkhanyakude District in northern KwaZulu-Natal (South Africa)
Study design:	Adult men (18-29 years) will be recruited. Baseline and follow-up procedures will involve collection of behavioural, attitudinal and knowledge measures as well as a blood specimen for unnamed HIV testing. Collection of baseline data will occur at the time the participant completes the study's informed consent procedures. All men who agree to participate and complete enrolment will be invited to attend the intervention which will involve a half-day men's health fair. The men's health fairs will follow a format similar to the Africa Centre's regular road shows. They will consist of a programme of information and interactive sessions relating to key health issues identified by men in the earlier phases of the study and HIV prevention. On completing the intervention men will be randomised in equal numbers to one of two follow-up methods (face-to-face interview vs self-report using cellular telephone interviews) and then randomised a second time to provision of a follow-up blood specimen at the end of the study either at a clinic (venepuncture) or in the community (dried blood spots). Two follow-ups are planned, one at 3-months post enrolment (for behavioural measures only), and a second at 6-months post-enrolment (for behavioural measures and bio-specimens). Biological specimens will be tested for HIV to estimate prevalence in the cohort at baseline and after 6 months follow-up. Participants will not be informed of their results but rapid named HIV testing will be available either on-site (clinics) or via on-call VCT counsellor from the Africa Centre, as per routine service.
Number of subjects:	N = 200 men aged 18 -29 years from the community settings in the Hlabisa Health sub-district.
Cofunders:	• Bill & Melinda Gates Foundation (USA)
Status:	Completed
Results and Outcomes:	Community-based organisations (including social, sports, religious and employers) are efficient mechanisms to locate and engage men, and if properly supported can become genuine research partners with study investigators. Men are enthusiastic about participating in research that they feel takes account of their needs as men and that targets them specifically. Some of men's enthusiasm can be explained by social capital and cultural beliefs about the importance of contributing to community well-being and supporting activities that are perceived to bring wider benefits to their communities. The team reported that of the 223 male study participants, 7 (3.1%) reported sex with a male partner at least once in the survey rounds, which lasted 3 months. When looking at the study participants' responses, the team emphasised why detailed research into the sexual attitudes, lifestyles and experiences of young men - those that identify themselves as men who have sex with men (MSM) and men who do not, but report same-sex behaviour - is needed to ensure an appropriate sexual health, HIV prevention and treatment and care response.

	It is the team's hypothesis that MSM is underreported in these communities and propose making MSM a research priority in South Africa. The team also examined whether follow-up modality, biospeciment collection method or the form of participant reimbursement made a difference in improving male participant retention. They found that modality of follow-up interview and method of biospecimen collection method had no impact on follow-up completions. However, microcapillary collection facilitated men being followed-up in their communities, which was operationally easier, reduced staff-costs and the time between questionnaire completion and specimen delivery. Where possible, the team recommends that investigators consider varying, or allowing participants to choose the type of reimbursement they receive.
Study / Trial 5	**Johannesburg study (capacity building)**
Site Principal Investigator(s):	Sinead Delaney-Moretlwe (South Africa)
Trial/Study title:	Acceptability and Feasibility of Recruiting Men into a future Phase III HIV Vaccine Trial: Experiences of Surrogate Vaccination Use (AfrEVacc 001)
Goal:	The overall purpose of this study is to determine the feasibility and acceptability of recruiting HIV sero-negative men into a future phase III HIV vaccine trial.
Primary Objective(s):	1. To assess the feasibility of recruiting a cohort of HIV negative men and following them up at regular intervals for a period of 12 months
Secondary Objective(s):	1. To assess whether men's social, and/or economic background and cultural context influences their participation in the study 2. To assess the acceptability of study procedures 3. To determine prevalence of HIV, STIs and non-specific symptoms such as fever, headache and cough and to estimate HIV incidence in this population 4. To evaluate and identify the most appropriate methods of methods of data collection in this population of men.
Clinical Trial/Study site(s):	RHRU Research & Training Centre in Hillbrow, Johannesburg (South Africa)
Study design:	Randomised controlled trial. A surrogate vaccine (hepatitis B vaccine ENGERIX-B or equivalent generic) will compared to no vaccination among healthy HIV sero-negative male (over 18yrs) volunteers to assess the feasibility and acceptability of enrolling HIV seronegative men into a future phase III HIV vaccine trial
Number of subjects:	N = 150
Product(s):	Heberbiovac HB
Manufacturer/Developer:	GSK Biologicals (UK)
Status:	Completed
Results and Outcomes:	The group implemented a randomised controlled trial to assess the feasibility and acceptability of enrolling HIV seronegative men into a future Phase III HIV vaccine trial in inner city Johannesburg. Hepatitis B vaccine was used as a surrogate for a future HIV vaccine, and randomised men received either immediate vaccination or vaccination deferred until the end of the 12-month follow up period. In all, 287 men were screened for the study and 150 were enrolled. In total, 93% of participants completed follow up. The study found that it is feasible and acceptable to recruit and

	retain a cohort of high-risk HIV negative men. Follow-up was equal by randomization arm, suggesting that men were motivated to join the trial irrespective of the randomization arm, and benefited from access to quality services and information about sexual and reproductive health. Fifteen focus group discussions, 64 in-depth interviews and 8 home visits were conducted. Preliminary results show that the majority of men (mean age of 30yrs) were South African-born (67%), single (81%), employed (54%) and perceived themselves to be in good health (87%). 40% reported >10 lifetime sexual partners, 32% had never used a condom in the last 3 months, and 36% were circumcised. 8% reported genital symptoms at screening, and 12% were found to have chlamydia while <3% had gonorrhoea or trichomoniasis respectively. HIV, HSV-2 and HepB prevalence were 9%, 33% and 34%. HepB was found to be associated with number of lifetime sexual partner and a history of STIs.
Total number of subjects (cohort/epidemiological/ other studies):	N = 3036
PhD studies:	Title: "Engaging young men in biomedical HIV prevention research: Lessons from a community-based study in rural KwaZulu-Natal" Candidate: Sebastian Fuller (University College London Centre for Sexual Health & HIV Research, UK) Dates: March 2008-Ocotber 2011
	Title: "What is it 'to do' in the context of change? Toward and operational model of the act for school-community-based HIV prevention." Candidate: Graeme Hoddinott (University of KwaZulu-Natal, South Africa) Dates: September 2011-September 2014
MSc studies:	Title: MSc Data Networks & Security Candidate: Gerald Feldmann (Birmingham City University, UK) Dates: January 2009-November 2010
	Title: MSc in public health Candidate: Helena Boene (London School of Hygiene & Tropical Medicine, UK) Dates: September 2011-October 2013
	Title: HIV testing patterns in 2 population probability samples from South Africa and the UK Candidate: Kyle Jones (London School of Hygiene & Tropical Medicine, UK) Dates: September 2011-September 2012
	Title: Popping the bubble: Do bubble plot presentations distort interpretation of circle size and data values Candidate: Stephen Oliver (University of KwaZulu-Natal, South Africa) Dates: September 2010-September 2012
	Title: Development Studies: Community engagement/involvement in biomedical HIV prevention trials Candidate: Ntombikayise Mncwango (University of South Africa) Dates: September 2011-December 2014
	Title: MSc in epidemiology with AfrEVacc data Candidate: Ivete Meque (University of Queensland, Australia) Dates: January 2012-January 2014
	Title: MSc in public health Candidate: Arlinda Zango (Eduardo Mondlane University,

	Mozambique) Dates: February 2012-pending
	Title: Masters in Epidemiology Candidate: Chacha Mangu (University of London (online course)) Dates: November 2011-September 2014
	Title: A Review of AfrEVacc 001 and Informed Consent Practices Candidate: Robin Jakob (University of Edinburgh, UK) Dates: September 2011-July 2012
Publications:	1. Serna-Bolea C., de Deus, N., Acácio S., Muñoz J., Nhalungo D., Letang E., Alonso P., Naniche D. (2012) Recent HIV-1 infection: Identification of individuals with high viral load setpoint in a voluntary counselling and testing centre in rural Mozambique. *Plos One* 7(2):e31859. Feb 21. 2. González R, Munguambe K, Aponte J, Bavo C, Nhalungo D, Macete E, Alonso P, Menéndez C, Naniche D. (2012) High HIV prevalence in a southern semi-rural area of Mozambique: a community-based survey. *HIV Medicine*. Nov 13(10), 581-588.

1.5 HIV/AIDS vaccines clinical trials

Project Acronym (Coordinator)	Phase of trial	Product(s)	Insert	Virus subtype	Manufacturer/ Developer	Study population	Status
TaMoVac I: HIVIS03 continuation	I	Plasmid DNA + MVA-CMDR	Env, Rev, Gag, RTmut + Gag, Pol, Gp160	Clade A, B, C + Clade A, E	Vecura	Healthy adults (Police Officers) N = 60	Completed
TaMoVac I Phase I/II Tanzania + AfrEVacc	I	Plasmid DNA + MVA-CMDR + rpg 140/GLA-AF	Plasmid: Env, Rev, Gag, RTmut + MVA-CMDR: Gag, Pol, Gp150 + MVA-CMDR: rgp140/GLA-AF	Clade A, B, C + Clade A, E + Clade C	Vecura and Imperial College	Healthy adults (Police Officers) N = 40	Completed
TaMoVac I Phase I trial in Maputo with youths	I	Plasmid DNA + MVA-CMDR	Env, Rev, Gag, RTmut + Gag, Pol, Gp160	Clade A, B, C + Clade A, E	Vecura at KI, Sweden (DNA) WRAIR of USA (MVA-CMDR)	Youths, N = 24	Completed
TaMoVac II	II	DNA + MVA-CMDR	Env + gp160 (subtype E, CM235), gag and pol (integrase-deleted and reverse transcriptase non-	Clade A, B, C + Clade A	Vecura/ WRAIR	Healthy young adults (Police and Prison officers and high-risk workers) N=1400	Ongoing

			functional, subtype A, CM240).				
PedVacc (PV001)	I	MVA-HIVA	HIVA (Gag+CD8+ T cell polyepitope)	Clade A	IDT, Germany / University of Oxford, UK	Healthy infants born to HIV-1/2-negative mothers, n= 48	Completed
PedVacc (PV002)	I	MVA-HIVA	HIVA (Gag+CD8+ T cell polyepitope)	Clade A	IDT, Germany / University of Oxford, UK	Healthy infants born to HIV-1-positive mothers, n= 72	Completed
HIV-CORE004	I	pSG2.HIVconsv DNA MVA.HIVconsv ChAdV63.HIVconsv	chimaeric protein with segments of HIV-1 clades A, B, C and D	Clade A, B, C and D	MRC UK	HIV-1/2-negative adults ages 18-40, n = 72	Not yet recruiting

1.5.1 PedVacc

EDCTP Project Coordinator:	Tomáš Hanke (University of Oxford, UK)
EDCTP Call Title:	Capacity building in preparation for the conduct of preventive HIV vaccine trials (EDCTP/Gates Foundation/MS joint call)
EDCTP Project Title:	Building capacity of Infant HIV-1 Vaccine Clinical Trial Centres in Nairobi, Kenya and Fajara, The Gambia
EDCTP Project Code:	CT.2006.33111.002
EDCTP Project Start Date:	7 April 2008
EDCTP Project End Date:	30 April 2012
Collaborators:	• Katie Flanagan (formerly at MRC Gambia now at Launceston General Hospital, Australia) • Walter Jaoko (University of Nairobi, Kenya) • Grace John-Stewart (University of Washington, US) • Joan Joseph (Hospital Clinic of Barcelona) • Andrew McMichael (University of Oxford, UK) • Marie Reilly (Karolinska Institute, Sweden) • Sarah Rowland-Jones (MRC The Gambia)
Study/Trial 1	**PV001 Gambian trial**
Site Principal Investigator(s):	Katie Flanagan (The Gambia)
Clinical Trial/Study Sponsor:	Medical Research Council (UK)
Trial/Study title:	An open randomised phase I study evaluating safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1 and HIV-2-uninfected mothers
Goal:	To establish infant phase I HIV-1 vaccine safety and immunogenicity
Primary Objective(s):	1. To evaluate the safety and immunogenicity of MVA.HIVA vaccine in 20-week old healthy Gambian infants born to HIV-1/2-uninfected mothers
Secondary Objective(s):	1. To determine the gross impact of MVA.HIVA on the immunogenicity of expanded programme on immunisation (EPI) vaccines (DTwPHib, HepB, PCV-7 and OPV) when administered at 20 weeks (4 weeks after the last EPI vaccines) to infants who have had Bacillus Calmette-Guérin (BCG) anti-TB vaccine within the first 4 weeks of life 2. To build capacity for infant HIV-1 vaccine clinical trials centre in Fajara, The Gambia.
Clinical Trial/Study site(s):	Sukuta Health Centre (The Gambia)
Collaborating site(s):	• University of Oxford (UK) • MRC Laboratories (The Gambia) • Karolinska Institute (Sweden)
Study design:	Phase I open-label randomised controlled trial (immunology lab blinded)
Number of subjects:	Group 1: EPI+MVA.HIVA administered at 20 weeks of age (N=24) Group 2: EPI and no MVA.HIVA (control group, N=24)
Product(s):	MVA.HIVA (recombinant non-replicating modified vaccinia virus Ankara expressing HIV-1-derived immunogen HIVA) focusing on induction of anti-HIV-1 T cell immunity
Manufacturer/ Developer:	Impfstoffwerk Dessau-Tornau Biologika GmbH, Germany/University of Oxford, UK
Cofunders:	• Bill & Melinda Gates Foundation (USA) • SIDA and Karolinska Institut (Sweden)

	• Institute of Health Carlos III (ISCIII, Spain) • MRC (UK)
Trial Registration number(s):	NCT00982579 ATMR2008120000904116
Status:	Completed
Results and Outcomes:	Two infant vaccine clinical trials PV001 (HIV-1-negative mothers) and PV002 (HIV-1-positive mothers) were successfully completed. A total of 121 infant-mother pairs were randomised, of whom half received the Investigational Medicinal Product. These trials showed that the vaccine MVA.HIVA was well tolerated in 20-week old infants with no reported serious adverse reactions, neither study detected MVA.HIVA interference with antibodies induced by other childhood vaccines (the Expanded Programme on Immunization) and preliminary analysis of the vaccine immunogenicity in PV001 suggests induction of weak, but definite T cell responses specific for HIV-1 elicited in small number of vaccinated infants. These responses are expected to increase by a priming vaccination and when a standard rather than low (safety) boosting dose of rMVA is used. The trials have been conducted to the highest scientific and ethical standards in compliance with the protocol, ICH/GCP and applicable regulatory requirements. GLP BCG.HIVA preparation BCG.HIVACAT antibiotic selection-free master seed and working vaccine seed stocks have been prepared in compliance with Good Laboratory Practice and its immunogenicity confirmed in preclinical models.
Study / Trial 2	**PV002 Kenyan trial**
Site Principal Investigator(s):	• Walter Jaoko (Kenya) • Grace John-Stewart (Kenya)
Clinical Trial/Study Sponsor:	Medical Research Council (UK)
Trial/Study title:	An open randomised phase I/II study evaluating safety and immunogenicity of a candidate HIV-1 vaccine, MVA.HIVA, administered to healthy infants born to HIV-1-infected mothers
Goal:	To establish safety and immunogenicity of candidate HIV-1 vaccine MVA.HIVA
Primary Objective(s):	1. To evaluate the safety and immunogenicity of MVA.HIVA vaccine in 20 week old healthy Kenyan infants born to HIV-1-infected mothers
Secondary Objective(s):	1. Comparison of HIV-1-specific T cell responses between MVA.HIVA-vaccinated and age-matched unvaccinated infants 2. Comparison of responses to certain Kenyan Extended Programme on Immunization (KEPI) vaccines (OPV, DTP, HBV, and HiB) between MVA.HIVA-vaccinated and age-matched unvaccinated infants 3. Comparison of immune activation and phenotypic profile of lymphocytes between MVA.HIVA-vaccinated and age-matched unvaccinated infants 4. Build capacity for Infant HIV-1 Vaccine Clinical Trials Centre in Nairobi, Kenya.
Clinical Trial/Study site(s):	Kenyatta National Hospital (Kenya)
Collaborating site(s):	• University of Oxford (UK) • MRC (UK) • University of Nairobi (Kenya) • Kenya AIDS Vaccine Initiative (Kenya) • University of Washington (USA) • Karolinska Institute (Sweden)

Study design:	Open, randomised, controlled phase I/II trial (immunology laboratory blinded)
Number of subjects:	Group 1: KEPI+MVA.HIVA administered at 20 weeks of age (N=36) Group 2: KEPI and no MVA.HIVA (control group, N=36)
Product(s):	MVA.HIVA (recombinant non-replicating modified vaccinia virus Ankara expressing HIV-1-derived immunogen HIVA) focusing on induction of anti-HIV-1 T cell immunity
Manufacturer/ Developer:	Impfstoffwerk Dessau-Tornau Biologika GmbH, Germany/University of Oxford, UK
Cofunders:	• Bill & Melinda Gates Foundation (USA) • Swedish International Developmental Cooperation Agency (SIDA) Karolinska Institut (Sweden) • Institute of Health Carlos III (ISCIII, Spain) • MRC (UK)
Trial Registration number(s):	NCT00981695 PACTR2009010001152787
Status:	Completed
Results and Outcomes:	Two infant vaccine clinical trials PV001 (HIV-1-negative mothers) and PV002 (HIV-1-positive mothers) were successfully completed. A total of 121 infant-mother pairs were randomised, of whom half received the Investigational Medicinal Product. These trials showed that the vaccine MVA.HIVA was well tolerated in 20-week old infants with no reported serious adverse reactions, neither study detected MVA.HIVA interference with antibodies induced by other childhood vaccines (the Expanded Programme on Immunization) and preliminary analysis of the vaccine immunogenicity in PV001 suggests induction of weak, but definite T cell responses specific for HIV-1 elicited in small number of vaccinated infants. These responses are expected to increase by a priming vaccination and when a standard rather than low (safety) boosting dose of rMVA is used. The trials have been conducted to the highest scientific and ethical standards in compliance with the protocol, ICH/GCP and applicable regulatory requirements. GLP BCG.HIVA preparation BCG.HIVACAT antibiotic selection-free master seed and working vaccine seed stocks have been prepared in compliance with Good Laboratory Practice and its immunogenicity confirmed in preclinical models.
PhD study:	Title: Regulatory T cells and vaccines: correlation or coincidence? Candidate: Jorjoh Ndure (MRC The Gambia) Dates: January 2011-December 2013
MSc studies:	Topic: Epidemiology Candidate: Christine Gichuhi (LSHTM, UK (distance learning)) Dates: September 2009-June 2013
	Title: The BCG transcriptome signature and relationship with host immune responses Candidate: Fatoumatta Darboe (MRC The Gambia) Dates: December 2011-March 2013
	Title: Anxiety and depression in HIV positive mothers whose infants are completing HIV vaccine studies Candidate: Dorcas Murei (University of Nairobi, Kenya) Dates: October 2009-August 2012
	Title: A software system for advanced flow cytometry data analysis Candidate: Amos Thairu (KAVI, Kenya/KI, Sweden) Dates: February 2011-April 2012

	Title: Immune Responses in HIV/Schistosoma mansoni Coinfection and Associations to Disease Progression Candidate: Moses Muriuki Mundia (KAVI/University of Hertfordshire, UK) Dates: January 2012-January 2015
Postdoc studies:	Yaowaluck Roshorm (University of Oxford, UK) Dates: April 2008-May 2012
	Raquel Fernandez Lloris (University of Barcelona, Spain) Dates: April 2008-May 2012
Other/Sub-studies:	Preparation of GLP grade BCG.HIVA222 vaccine for GMP production
Publications:	1. Saubi, N, Mbewe-Mvula, A, Gea, E, Rosario, M, Gatell, JM, Hanke, T, Joseph, J. (2012) Pre-clinical development of BCG.HIVA^{CAT}, an antibiotic-free selection strain, for HIV-TB pediatric vaccine vectored by lysine auxotroph of BCG. *PLoS ONE*, 7: 10.1371/journal.pone.0042559.
Press releases:	EDCTP press release MRC press release

1.5.2 TaMoVac-01

EDCTP Project Coordinator:	Muhammad Bakari (Muhimbili University College of Health Sciences, Tanzania)
EDCTP Call Title:	Capacity building in preparation for the conduct of preventive HIV vaccine trials (EDCTP/Gates Foundation/MS joint call)
EDCTP Project Title:	HIV vaccine trial capacity building in Tanzania and Mozambique by continued exploration of optimal DNA priming and MVA boosting strategies
EDCTP Project Code:	CT.2006.33111.007
EDCTP Project Start Date:	4 March 2008
EDCTP Project End Date:	31 December 2012
Collaborators:	• Sören Andersson (Örebro University Hospital, Sweden) • Gunnel Biberfeld (Karolinska Institute, Sweden) • Pontus Blomberg (Karolinska Institute, Sweden) • Frances Gotch (Imperial College, UK) • Bo Hejdeman (Karolinksa Institute, Sweden) • Michael Hoelscher (LMU, Germany) • Nesrina Imami (Imperial College, UK) • Ilesh Jani (Instituto Nacional de Saúde (INS), Mozambique) • Andrew Kitua (WHO/Special Programme for Research and Training in Tropical Diseases, Switzerland) • Leonard Maboko (MMRP, Tanzania) • Sayoki Mfinanga (NIMR, Tanzania) • Fred Mhalu (University of Dar es Salaam, Tanzania) • Charlotta Nilsson (Karolinska Institute, Sweden) • Nafissa Osman (Instituto Nacional de Saúde (INS), Mozambique) • Eric Sandstrom (Karolinska Institute, Sweden) • Willy Urassa (MUHAS, Tanzania) • Paula Vaz (Instituto Nacional de Saúde (INS), Mozambique) • Jonathan Weber (Imperial College, UK)
Study/Trial 1	**HIVIS 03 continuation**
Site Principal Investigator(s):	Fred Mhalu (Tanzania)
Clinical Trial/Study Sponsor:	Muhimbili University College of Health & Allied Sciences/Swedish Institute of Infectious diseases
Trial/Study title:	A Phase I/II trial to assess the safety and immunogenicity of a plasmid DNA-MVA prime boost HIV-1 vaccine candidate among volunteers in Dar es Salaam, Tanzania
Goal:	Assess the safety and immunogenicity of a plasmid DNA-MVA prime boost HIV-1 vaccine candidate. HIVIS 03 is a follow-up phase I/II HIV vaccine study in Tanzania of HIV plasmid DNA prime MVA boost that was successfully completed in Sweden
Primary Objective(s):	To determine safety and immunogenicity of HIVIS-DNA candidate vaccine
Secondary Objective(s):	To build expertise and capability in evaluating HIV-1 vaccine candidates in Dar es Salaam, Tanzania
Clinical Trial/Study site(s):	Muhimbili University College of Health & Allied Sciences, Dar es Salaam (Tanzania)
Collaborating site(s):	• Swedish Institute for Infectious Disease Control (Sweden)
Study design:	Phase I/II double-blinded randomised controlled trial
Number of subjects:	Healthy adults (police officers), N= 60

Product(s):	Priming – env (HIV-1 subtype A, B, C), rev (HIV-1 subtype B), gag (HIV-1 subtype A, B) and RTmut (HIV-1, subtype B) Boosting – MVA-CMDR expressing HIV-1 genes – gp160 (subtype E, CM235) and gag and pol (subtype A, CM240)
Manufacturer/Developer:	Vecura Company (Sweden) (DNA) WRAIR (USA) (MVA-CMDR)
Cofunders:	• Bill & Melinda Gates Foundation (US) • Walter Reed Army Institute of Research (WRAIR, US) • BMBF (Germany) • LMU München (Germany) • NACCAP (Netherlands) • EU • SIDA (Sweden) • Embassy of Sweden (Sweden) • MRC (UK) • Imperial College (UK)
Trial Registration number(s):	ISRCTN90053831 ATMR2009040001075080
Status:	Completed
Results and Outcomes	First patient in: February 2009 Last patient out: July 2010 42 volunteers out of 60 received the second MVA boost. The vaccine was deemed safe, and a total of 11 SAE unrelated to vaccination have been observed. Study closure visit was done on 24 June 2010. Preliminary results of the immunological analyses show a broad and potent immune response in volunteers.
Study/Trial 2	**Phase I/II Tanzania combined project with Weber's AfrEVacc (CT.2006.33111.001)**
Site Principal Investigator(s):	Muhammad Bakari (Tanzania) Leonard Maboko (Tanzania)
Clinical Trial/Study Sponsor:	Swedish Institute for Communicable Disease Control (Sweden) MUHAS (Tanzania)
Trial/Study title:	A phase I/II trial to assess safety and immunogenicity of i.d. DNA priming, i.m. MVA and i.m. rgp140/GLA-AF boosting in healthy volunteers in Tanzania and to develop further HIV vaccine trial capacity building in Tanzania.
Goal:	Exploration of the optimal delivery method of HIV-1 DNA vaccine
Primary Objective(s):	1. Determine safety of HIVIS-DNA at a dose of 600 µg or 1000 µg delivered ID in combination with MVA-CMDR boost IM 2. Determine immunogenicity of HIVIS-DNA at a dose of 600 µg or 1000 µg delivered ID in combination with MVA-CMDR boost IM
Secondary Objective(s):	1. Compare immunogenicity of HIVIS-DNA at a dose of 600 µg given as combined plasmid pools or separate plasmid pools ID in combination with MVA-CMDR boost IM 2. Explore the safety and immunogenicity of boosting with two doses of rgp140 in the adjuvant GLA-AF, administered IM 3. To build expertise and capability in evaluating HIV-1 vaccine candidates in Tanzania
Clinical Trial/Study site(s):	MUHAS, Dar es Salaam (Tanzania) NIMR-MMRP, Mbeya (Tanzania)
Collaborating site(s):	• NIMR (Tanzania) • Swedish Institute for Infectious Disease Control (Sweden) • WRAIR (USA)

	• University of München (Germany) • Imperial College (UK)
Study design:	Phase I/II double-blinded randomised controlled trial
Number of subjects:	Healthy adults (Police Officers, no less than 30 females), N = 120
Product(s):	**Priming** Pool 1: env (HIV-1 subtype A, B, C) and rev (HIV-1 subtype B) Pool 2: gag (HIV-1 subtype A, B) and RTmut (HIV-1, subtype B) **Boosting:** Modified Vaccinia Ankara vaccine (MVA-CMDR) expressing HIV-1 genes – gp150 (subtype E, CM235) and gag and pol (subtype A, CM240) **Further boosting (amended protocol):** Recombinant C clade trimeric envelope protein (rgp140) derived from the Chinese isolate CN54 mixed with glucopyranosyl lipid A (GLA)
Manufacturer/Developer:	DNA: Vecura (Sweden) MVA-CMDR: WRAIR (USA) rgp140/GLA: Imperial College (London, UK)
Cofunders:	• Bill & Melinda Gates Foundation (USA) • WRAIR (USA); • BMBF (Germany) • LMU München (Germany); • NACCAP (Netherlands); • SIDA and Embassy of Sweden (Sweden); • MRC UK and Imperial College (UK); • AfrEVacc project, Imperial College (UK); • Wellcome Trust UK HIV Vaccine Consortium (UK)
Trial Registration number(s):	PACTR2010050002122368
Status:	Completed
Results and Outcomes	A total of 509 individuals were screened of whom 129 received the 1st DNA/placebo vaccine in MUHAS and MMRP. 116 received the 2nd MVA placebo, and a further 40 of the above received rgp140/GLA. The vaccines were safe. Preliminary analysis has shown that there is no difference in giving DNA as Env and Gag plasmids either in separate or combined pools. DNA priming with 2 i.d. injections, each containing 300mg (total 600mg) is almost as equivalent to 5 i.d. injections each with 200mg (total 1000mg). Additionally, giving DNA as 0.2 mL i.d. was well tolerated and feasible with a Zetajet. Follow-up of volunteers has been completed. Data cleaning and analysis is being finalised so as to write the respective manuscripts. Additional testing of HIV specific antibody responses induced by the rgp140/GLA boosting vaccinations will be performed.
Study/Trial 3	**Phase I HIV Vaccine Trial in youths**
Site Principal Investigator(s):	Ilesh Vinodrai Jani (Mozambique) Nafissa Bique Osman (Mozambique)
Clinical Trial/Study Sponsor:	Swedish Institute for Communicable Disease Control (SMI, Sweden)
Trial/Study title:	A phase I trial to assess safety and immunogenicity of i.d. DNA priming and i.m. MVA boosting in healthy volunteers in Mozambique and to develop further HIV vaccine trial capacity

	building in Mozambique.
Goal:	Assess the safety and immunogenicity of a plasmid DNA-MVA prime boost HIV-1 vaccine candidate.
Primary Objective(s):	1. Determine safety of the DNA vaccine at a dose of 600 µg and 1200 µg delivered i.d in combination with MVA-CMDR boost i.m. 2. Determine immunogenicity of HIVIS-DNA at a dose of 600 µg and 1200 µg delivered i.d in combination with MVA-CMDR boost i.m.
Secondary Objective(s):	1. To build expertise and capability in evaluating HIV-1 vaccine candidates in Mozambique.
Clinical Trial/Study site(s):	Instituto Nacional de Saúde – Centro de Investigação e Treino em Saúde da Polana Caniço (CISPOC, Mozambique)
Collaborating site(s):	• Instituto Nacional de Saúde (INS, Mozambique) • The Swedish Institute for Communicable Disease Control (Sweden) • U.S. Military HIV Research Program-Walter Reed Army Institute of Research (MHRP-WRAIR, USA) • Imperial College (UK)
Study design:	Phase I double-blinded randomised placebo-controlled vaccine trial
Number of subjects:	A Phase I/II HIV Vaccine Trial will be performed on 24 consenting youths (18-26 years)
Product(s):	**Priming:** Pool 1: env (HIV-1 subtype A, B, C) and rev (HIV-1 subtype B) Pool 2: gag (HIV-1 subtype A, B) and Rtmut (HIV-1, subtype B) **Boosting:** Modified Vaccinia Ankara vaccine (MVA-CMDR) expressing HIV-1 genes – gp150 (subtype E, CM235) and gag and pol (subtype A, CM240)
Manufacturer/Developer:	DNA: Vecura (Sweden) MVA-CMDR: WRAIR (USA)
Cofunders:	Swedish International Development Cooperation Agency (SIDA)
Trial Registration number(s):	NCT01407497 PACTR201106000304583
Status:	Completed
Results and Outcomes:	All vaccinations have been completed. Follow up was completed in March 2013. Some immunological assays will continue to be performed throughout the year 2013.
Total number of subjects (clinical trials only):	204
PhD studies:	Title: Evaluation of HIV testing strategies and monitoring of immune responses in HIV vaccinated individuals in Tanzania Candidate: Said Aboud (Karolinska Institute, Sweden) Dates: December 2004-October 2011
	Title: Tuberculosis and HIV infections: Magnitude of HIV in the Police cohort and its suitability for HIV Vaccine trials, suitability of rapid tests for diagnosis of HIV associated TB Candidate: Patricia Munseri (Karolinska Institute, Sweden) Dates: May 2007-May 2013
	Title: What motivates participation in HIV vaccine trials: A study among Police Officers in Dar es Salaam, Tanzania Candidate: Edith Tarimo (Karolinska Institute, Sweden) Dates: April 2007-June 2011
	Title: Studies of immune responses induced by immunization with HIV-1 DNA followed by HIV-1 MVA in healthy individuals in Dar es Salaam, Tanzania Agricola Joachim (Karolinska Institute, Sweden)

	Dates: December 2011-December 2015
Other/Sub-studies:	In Maputo, Mozambique: Sub-study of HBV (Hepatitis B) frequency: HBV and HPV testing will be performed for both HIV negative and positive volunteers Sub-study of Immune response patterns against HIV antigens and control antigens: Determined the frequencies and types of cells that are responding to antigenic stimulus, the quantity and specificity of neutralizing antibodies, and the molecular characterization of HIV isolates. The establishment of reference values: The establishment of reference values for haematological, biochemistry, and immunological parameters Strengthening of group for education on prevention: This component aims to improve the functioning and train the existing group in education for prevention.
Publications:	1. Bakari, M, Aboud, S, Nilsson, C, Francis, J, Buma, D, Moshiro, C, Aris, EA, Lyamuya, EF, Janabi, M, Godoy-Ramirez, K, Joachim, A, Polonis, VR, Bråve, A, Earl, P, Robb, M, Marovich, M, Wahren, B, Pallangyo, K, Biberfeld, G, Mhalu, F, Sandström, E. (2011) Broad and potent immune responses to a low dose intradermal HIV-1 DNA boosted with HIV-1 recombinant MVA among healthy adults in Tanzania. *Vaccine*, 29(46): 8417-8428.

1.5.3 TaMoVac II

EDCTP Project Coordinator:	Eligius Lyamuya (Muhimbili University College of Health Sciences, Tanzania)
EDCTP Call Title:	Call for the support of clinical trials, capacity building and networking in HIV/AIDS vaccines development
EDCTP Project Title:	HIV vaccine trial capacity building in Tanzania and Mozambique by continued exploration of optimal DNA and MVA boosting strategies: TaMoVac II
EDCTP Project Code:	IP.2007.33112.001
EDCTP Project Start Date:	1 July 2009
EDCTP Project End Date:	30 June 2014
Collaborators:	• Said Aboud (Muhimbili University College of Health Sciences, Tanzania) • Sören Andersson (Karolinska Institute, Sweden) • Gunnel Biberfeld (Karolinska Institute, Sweden) • Pontus Blomberg (Karolinska Institute, Sweden) • Frances Gotch (Imperial College London, UK) • Bo Hejdeman (Karolinska Institute, Sweden) • Michael Hoelscher (Ludwig-Maximilians Universitat Munchen, Germany) • Nesrina Imami (Imperial College London, UK) • Mohamed Yakub Janabi (Muhimbili University College of Health Sciences, Tanzania) • Ilesh Jani (Instituto Nacional de Saúde (INS), Mozambique) • Andrew Kitua (National Institute for Medical Research (NIMR), Tanzania) • Leonard Maboko (Mbeya Medical Research Programme, Tanzania) • Eulália Macovala Clara Américo (Karolinska Institute, Sweden) • Theodora Mbunda (Muhimbili University College of Health Sciences, Tanzania) • Sheena McCormack (Medical Research Council, UK) • Sayoki Mfinanga (National Institute for Medical Research (NIMR), Tanzania) • Fred S Mhalu (University of Dar es Salaam, Tanzania) • Candida Moshiro (Muhimbili University College of Health Sciences, Tanzania) • Patricia Jane Munseri (Muhimbili University College of Health Sciences, Tanzania) • Charlotta Nilsson (Karolinska Institute, Sweden) • Nafissa Osman (Instituto Nacional de Saúde (INS), Mozambique) • Kisali Pallangyo (Muhimbili University College of Health Sciences, Tanzania) • Eric Sandstrom (Karolinska Institute, Sweden) • Erica Sanga (Mbeya Medical Research Programme, Tanzania) • Willy Urassa (Muhimbili University College of Health Sciences, Tanzania) • Paula Vaz (Instituto Nacional de Saúde (INS), Mozambique) • Britta Wahren (Karolinska Institute, Sweden)
Site Principal Investigator(s):	• Leonard Maboko (NIMR, Tanzania) • Muhammad Bakari (MUHAS, Tanzania) • Ileshi Jani (INS, Mozambique)

Clinical Trial/Study Sponsor:	• Muhimbili University College of Health & Allied Sciences (MUHAS, Tanzania) • Swedish Institute of Infectious Disease Control (SMI, Sweden)
Trial/Study title:	HIV vaccine trial capacity building in Tanzania and Mozambique by continued exploration of optimal DNA and MVA boosting strategies; TaMoVac II
Goal:	To increase the immunogenicity of DNA plasmid HIV vaccines and to continue EU, EDCTP and Sida/SAREC investments in a DNA prime/ MVA boost HIV vaccine concept in Dar es Salaam, Mbeya and Maputo, in addition to preparations for a comparison with the AfrEVac immunogens
Primary Objective(s):	1. To evaluate if electroporation (or VaxFectin) can augment cellular immune responses and humoral responses to HIV-1 containing plasmid DNA priming
Secondary Objective(s):	1. Further document the immunogenicity and safety of the HIVIS DNA/MVA immunogens 2. Introduce novel delivery technologies of the HIVIS DNA vaccine to induce long-term memory and antibody production in phase I/II trials 3. Sustain the youth and adult cohorts in Tanzania and Mozambique from which volunteers will be recruited into phase IIa trials for safety and immunogenicity testing 4. Prepare for comparisons between the HIVIS and EuroVacc HIV vaccines by intensive technology sharing 5. Take the first steps to allow integration of parallel DNA prime/pox boost HIV vaccine efforts supported by EDCTP.
Clinical Trial/Study site(s):	• NIMR-MMRP Mbeya (Tanzania) • MUHAS (Tanzania) • Instituto Nacional de Saúde (INS) Maputo (Mozambique)
Collaborating site(s):	• National Institute for Medical Research (NIMR) Muhimbili station (Tanzania) • Central Hospital Maputo (Mozambique) • Karolinska Institute (Sweden) • Vecura (Sweden) • University of Munich (Germany) • Imperial College (UK) • MRC-CTU (UK) • Venhälsan, Södersjukhuset (Sweden) • SMI (Sweden)
Study design:	Phase I/II double blinded randomised controlled trial
Number of subjects:	198
Product(s):	Priming: DNA plasmids derived from puC8 with a kanamycin resistance gene, hCMV promotor, HPV 16 poly A and origin of replication for E. coli. Env HIV-1 genes of subtypes A, B, C : pKCMVgp160A, KCMVgp160B, pKCMVgp160C, pKCMVrev, pKCMVp37A(ba), pKCMVp37B, and pKCMVpRTB. Boosting: MVA CMDR expressing HIV-1 genes: gp160 (subtype E, CM235), gag and pol (integrase-deleted and reverse transcriptase non-functional, Subtype A, CM240).
Manufacturer/Developer:	DNA plasmids from Vecura (Sweden) MVA CMDR from Walter Reed Army Institute of Research (WRAIR) (USA)
Cofunders:	• Sida (Sweden) • DfID (UK) • MRC (UK) • Klinikum University of München (Germany) • Federal Ministry of Education and Research (Germany)

Trial Registration number(s):	NCT01697007 PACTR201211000435126
Sub-studies:	Baseline Epidemiological Study: Epidemiological and Social-Behavioural Studies Among High-Risk Young Women in Dar es Salaam, Tanzania; Preparation for HIV Vaccine Studies. The objectives are: to determine the prevalence of HIV, Syphilis and Hepatitis B. (Other STIs will be investigated under a different grant); to study the acceptability of vaccines against STIs such as HIV and HBV on an individual and societal level; and, to study how services can best be tailored so that the risk of transmission of HIV/STIs and unwanted pregnancies is reduced. (protocol finalised and pending approval by IRB)
Status:	Ongoing
Results and Outcomes:	The Clinical Trial protocol was finalized in March 2012, submitted for IRB processing in Tanzania in March 2012 and for IRB processing in Mozambique in August 2012. Ethical clearances were given by MUHAS, NIMR, Mbeya-REC on 28th June 2012, 6th September 2012, and 12th November 2012, respectively. Regulatory approval was received from the Tanzania Food and Drug Authority on the 10th October 2012.
Total number of subjects (clinical trials only):	198
PhD studies:	Title: Studies of immune responses induced by immunization with HIV-1 DNA followed by HIV-1 MVA with or without gp 140 in healthy individuals in Dar es Salaam, Tanzania Candidate: Agricola Joachim (MUHAS, Tanzania) Dates: December 2011-end 2015
	Title: Recruitment, retention and participation in HIV vaccine trials targeting youth in Tanzania Candidate: Theodora Mbunda (MUHAS, Tanzania) Dates: 30 September 2011-June 2015
	Title: Virus infections in Obstetrics in Mozambique Candidate: Eulalia Macovela (INS, Mozambique) Dates: 2011-2016
MSc studies:	Title: International Health Master Programme Candidate: Doreen Pamba (NIMR-MMRC, Tanzania) Dates: 5 April 2012-5 April 2015

2 Tuberculosis

2.1 Tuberculosis treatment clinical trials

Project Acronym (Coordinator)	Phase of trial	Product(s)	Manufacturer / Developer	Study population	Status
TB SurMark (vanHelden)	Not applicable	Not applicable (Surrogate biomarkers)	Not applicable	Adults TB patients' stored samples and cultured isolates N=313	Completed
HIV-TB Pharmagene (Bertilsson)	IV	Efavirenz Rifampicin 3TC D4T	GlaxoSmith Kline	HIV positive adults and HIV/TB positive adults N= 400	Completed
PPK.DDK (Merry)	IV	Efavirenz Nevirapine Lopinavir Ritonavir Rifampicin	DuPont Pharmaceuticals, Tübingen, Boehringer Ingelheim	Adult and Paediatric patients with HIV/TB coinfection N=178	Completed
RIFAQUIN (Jindani)	III	Ethambutol Isoniazid Moxifloxacin Pyrazinamide Rifampicin Rifapentine	All the drugs were supplied by INTERTB, London.	Newly diagnosed pulmonary tuberculosis patients over 18 years of age with no previous anti-tuberculosis chemotherapy. N=827	Completed
PanACEA REMox I and II (Gillespie)	III	Moxifloxacin Rifampicin Isoniazid Pyrazinamide Rifampicin Ethambutol	Bayer Tubingen	Adults newly diagnosed with TB, previously untreated, sputum smear positive pulmonary tuberculosis N=900	REMox I completed (study continuing in REMox II with an expanded enrolment)

PanACEA REMox I and II (Gillespie)	III	Moxifloxacin	Aptuit, GATB, Bayer, Sanofi-Aventis, Svizera	Adults newly diagnosed with TB, previkously untreated, sputum smear positive pulmonary tuberculosis N=1000 Total Remox I+II=1900	Ongoing
PanACEA-HIGHRIF (Boeree)	II	Rifampicin Moxifloxacin Isoniazid Pyrazinamide Ethambutol	Svizera Sanofi-Aventis	Adults (aged 16-65) newly diagnosed with TB, previously untreated, uncomplicated sputum smear positive pulmonary tuberculosis Study 1: 68 patients – enrolment completed Study 2: 150 patients– enrolment completed Study 3 & 4: up to 372 adult patients - High dose rifampicin combined with other TB drugs, study 4 inclusive of moxifloxacin	Ongoing
PanACEA SQ-109 (Hoelscher)	II	novel TB drug (SQ109)	Sequella Inc.	Phase IIa: n = 90 MSMA project design: A maximum of 372 adult (≥ 18 years of age) patients with newly diagnosed, smear positive pulmonary TB.	Completed
PANBIOME (Gillespie)	Not applicable (Cohort Study)	Not Applicable (Biomarkers study)	Not applicable	50 tuberculosis patients Adults (aged 16-65) newly diagnosed with TB, previously untreated, uncomplicated sputum smear positive pulmonary tuberculosis	Ongoing

2.1.1 TB SurMark

EDCTP Project Coordinator:	Paul van Helden (Stellenbosch University, South Africa)
EDCTP Call Title:	Trials of studies of surrogate markers of drug efficacy. These should emphasise non-clinical predictors of sterilizing activity and relapse following anti-TB therapy
EDCTP Project Title:	Surrogate markers to predict the outcome of antituberculosis therapy
EDCTP Project Code:	CT.2004.32040.001 (2004.01.T.d1)
EDCTP Project Start Date:	19 September 2005
EDCTP Project End Date:	30 June 2009
Collaborators:	• Nulda Beyers (Stellenbosch University, South Africa) • Gillian Black (Stellenbosch University, South Africa) • Jacqueline Cliff (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Hazel Dockrell (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Ken Duncan (GlaxoSmithKline, UK) • Nsovo Mathebula (University of Pretoria, South Africa) • Jen Page (Aeras Global Tuberculosis Foundation, USA) • Simon Thanyani (University of Pretoria, South Africa) • Jan Verschoor (University of Pretoria, South Africa) • Gerhard Walzl (Stellenbosch University, South Africa)
Study / Trial 1	
Site Principal Investigator(s):	Paul van Helden (South Africa)
Clinical Trial/Study Sponsor:	Stellenbosch University
Trial/Study title:	Surrogate markers to predict the outcome of antituberculosis therapy
Goal:	To analyse stored samples and identify biomarkers that correlate with clinical outcome and to validate them in a multi-centre prospective study recruiting new TB patients
Primary Objective(s):	6. To complete the follow-up of the patient cohort (funded by GSK) 7. To analyse stored samples from TB patients, particularly those samples collected before initiation of therapy and during the early phases of treatment from recurrent/relapse patients, using microbiological, serum, blood parameters, immunological and genetic markers 8. To develop a test (algorithm) based on the findings that these parameters can be used to discriminate between disease states, enabling selection of specific patient type for PoC study and detection of 'cured' patients early during treatment and detection of relapse patients much sooner than the standard two-year follow up.
Clinical Trial/Study site(s):	Stellenbosch University
Collaborating site(s):	• Stellenbosch University (South Africa) • London School of Hygiene and Tropical Medicine (LSHTM, UK) GlaxoSmithKline (UK) • University of Pretoria (South Africa)
Study design:	Prospective study to validate biomarkers
Number of subjects:	313
Cofunders:	• Medical Research Council South Africa (MRC, South Africa) • Stellenbosch University (South Africa) • NRF Centre of Excellence for Biomedical TB Research (South Africa)

Status:	Completed
Results and Outcomes:	Patients who subsequently relapse or who remain healthy following drug cure can be readily discriminated during their first episode of TB based on their gene expression profile in the peripheral blood. While this pattern was seen in ex vivo blood, it was much more striking and statistically significant when TB-specific responses were measured in diluted whole blood cultures. From these data, the patients who were to suffer relapse after initial apparent cure had exaggerated cytotoxic and proliferative responses, which were evident at diagnosis and in the first four weeks of treatment, when compared to patients who would remain disease-free. There was a consistent pattern of differential expression of around 2000 genes between relapse and cured patients.
PhD studies:	Candidate: JF Djoba Siawaya (Stellenbosch University, South Africa)
	Candidate: C Babb (Stellenbosch University, South Africa)
	Candidate: N Chegou (Stellenbosch University, South Africa)
	Title: Downstream validation of results obtained from the microarray gene expression profiling including the collection of fresh TB patient samples Gulab Devi hospital, Lahore, Pakistan and qRT-PCR validation of identified biomarkers Candidate: Syeda Saleha (LSHTM, UK)
	Title: An assessment of two evanescent field biosensors in the development of an immunoassay for tuberculosis Candidate: Simon T Thanyani (University of Pretoria, South Africa)
Publications:	1. Djoba Siawaya JF, Chegou NN, van den Heuvel MM, Diacon AH, Beyers N, Helden PV, Walzl G. Differential cytokine/chemokines and KL-6 profiles in patients with different forms of tuberculosis. Cytokine. 2009; 47(2):132-136. (PMID: 19570688) 2. Hesseling AC, Walzl G, Enarson DA, Carroll NM, Duncan K, Lukey PT, Lombard C, Donald PR, Lawrence KA, Gie RP, van Helden PD, Beyers N. Baseline sputum time to detection predicts month two culture conversion and relapse in non-HIV-infected patients. Int J Tuberc Lung Dis. 2010 May;14(5):560-70 3. S. Brahmbhatt, G. F. Black, N. M. Carroll, N. Beyers, F. Salker, M. Kidd, P. T. Lukey, K. Duncan, P. van Helden and G. Walzl. Immune markers measured before treatment predict outcome of intensive phase tuberculosis therapy. Clinical and Experimental Immunology 2006;146:243-252 4. Hanne Veenstra, Ralf Baumann, Pauline T. Lukey, Nulda Beyers, Paul D. van Helden and Gerhard Walzl. High levels of intracellular IL-4 are expressed in circulating apoptotic T cells in patients with tuberculosis and in community controls. Tuberculosis 2008;88:21-30 5. Joel Fleury Djoba Siawaya, Nchinya Bennedict Bapela, Katharina Ronacher, Hanne Veenstra, Martin Kidd, Robert Gie, Nulda Beyers, Paul van Helden and Gerhard Walzl. Immune parameters as markers of tuberculosis extent of disease and early prediction of anti-tuberculosis chemotherapy response. Journal of Infection 2008;56:340-347 6. N.M. Carroll, P. Uys, A. Hesseling, K. Lawrence, C.

	Pheiffer, F. Salker, K. Duncan, N. Beyers and P.D. van Helden. Prediction of delayed treatment response in pulmonary tuberculosis: Useof time to positivity values of Bactec cultures. Tuberculosis, 2008;88(6)624-630 7. Chegou NN, Black GF, Kidd M, van Helden PD and Walzl G. Host markers in Quantiferon supernatants differentiate active TB from latent TB infection: preliminary report. BMC Pulmonary Medicine, 2009;9:21-56.

2.1.2 HIV-TB Pharmagene

EDCTP Project Coordinator:	Leif Bertilsson (Karolinska Institute, Sweden)
EDCTP Call Title:	Identification of safe and efficacious ARV in combination with tuberculosis drugs in tuberculosis patients with HIV infection
EDCTP Project Title:	Optimisation of tuberculosis and HIV co-treatment in Africa: Pharmacokinetic and pharmacogenetic aspects on drug-drug interactions between rifampicin (rif) and efavirenz (efv).
EDCTP Project Code:	CT.2005.32030.001
EDCTP Project Start Date:	9 January 2007
EDCTP Project End Date:	9 January 2012
Collaborators:	• Eleni Aklillu (Karolinska Institute, Sweden) • Wondwossen Amogne Degu (University of Addis Ababa, Ethiopia) • Ahmed Bedru (Armauer Hansen Research Institute (AHRI), Ethiopia) • Jurgen Burhenne (University of Heidelberg, Germany) • Miles Davies (Karolinska Institute, Sweden) • Getachew Aderaye Desta (University of Addis Ababa, Ethiopia) • Ulf Diczfalusy (Karolinska Institute, Sweden) • Eliford Engamisi (Karolinska Institute, Sweden) • Lars Gustafsson (Karolinska Institute, Sweden) • Abiy Habtewolde (Karolinska Institute, Sweden) • Walter Emil Haefeli (University of Heidelberg, Germany) • Mohamed Yakub Janabi (Muhimbili University College of Health Sciences, Tanzania) • Gideon Kwesigabo (Muhimbili University College of Health Sciences, Tanzania) • Lars Lindqvist (Karolinska Institute, Sweden) • Eyasu Makonnen, (University of Addis Ababa, Ethiopia) • Collen Masimirembwa (African Institute of Biomedical Science & Technology (AIBST), Zimbabwe) • Omari Minzi (Muhimbili University College of Health Sciences, Tanzania) • Ferdinand Mugusi (Muhimbili University College of Health Sciences, Tanzania) • Sabina Mugusi (Karolinska Institute, Sweden) • Eric Sandstrom (Karolinska Institute, Sweden) • Jane Sayi (Muhimbili University College of Health Sciences, Tanzania) • Anders Sonnerborg (Karolinska Institute, Sweden)
Study / Trial 1	
Site Principal Investigator(s):	• Getachew Aderaye (Ethiopia) • Ferdinand Mugusi (Tanzania) • Eleni Aklillu (Sweden)
Clinical Trial/Study Sponsor:	Karolinska Institute (Sweden)
Trial/Study title:	Population pharmacokinetics, pharmacogenetics, safety/efficacy of efavirenz (EFV) based HAART, defined as stavudine (d4T) + lamivudine (3TC) + efavirenz, with and without RIF in Ethiopians and Tanzanians
Goal:	To investigate the magnitude and variation of 16 h EFV plasma and intracellular drug concentration and metabolic ratios at steady state, safety/efficacy of EFV based HAART in patients with and without TB treatment; influence of genetic polymorphisms in drug metabolizing enzymes and transporters on plasma/intracellular levels of EFV, metabolic ratio and on

	drug interaction between RIF and EFV. Thirty patients TB/HIV patients from Trial 1 to be treated for HIV and TB will be requested randomly to participate into a three-phase intensive PK study during RIF based TB
Primary Objective(s):	To identify the optimal dose of EFV to be used with RIF in African patients receiving TB treatment. Specific objectives are: 9. To identify the optimal dose of EFV to be used with RIF 10. To evaluate plasma and intracellular pharmacokinetics of EFV depending on genetic polymorphisms, co-administration of RIF, and drug transporter expression 11. To evaluate the extent of RIF interaction on detailed EFV pharmacokinetics and treatment outcome 12. To investigate the pharmacogenetics of CYP3A and CYP2B6 and their influence on EFV pharmacokinetics and induction by RIF using EFV metabolic ratio and the endogenous CYP3A4/5 marker, 4 β-OH cholesterol plasma level.
Secondary Objective(s):	13. To train African clinicians and researchers at PhD and Masters level in clinical trial research and capacity building 14. To develop research capacities to conduct clinical trials in developing countries and provide the necessary infrastructure through appropriate training and technology transfer with the aim of developing a network of clinical trial centres for HIV/TB research.
Clinical Trial/Study site(s):	Black Lion Medical University Hospital Addis Ababa, Ethiopia St. Peter's TB Specialized Hospital, Addis Ababa, Ethiopia. Muhimbili National Hospital, Dar es Salaam, Tanzania
Collaborating site(s):	• Armauer Hansen Research Institute (AHRI, Ethiopia) • Muhimbili University College of Health Sciences (Tanzania) • African Institute of Biomedical Science & Technology (AIBST, Zimbabwe) • Karolinska Institute (Sweden) • University of Heidelberg (Germany)
Study design:	Non-randomised, open label, active control, parallel assignment, PK and safety/efficacy, pharmacogenetic study. **Control group Arm-1:** A cohort of 200 HIV patients without TB co-infection receiving EFV 600 mg based HAART **Case group Arm-2:** A cohort of 200 newly diagnosed treatment naive HIV+TB co-infected patients on concomitant RIF based anti-TB and EFV based HAART) participated in the study.
Number of subjects:	400 subjects. At end of enrolment 486 patients ultimately enrolled.
Product(s):	Efavirenz, Rifampicin (RIF)
Manufacturer/Developer:	• GlaxoSmithKline (lamivudine) • Bristol Myers Squibb (stavudine) • DuPont Pharmaceuticals (efavirenz) • Tubingen (rifampicin)
Cofunders:	• University of Heidelberg (Germany) • Karolinska Institute (Sweden) • Stockholm County Council (Sweden)
Trial Registration Number(s):	PACTR2009040001261177
Status:	Completed
Results and Outcomes:	Efavirenz is the preferred non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) to be used with rifampicin in TB-HIV coinfected patients. When used together, rifampicin reduces plasma efavirenz concentration by about 25%. Hence some

	treatment guidelines (The British HIV association (BHIVA) and Center for Diseases Control and Prevention (CDC) revised the HIV/TB co-treatment guideline) suggested increasing the dose of efavirenz from 600 mg/day to 800mg/day during concomitant TB-HIV co-treatment. However the use of a higher dose of efavirenz manifested increased Central Nervous System (CNS) side effects mainly in black HIV patients. Thus the main objective of the project was to determine whether there is a need for efavirenz dosage adjustment when it is co-administered with rifampicin. This was done by comparing efavirenz pharmacokinetics, safety and efficacy between HIV patients receiving efavirenz based HAART alone versus those receiving with rifampicin. The study was conducted in two countries (Ethiopia and Tanzania). Study results: Rifampicin co-administration had no significant effect on efavirenz pharmacokinetics or on the efficacy of 600mg/day efavirenz based HAART in Ethiopian and Tanzanian HIV patients. Mortality and DILI was relatively higher in Arm-2 (TB/HIV coinfection) patients mainly due to TB coinfection and concomitant TB treatment. Thus increasing efavirenz dose in Arm-2 patients may aggravate the relatively higher adverse events. The conclusion is that there is no need to increase efavirenz dosage during concomitant therapy when given with rifampicin based anti-tuberculosis therapy in TB-HIV coinfected patients.
PhD studies:	Title: Optimization of HIV/TB co treatment in Ethiopian Patients: Pharmacokinetic and pharmacogenetic aspects of drug interaction between Rifampicin and Efavirenz) Candidate: Abiy Habtewold Eyakem (Ethiopia) Dates: 10 September 2007-Spring 2013
	Title: Optimization of TB/HIV co-treatment in Ethiopian patients Candidate: Wondwossen Amogne (Ethiopia) Dates: 28 September 2008-Spring 2013
	Title: Optimization of HIV/TB co treatment in Tanzania: Pharmacokinetic and pharmacogenetic aspects of drug interaction between Rifampicin and Efavirenz in patients undergoing HIV/TB co treatment Candidate: Eliford Ngaimisi (Tanzania) Dates: 28 Septmber 2008-Spring 2013
	Title: Treatment outcome, Safety and Efficacy in Concomitant use of Efavirenz and Rifampicin in HIV and Tuberculosis patients Candidate: Sabina Mugusi (Tanzania) Dates: 29 February 2008-21 November 2012
Publications:	1. Mugusi S, Ngaimisi E,. Janabi M, Minzi O, Bakari M, Riedel KD, Burhenne J, Lindquist L, Mugusi F, Sandstrom E. Aklillu E, Liver enzyme abnormalities and associated risk factors in HIV patients on Efavirenz-based HAART with or without Tuberculosis co-infection in Tanzania" *Plos One*. 2012; doi: 10.1371/journal.pone.0040180 2. Mugusi S, Ngaimisi E,. Janabi M, Mugusi F, Minzi O, Sasi P, Bakari M, Lindquist L, Aklillu E, Sandstrom E. Risk factors for mortality among HIV positive patients with and without active TB in Dar es Salaam, Tanzania. *Antiretroviral therapy* 2012;17:265-274 3. Yimer G, Amogne W, Habtewold A, Makonnen E, Ueda N, Suda A, Worku A, Haefeli WE, Burhenne J, Aderaye G, Lindquist L, Aklillu E. High plasma efavirenz level and CYP2B6*6 are associated with efavirenz based HAART

induced liver injury in treatment naïve HIV patients from Ethiopia: a prospective cohort study. *Pharmacogenomics J*. 2011; Aug 23. doi: 10.1038/tpj.2011.34
4. Yimer G, Ueda N, Habtewold A, Amogne W, Suda A, Worku A, Riedel KD, Burhenne J, Aderaye G, Lindquist L, Makonnen E, Aklillu E. Pharmacogenetic & pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury in TB-HIV infected patients. *Plos One*. 2011;6: e27810 doi: 10.1371/journal.pone.0027810
5. Habtewold A Amogne W, Makonnen E, Yimer G, Riedel K-D, Ueda N, Worku A, Haefeli WE, Lindquist L, Aderaye G, Burhenne J, Aklillu E. Long-term effect of efavirenz autoinduction on plasma/PBMC drug exposure and CD4 count is influenced by UGT2B7 and CYP2B6 genotype among HIV patients. *J Antimicrob Chemother* 2011: 66: 2350-61
6. Jackson K. Mukonzo, Nanzigu S, Rekić D, Waako P, Röshammar D, Ashton M, Ogwal-okeng J, Gustafsson LL, Aklillu E. HIV/AIDS Patients Display Lower Relative Bioavailability of Efavirenz than Healthy Subjects. *Clin Pharmacokinet* 2011; 50:531-540
7. Ngaimisi E, Mugusi S, Minzi O, Sasi P, Riedel K-D, Suda A, Ueda N, Janabi M, Mugusi F, Haefeli WE, Bertilsson L, Burhenne J, Aklillu E. Effect of rifampicin and CYP2B6 genotype on long-term efavirenz autoinduction and plasma exposure in HIV patients with and without tuberculosis. *Clin Pharmacol Ther* 2011:90;406-13. doi:10.1038/clpt.2011.129
8. Aklillu E, Mugusi S, Ngaimisi E, Hoffmann MM, Konig S, et al. Frequency of the SLCO1B1 388A>G and the 521T>C polymorphism in Tanzania genotyped by a new LightCycler(R)-based method. *Eur J Clin Pharmacol* 2011: DOI 10.1007/s00228-011-1065-9
9. Ngaimisi E, Mugusi S, Minzi OM, Sasi P , Riedel K-D, Suda A, Ueda N, Janabi M, Mugusi F, Haefeli WE, Burhenne J, Aklillu E. Long-term efavirenz autoinduction and its effect on plasma exposure in HIV patients. *Clin Pharmacol Ther* 2010; 88: 676-684.
10. Mukonzo JK, Waako P, Ogwal-Okeng J, Gustafsson LL, Aklillu E. Genetic variations in ABCB1 and CYP3A5 as well as sex influence quinine disposition among Ugandans. *Ther Drug Monit*. 2010; 32:346-352
11. Diczfalusy U, Miura J, Roh HK, Mirghani RA, Sayi J, Larsson H, Bodin KG, Allqvist A, Jande M, Kim JW, Aklillu E, Gustafsson LL, Bertilsson L. 4Beta-hydroxycholesterol is a new endogenous CYP3A marker: relationship to CYP3A5 genotype, quinine 3-hydroxylation and sex in Koreans, Swedes and Tanzanians. *Pharmacogenet Genomics* 2008;18: 201-208
12. Burhenne J, Matthee AK, Pasakova I, Roder C, Heinrich T, Haefeli WE, Mikus G, Weiss J No evidence for induction of ABC transporters in peripheral blood mononuclear cells in humans after 14 days of efavirenz treatment. *Antimicrob Agents Chemother* 2010: 54: 4185-4191
13. Diczfalusy U, Nylen H, Elander P, Bertilsson L 4beta-Hydroxycholesterol, an endogenous marker of CYP3A4/5 activity in humans. *Br J Clin Pharmacol* 2011:71: 183-189
14. Kanebratt KP, Diczfalusy U, Backstrom T, Sparve E,

Bredberg E, Bottiger Y, Andersson TB, Bertilsson L. Cytochrome P450 induction by rifampicin in healthy subjects: determination using the Karolinska cocktail and the endogenous CYP3A4 marker 4beta-hydroxycholesterol. *Clin Pharmacol Ther* 2008: 84: 589-594

15. Diczfalusy U, Kanebratt KP, Bredberg E, Andersson TB, Bottiger Y, Bertilsson L () 4beta-hydroxycholesterol as an endogenous marker for CYP3A4/5 activity. Stability and half-life of elimination after induction with rifampicin. *Br J Clin Pharmacol* 2009; 67: 38-43
16. Aklillu E, Dandara C, Bertilsson L, Masimirembwa C: Pharmacogenetics of cytochrome p450s in African populations: Clinical and molecular evolutionary implications (http://eurekah.Com/chapter/3164); in Suarez-Kurtz G (ed Pharmacogenomics in admixed populations. Rio de Janeiro, Brazil, 2006
17. Josephson F, Bertilsson L, Bottiger Y, Flamholc L, Gisslen M, Ormaasen V, et al. CYP3A induction and inhibition by different antiretroviral regimens reflected by changes in plasma 4beta-hydroxycholesterol levels. *European journal of clinical pharmacology* 2008; 64:775-781.
18. Habetewold A, Amogne W, Makonnen E, Yimer G, Hylen H, Riedel K-D, Aderaye G, Bertilsson L, Burhenne J, Diczfalusy U and Aklillu E. Pharmacogenetic and pharmacokinetic aspects of CYP3A induction by efavirenz in HIV patients. *The Pharmacogenomics Journal* (2012), 1-6
19. Tafireyi Nemaura, Charles Nhachi and Collen Masimirembwa; Impact of gender, weight and CYP2B6 genotype on efavirenz exposure in patients on HIV/AIDS and TB treatment: Implications for individualising therapy. Vol. 6(29), pp. 2188-2193, 8 August, 2012
20. McIlleron H, Gous H; Pharmacokinetics of antiretroviral drugs in infancy; *Southern African Journal of HIV Medicine* Dec 2009, Vol 10 Source Issue 4, Accession Number 215250109
21. Milimo Maimbo, Kazuma Kiyotani, Taisei Mushiroda, Collen Masimirembwa, Yusuke Nakamura; CYP2B6 genotype is a strong predictor of systemic exposure to efavirenz in HIV-infected Zimbabweans; *European journal of clinical pharmacology* 2012 Vol 68 pages 267–271
22. Mugusi SF, Ngaimisi E, Janabi MY, Mugusi FM, Minzi OM, Sasi PG, Bakari M, Lindquist L, Aklillu E, Sandstrom EG. Risk factors for mortality among HIV-positive patients with and without active tuberculosis in Dar es Salaam, Tanzania, *Antiviral Therapy*, 2012;17(2):265-74. doi: 10.3851/IMP1956. Epub 2011 Nov 17

2.1.3 PPK.DDK - HIV and TB medications

EDCTP Project Coordinator:	Concepta Merry (University of Cape Town, South Africa)
EDCTP Call Title:	Phase II-III trials of drug regimens that shorten or simplify current treatment options. Emphasis will be on novel regimens. In addition to efficacy and tolerability assessments, evaluation of pharmacokinetics and drug-drug interactions and drug absorption may be included. Proposals should include assessment of the proposed regimens in HIV- and/or HIV+ infected tuberculosis patients, including patients receiving anti-retroviral drugs (EDCTP Code 2004.01.T.d2).
EDCTP Project Title:	Determining the optimal doses of antiretroviral and antituberculous medications when used in combination for the treatment of HIV/TB in co-infected patients
EDCTP Project Code:	CT.2004.32011.003
EDCTP Project Start Date:	30 June 2006
EDCTP Project End Date:	6 July 2010
Collaborators:	• David J Back (University of Liverpool, UK) • David Marinus Burger (Radboud University Nijmegen, Netherlands) • Bill Burman (University of Colorado at Denver and Health Sciences Center, USA) • Linelle Campbell (South African Clinical Research Organisation (SACRA), South Africa) • Chifumbe Chintu (University Teaching Hospital, Zambia) • Peter Coakley (Makerere University, Uganda) • Eric Decloedt (University of Cape Town, South Africa) • Saye Khoo (University of Liverpool, UK) • Mohammed Lamorde (Trinity College, Ireland) • Gary Maartens (University of Cape Town, South Africa) • Helen McIlleron (University of Cape Town, South Africa) • Mirjam Oudijk (University Teaching Hospital, Zambia) • Mairin Ryan (Trinity College, Ireland) • Peter John Smith (University of Cape Town, South Africa) • Doug Wilson (University of KwaZulu-Natal, South Africa)
Study/Trial 1:	
Site Principal Investigator(s):	Concepta Merry (South Africa)
Clinical Trial/Study Sponsor:	University of Cape Town (South Africa)
Trial/Study title:	Determining the optimal doses of antiretroviral and antituberculous medications when used in combination for the treatment of HIV/TB in co-infected patients
Goal:	To investigate the bi-directional interactions of efavirenz (EFV), nevirapine (NVP), lopinavir (LPV; with ritonavir) and ritonavir (RTV; with lopinavir) with rifampicin-based anti-TB therapy in South African adult and paediatric HIV-infected patients.
Primary Objective(s):	**Adult study:** 23. To compare PK of EFV, NVP, LPV and RTV in adult HIV-infected patients who are receiving rifampicin based ant-TB therapy with the PK profiles of EFV, NPV, LPV, and RTV in the same patients when they have completed anti-TB therapy 24. To compare the PK of rifampicin and isoniazid in patients receiving ARVs in accordance with national guidelines with historical population PK profiles of rifampicin and isoniazid in patients who do not require ARV therapy.

	Paediatric study: 25. To compare the trough levels of EFV, NVP, LPV and RTV in HIV-infected paediatric patients who are receiving rifampicin based anti-TB therapy with the PK profiles of EFV, NPV, LPV, and RTV in the same patients when they have completed anti-TB therapy.
Secondary Objective(s):	**Adult study:** 26. To develop the University of Cape Town as a regional reference centre for the conduct of clinical PK of HIV studies and the determination of ARV drug assays by building human laboratory capacity 27. To develop efficient methods appropriate to a resource-limited setting for estimation of EFV, NVP, LPV, and RTV concentrations 28. To determine the impact of covariate patient and drug factors on the PK of EFV, NPV, LPV, rifampicin and isoniazid. **Paediatric study:** 29. To test filter paper method developed in the adult study for the determination of EFV, NVP, LPV and RTV under field conditions, using 0.2ml of whole blood (obtained from a heel prick in children) 30. To determine the impact of covariate patient and drug factors on the pre-dose levels of EFV, NVP, LPV and RTV.
Clinical Trial/Study site(s):	• Groote Schuur Hospital, University of Cape Town (South Africa) • Red Cross Hospital, University of Cape Town (South Africa) • Tygerberg Hospital , Cape Town (South Africa) • PK-Laboratory Division of Pharmacology, University of Cape Town (South Africa)
Collaborating site(s):	• University of Liverpool (UK) • Radboud University Nijmegen (Netherlands) • South African Clinical Research Organisation (SACRA, South Africa) • University Teaching Hospital (Zambia) • Makerere University (Uganda) • University of Cape Town (South Africa) • Trinity College Dublin (Ireland) • University of KwaZulu-Natal (South Africa)
Study design:	Non-randomised, open label study
Number of subjects:	178
Product(s):	• Efavirenz (EFV) • nevirapine (NVP) • lopinavir (LPV) • ritonavir (RTV) • rifampicin
Manufacturer/Developer:	• DuPont Pharmaceuticals • Tübingen • Boehringer Ingelheim
Trial registration number(s):	ATM 2008060000852767
Status:	Completed
Results and Outcomes:	The key findingsare that double dose of Kaletra does not overcome induction by rifampicin in HIV/TB infected children while double dose of Kaletra does appear to overcome induction by rifampicin in HIV/TB co-infected adults. The project has generated valuable data on the management of

	HIV/TB co-infected patients, built capacity both institutionally and for individuals in clinical pharmacokinetics and forged new collaborations north-south-south. A complementary study that has resulted from this study is a PhD project by Chao Zhang (funded by Wellcome Trust through PKPDia collaborative network). Integrated population PK models describing induction and inhibition interactions in children and adults receiving LPV/r-based ART and rifampicin-based antitubercular treatment.
PhD study:	Title: Antiretroviral Therapy – Pharmacological considerations in developing countries Candidate: Mohammed Lamorde (Infectious Diseases Institute, Faculty of Medicine, Makerere University, Kampala, Uganda)
Publications:	1. McIlleron H, Ten Y, Nuttall J, Fairlie L, Rabie H, Cotton M, Eley B, Meyers T, Smith PJ, Merry C, Maartens G. Lopinavir exposure is insufficient in children given double doses of lopinavir/ritonavir during rifampicin-based treatment for tuberculosis. *Antiviral Therapy*, 2011;16(3):417-21. doi: 10.3851/IMP1757 2. Decloedt E, McIlleron Smith P, Merry C Orrell, C Maartens. The Pharmacokinetics of lopinavir in HIV-infected adults receiving rifampicin with adjusted doses of lopinavir/ritonavir tablets. *Antimirobial Agents and Chemotherapy* 2011 Jul;55(7):3195-200. doi: 10.1128/AAC.01598-10. Epub 2011 May 2 3. Maartens G, Decloedt E, Cohen K. Effectiveness and safety of antiretrovirals with rifampicin: critical issues for high burden countries. *Antiviral Therapy* 2009;14(8):1039-43 4. McIlleron H, Gous H. Pharmacokinetics of antiretroviral drugs in infancy. *Southern African Journal of HIV Medicine* 2009; 10:54-61 5. Zvada SP, Van Der Walt J, Smith PJ, Fourie PB, Roscigno G, Mitchison D, Simonsson USH, McIlleron HM. Effect of Four Different Meals Types on the Population Pharmacokinetics of a single 900 mg Dose of Rifapentine in Healthy Male Volunteers. *Antimicrob Agents Chemother*. 2010 Aug;54(8):3390-4. doi: 10.1128/AAC.00345-10. Epub 2010 Jun 1 6. Pepper DJ, Marais S, Wilkinson RJ, Bhaijee F, Maartens G, McIlleron H, De Azevedo V, Cox H, McDermid C, Sokhela S, Patel J, Meintjes G. The initiation of antiretroviral treatment at higher CD4 counts to reduce the burden of clinical deterioration during antituberculosis treatment in Africa. *BMC Infectious Diseases* 2010 Mar 30 ;10:83. doi: 10.1186/1471-2334-10-83 7. Ren Y, Nuttall JJC, Egbers C, Eley BS, Meyers TM, Smith PJ, Maartens G, McIlleron HM. Effect of Rifampicin on Efavirenz Pharmacokinetics in HIV-infected Children with Tuberculosis. *J Acquir Immune Defic Syndr* 2009. 50(5):439-43. 8. Decloedt, EH; Maartens, G; Smith, P; Merry, C; Bango, F; McIlleron, H. The Safety, Effectiveness and Concentrations of Adjusted Lopinavir/Ritonavir in HIV-Infected Adults on Rifampicin-Based Antitubercular Therapy, *PLOS ONE*, 2012, Vol 7 issue 3 9. Helen McIlleron, Hermien Gous. Pharmacokinetics of antiretroviral drugs in infancy. *The Southern African Journal of HIV Medicine.* Dec 2009, pp54-61

	10. Oudijk, J. Mirjam ; McIlleron, Helen; Mulenga, Veronica; Chintu, Chifumbe; Merry, Concepta; Walker, A. Sarah; Cook, Adrian; Gibb, Diana M.; Burger, David M. Pharmacokinetics of nevirapine in HIV-infected children under 3 years on rifampicin-based antituberculosis treatment. *AIDS Official Journal of the International AIDS society*. 31 July 2012 - Volume 26 - Issue 12 - p 1523–1528.

2.1.4 Rifaquin

EDCTP Project Coordinator:	Amina Jindani (St. George's University of London, UK)
EDCTP Call Title:	Phase II-III trials of drug regimens for TB that shorten or simplify current treatment option
EDCTP Project Title:	A controlled clinical trial to evaluate high dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis
EDCTP Project Code:	CT.2004.32011.002
EDCTP Project Start Date:	23 November 2006
EDCTP Project End Date:	31 December 2012
Collaborators:	• Salome Charalambous (Aurum Institute for Health Research, South Africa) • Gavin John Churchyard (Aurum Institute for Health Research, South Africa) • Heather Clouting (Medical Research Council (MRC), UK) • Elizabeth Corbett (Biomedical Research and Training Institute (BRTI), Zimbabwe) • Paul Craven (St. George's University of London, UK) • Zulmira Almeida Da Silva (Ministry of Health, Mozambique) • Janneke van Dijk (Medical Institute at Macha, Zambia) • Innocent Tichaona Gangaidzo (University of Zimbabwe) • Mark Hatherill (University of Cape Town, South Africa) • Gary Maartens (University of Cape Town, South Africa) • Helen McIlleron (University of Cape Town, South Africa) • Denis Mitchison (St. George's University of London, UK) • Mungofa, Stanley (Harare City Health Department, Zimbabwe) • Andrew Nunn (MRC, UK) • Paula Perdigao (ministry of Health, Mozambique) • James Christopher Shepherd (BOTUSA, Botswana) • Peter John Smith (University of Cape Town, South Africa) • Michelle Tetlow (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Simukai T. Zizhou (University of Zimbabwe)
Study / Trial 1	
Site Principal Investigator(s):	Amina Jindani (UK)
Clinical Trial/Study Sponsor:	St Georges Hospital Medical School trading as St Georges University of London
Trial/Study title:	An international multicentre controlled clinical trial to evaluate high-dose rifapentine and a quinolone in the treatment of pulmonary tuberculosis
Goal:	To shorten the tuberculosis treatment duration or simplify treatment administration
Primary Objective(s):	1. To evaluate the effect of an increase in rifapentine dose size in reducing or eliminating the risk of rifamycin mono resistance (RMR) in relapse cultures in HIV positive patients 2. To evaluate the effect of an increase in Rifapentine dose size in decreasing the relapse rate so that it would be equivalent to the aret found in a control regimen of rifampicin/isoniazid 3. To assess whether moxifloxacin can substitute for isoniazid in treatment regimens.
Clinical Trial/Study site(s):	• SATVI Institute of Infectious Diseases & Molecular Medicine (South Africa) • BOTUSA, Gaborone (Botswana) • Harare City Health Department (Zimbabwe)

	• Medical/Malaria Institute at Macha, Macha Mission Hospital (Zambia) • Biomedical Research and Training Institute (Zimbabwe) • Provincial Medical Directorate Mashonaland East (Zimbabwe) • Aurum Insitute for Health Research (South Africa)
Collaborating site(s):	• Direcção de Saúde da Cidade de Maputo (Mozambique) • Harare City Health Department (Zimbabwe) • Biomedical Research and Training Institute (Zimbabwe) • Medical/Malaria Institute at Macha, Macha Mission Hospital (Zambia) • MRC Clinical trials Unit(UK); SATVI, Institute of Infectious Diseases and Molecular Medicine (South Africa).
Study design:	Randomised, open label study
Number of subjects:	1100
Product(s):	• Ethambutol • Isoniazid • Moxifloxacin • Pyrazinamide • Rifampicin (RIF) • Rifapentine
Manufacturer/Developer:	• Bayer • Sanofi-Aventis
Cofunders:	• Medical Research Council (MRC, UK) • Wellcome Trust (UK) • Sanofi-Aventis (France)
Sub-studies:	4. Population studies of INH, rifapentine and moxifloxacin blood levels will be carried out on samples of patients, only in South African centres 5. The rate of acetylation of INH, measured by NAT2 genotyping, will also be done on all failure/relapse patients as compared to a sample that go on to a cure.
Trial Registration number(s):	ISRCTN 44153044 ATMR2008060000861040
Status:	Completed
Results and Outcomes:	
Publications:	1. Zvada, SP; Denti, P; Geldenhuys, H; Meredith, S; van As, D; Hatherill, M; Hanekom, W; Wiesner, L; Simonsson, USH; Jindani, A; Harrison, T; McIlleron, HM. Moxifloxacin Population Pharmacokinetics in Patients with Pulmonary Tuberculosis and the Effect of Intermittent High-Dose Rifapentine. *Antimicrobial Agents and Chemotherapy*. Vol 56, Issue 8, pp 4471-4473.

2.1.5 REMox I and II

EDCTP Project Coordinator:	Stephen Gillespie (University College London, UK)
EDCTP Call Title:	Phase II-III trials of drug regimens that shorten or simplify current treatment option
EDCTP Project Title:	Rapid Evaluation of Moxifloxacin in the treatment of sputum smear positive tuberculosis: REMoxTB (REMox I)
EDCTP Project Code:	CT.2004.32011.001
EDCTP Call Title:	Support of phase I, II and III clinical trials on new drugs and improved drug combinations for the treatment of tuberculosis
EDCTP Project Title:	Rapid Evaluation of Moxifloxacin in Tuberculosis (REMox II)
EDCTP Project Code:	IP.2007.32011.011
EDCTP Project Start Date:	21 October 2005
EDCTP Project End Date:	31 December 2013
Collaborators:	• Evans Amukoye (Kenya Medical Research Institute (KEMRI), Kenya) • Martin Boeree (Radboud University Nijmegen, Netherlands) • Salome Charalambous (Aurum Institute for Health Research, South Africa) • Gavin John Churchyard (Aurum Institute for Health Research, South Africa) • Francesca Miranda Conradie (University of the Witwatersrand, South Africa) • Rodney Dawson (University of Cape Town Lung Institute, South Africa) • Andreas Diacon, (Stellenbosch University, South Africa) • Jeannine Du Bois (Stellenbosch University, South Africa) • Anna Easton (University College London, UK) • Michael Hoelscher (Ludwig-Maximilians Universitat Munchen, Germany) • Gibson Kibiki (Kilimanjaro Christian Medical Centre (KCMC), Tanzania) • Shabir Lahki (University of Zambia (UNZA), Zambia) • Timothy McHugh (University College London, UK) • Peter Mwaba (University of Zambia (UNZA), Zambia) • Kim Narunsky (University of Cape Town, South Africa) • Andrew Nunn (Medical Research Council (MRC), UK) • Alphonse Okwera (Makerere University, Uganda) • Alex Pym (MRC, South Africa) • Andrea Rachow (Mbeya Medical Research Programme, Tanzania) • Noel Elisifa Sam (KCMC, Tanzania) • Ian Matthias Sanne (University of the Witwatersrand, South Africa) • Afsatou Ndama Traoré (Albert Schweitzer Hospital, Gabon) • Alimuddin Zumla (University College London, UK)
Study / Trial 1	**REMox I**
Site Principal Investigator(s):	• Stephen Gillespie (UK) • Andrew Nunn (UK) • Timothy McHugh(UK) • Sarah Meredith (UK) • Ali Zumla (UK)
Clinical Trial/Study Sponsor:	Global TB Alliance (USA)
Trial/Study title:	Controlled comparison of two moxifloxacin containing treatment shortening regimens in pulmonary tuberculosis
Goal:	To investigate the ability of moxifloxacin to substitute for either

	ethambutol or isoniazid.
Primary Objective(s):	To evaluate the appropriate role of the highly active fluoroquinolone moxifloxacin in shortening the duration of therapy using a novel trials methodology. This will be achieved by fulfilling the following objectives: 2. By trialling a regimen which replaces ethambutol with moxifloxacin to determine whether it can increase the proportion of patients culture negative at 2 months 3. By trialling a regimen which replaces isoniazid with moxifloxacin to determine whether it can increase the proportion of patients culture negative at 2 months.
Secondary Objective(s):	Capacity Building in sub-Saharan Africa to support future phase II and III clinical trials for TB treatment research.
Clinical Trial/Study site(s):	• Kibon'goto National Tuberculosis Hospital (Tanzania) • Tumaini University (Tanzania) • University Teaching Hospital, Lusaka (Zambia) • SAMRC Tuberculosis Programme, Durban (South Africa)
Collaborating site(s):	• University College London (UK) • Medical Research Council Clinical Trials Unit (UK) • University of Zambia (Zambia) • Kilimanjaro Christian Medical College (KCMC, Tanzania) • Triclinium Clinical Research (South Africa) • Medical Research Council (MRC, South Africa) • Pharmanet Development Group (United States)
Study design:	A randomised placebo-controlled, double-blind trial comparing two treatment-shortening regimens with the standard regimen (two months ethambutol, isoniazid, rifampicin and pyrazinamide followed by four months isoniazid and rifampicin) namely 1) two months moxifloxacin, isoniazid, rifampicin and pyrazinamide followed by two months moxifloxacin, isoniazid and rifampicin and 2) two months ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by two months moxifloxacin and rifampicin for the treatment of adults with pulmonary tuberculosis.
Number of subjects:	900
Product(s):	• Moxifloxacin • Ethambutol • Isoniazid • Pyrazinamide • Rifampicin (RIF)
Manufacturer/Developer:	• Bayer (Moxifloxacin) • Generic suppliers (Pyrazinamide, Rifampicin, Isoniazid, Ethambutol)
Cofunders:	• TB Alliance • Bayer • Sanofi-Aventis • Medical Research Council UK
Trial registration number(s):	NCT00864383
Status:	Ongoing
Results and Outcomes:	Recruitment reached the target of 1904 in January 2012. The follow-up study, REMox II, is detailed below.
Study/Trial 2	**REMox II**
Site Principal Investigator(s):	• Stephen Gillespie (UK) • Andrew Nunn (UK) • Timothy McHugh (UK) • Sarah Meredith (UK) • Ali Zumla (UK)
Clinical Trial/Study	Global TB Alliance (USA)

Sponsor:	
Trial/Study title:	Rapid Evaluation of Moxifloxacin in Tuberculosis
Goal:	To generate data that will permit registration of one or two treatment-shortening regimens for the treatment of pulmonary TB.
Primary Objective(s):	1. To evaluate the efficacy, safety, and acceptability of two moxifloxacin-containing regimens 2. To determine whether substitution for ethambutol or isoniazid makes it possible to reduce the duration of chemotherapy 3. To present the data to international regulatory agencies to permit the regimens to be implemented internationally in resource-poor settings.
Secondary Objective(s):	1. To assess determinants of the pharmacokinetics of the TB drugs used in Regimen 1, Regimen 2, and Regimen 3 of the REMoxTB study 2. To assess possible relationships between the pharmacokinetics of the TB drugs in the REMoxTB study on the one hand and pharmacodynamic measures of efficacy, bacteriological response, and tolerability on the other hand. In this way, possible differences between treatment arms may be explained.
Clinical Trial/Study site(s):	University Teaching Hospital Clinics in Lusakam (Zambia) SAMRC supported clinics in Durban Kwa-Zulu Natal (South Africa) The Lung Institute Clinics in Cape Town (South Africa) Kibon'goto National Tuberculosis Hospital (Tanzania) Tiervlei Centre in Tygerberg (South Africa) Clinics supported by KEMRI in Kibera, Nairobi (Kenya)
Collaborating site(s):	• Kenya Medical Research Institute (KEMRI, Kenya) • University of Cape Town Lung Institute (South Africa) • Stellenbosch University (South Africa) • University College London (UK) • Medical Research Council (UK) • University of Zambia • Medical Research Council (South Africa) • Kilimanjaro Christian Medical College (KCMC, Tanzania)
Study design:	A randomised placebo-controlled double blind trial involving a treatment-shortening regimen comparing 2 months moxifloxacin, isoniazid, rifampicin, and pyrazinamide followed by 2 months moxifloxacin, isoniazid, and rifampicin with the standard regimen (2 months ethambutol, isoniazid, rifampicin, and pyrazinamide followed by 4 months isoniazid and rifampicin); a treatment-shortening regimen comparing 2 months ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 2 months moxifloxacin and rifampicin with the standard regimen, for the treatment of adults with pulmonary TB.
Number of subjects:	Combined REMox I and REMox II (using the same protocol for the two projects) is 1900
Product(s):	• Moxifloxacin • Ethambutol • Isoniazid • Pyrazinamide • Rifampicin (RIF)
Manufacturer/Developer:	• Bayer (Moxifloxacin) • Generic suppliers (Pyrazinamide, Rifampicin, Isoniazid, Ethambutol)
Cofunders:	• Medical Research Council (UK)

	• TB Alliance (USA) • Bill & Melinda Gates Foundation (USA) • Netherlands Organisation for Scientific Research (NOW, Netherlands)
Trial registration number(s):	NCT00864383
Sub-studies:	**QTc sub-study:** Although moxifloxacin has been in use for many years and has an excellent safety record, an additional sub-study to investigate the effect of all three regimens on QTc in the context of patients with low weight who are receiving the drug for up to 4 months. **Pharmacokinetic (PK) study:** A pharmacokinetic study of this potential interaction between rifampicin and moxifloxacin in the context of patients with tuberculosis.
Status:	Ongoing
Results and Outcomes:	Enrolment to the study has been completed with a total of 1931 patients randomised by 17 January 2012. All patients have now finished active treatment and continue in the follow-up phase. Considerable effort is being given to database cleaning, finalising laboratory reports and molecular testing of relapse/re-infection patients. The statistical analysis plan is being finalised and shared with regulatory bodies. Intensive discussion is ongoing to ensure that programming of the database will generate the necessary data for the clinical study report.
Publications:	1. Phillips PP, Gillespie SH, Boeree M, Heinrich N, Aarnoutse R, McHugh T, Pletschette M, Lienhardt C, Hafner R, Mgone C, Zumla A, Nunn AJ, Hoelscher M. (2012) Innovative Trial Designs Are Practical Solutions for Improving the Treatment of Tuberculosis. *J Infect Dis*., Mar 23. PubMed PMID: 22448027. 2. Coxon GD, Cooper CB, Gillespie SH, McHugh TD. (2012) Strategies and Challenges Involved in the Discovery of New Chemical Entities During Early-Stage Tuberculosis Drug Discovery. J Infect Dis., Mar 23 3. Singh KP, Brown M, Murphy ME, Gillespie SH Moxifloxacin for tuberculosis. *Lancet Infect Dis*. 2012 Mar;12(3):176 4. Murphy ME, Singh KP, Laurenzi M, Brown M, Gillespie SH. (2012) Managing malaria in tuberculosis patients on fluoroquinolone-containing regimens: assessing the risk of QT prolongation. *Int J Tuberc Lung Dis*., Feb;16(2):144-9, i-iii. 5. Honeyborne I, McHugh TD, Phillips PP, Bannoo S, Bateson A, Carroll N, Perrin FM, Ronacher K, Wright L, van Helden PD, Walzl G, Gillespie SH. (2011) Molecular bacterial load assay, a culture-free biomarker for rapid and accurate quantification of sputum Mycobacterium tuberculosis bacillary load during treatment. *J Clin Microbiol*., Nov;49(11):3905-11. Epub 2011 Sep 7. PubMed PMID: 21900522; PubMed Central PMCID: PMC3209113. 6. van Ingen J, Aarnoutse RE, Donald PR, Diacon AH, Dawson R, Plemper van Balen G, Gillespie SH, Boeree MJ. (2011) Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment? *Clin Infect Dis*., May;52(9):e194-9. 7. Gillespie SH, Singh K. (2011) XDR-TB, what is it; how is it treated; and why is therapeutic failure so high? Recent Pat Antiinfect Drug Discov., May;6(2):77-83.

	8. McNerney R, Maeurer M, Abubakar I, Marais B, McHugh TD, Ford N, Weyer K, Lawn S, Grobusch MP, Memish Z, Squire SB, Pantaleo G, Chakaya J, Casenghi M, Migliori GB, Mwaba P, Zijenah L, Hoelscher M, Cox H, Swaminathan S, Kim P, Schito M, Harari A, Bates M, Schwank S, O'Grady J, Pletschette M, Ditui L, Atun R, Zumla A. (2012) Tuberculosis Diagnostics and Biomarkers: Needs, Challenges, Recent Advances, and Opportunities. *J Infect Dis*., Apr 10. [Epub ahead of print] PubMed PMID: 22496353. 9. Zumla A, Abubakar I, Raviglione M, Hoelscher M, Ditiu L, McHugh TD, Squire SB, Cox H, Ford N, McNerney R, Marais B, Grobusch M, Lawn SD, Migliori GB, Mwaba P, O'Grady J, Pletschette M, Ramsay A, Chakaya J, Schito M, Swaminathan S, Memish Z, Maeurer M, Atun R. (2012) Drug-Resistant Tuberculosis-Current Dilemmas, Unanswered Questions, Challenges, and Priority Needs*. J Infect Dis*., Apr 3. [Epub ahead of print] PubMed PMID: 22476720. 10. Phillips, PPJ; Gillespie, SH; Boeree, M; Heinrich, N; Aarnoutse, R; McHugh, T; Pletschette, M; Lienhardt, C; Hafner, R; Mgone, C; Zumla, A; Nunn, AJ; Hoelscher, M. (2012) Innovative Trial Designs Are Practical Solutions for Improving the Treatment of Tuberculosis. *Journal of Infectious Diseases*., Vol 205
Press releases:	TB Alliance press release EDCTP press release

2.1.6 PanACEA-HIGHRIF

EDCTP Project Coordinator:	Martin Boeree (Radboud University Nijmegen, Netherlands)
EDCTP Call Title:	Support of phase I, II and III clinical trials on new drugs and improved drug nations for the treatment of tuberculosis
EDCTP Project Title:	Rapid evaluation of high-dose rifamipicin and other rifamycins in tuberculosis
EDCTP Project Code:	IP.2007.32011.012
EDCTP Project Start Date:	11 June 2009
EDCTP Project End Date:	10 June 2014
Collaborators:	• Robert Edward Aarnoutse (Radboud University Nijmegen, Netherlands) • Salim Abdulla (Ifakara Health Research and Development Centre, Tanzania) • Hans-Peter Beck (Swiss Tropical Institute, Switzerland) • Boeree, Martin (Radboud University Nijmegen, Netherlands) • Gavin Churchyard (Aurum Institute for Health Research, South Africa) • Rodney Dawson (University of Cape Town Lung Institute, South Africa) • Andreas Henri Diacon (Stellenbosch University, South Africa) • Stephen Gillespie (University College London, UK) • Gibson Kibiki (Kilimanjaro Christian Medical Centre (KCMC), Tanzania) • Timothy McHugh (University College London, UK) • Alphonse Okwera (Makerere University, Uganda) • Georgette Plemper van Balen (Radboud University Nijmegen, Netherlands) • Noel Elisifa Sam (KCMC, Tanzania) • D. van Soolingen (National Institute for Public Health and the Environment (RIVM), Netherlands)
Study / Trial 1	
Site Principal Investigator(s):	• Andreas Henri Diacon (South Africa) • Rodney Dawson (South Africa)
Clinical Trial/Study Sponsor:	Radboud University Nijmegen Medical Centre (Netherlands)
Trial/Study title:	A Phase IIA Dose Ranging Trial to Evaluate the Safety, Tolerability, Extended Early Bactericidal Activity and Pharmacokinetics of Higher Doses of Rifampicin in Adult Subjects with Newly Diagnosed, Uncomplicated, Smear-Positive, Pulmonary Tuberculosis.
Goal:	Study 1 is a phase I/II maximum tolerability dosage (MTD) trial for rifampicin administered as a single drug and when combined with regular TB drugs in TB patients. In this MTD study a multiple dose rising approach is chosen to assess the safety/tolerability, pharmacokinetics and early bactericidal activity of increasing doses of rifampicin administered alone and with other TB drugs during a short period of 1 and 2 weeks respectively. To find the maximal tolerable dose of rifampicin.
Primary Objective(s):	1. 2. To establish the incidence and severity of adverse events of increasing dosages of rifampicin administered as a single drug and when combined with isoniazid, pyrazinamide and ethambutol in patients with newly

	diagnosed, uncomplicated, smear-positive pulmonary TB 3. To establish the maximum tolerated dose for rifampicin administered in increasing doses as a single drug and when combined with isoniazid, pyrazinamide and ethambutol in patients with newly diagnosed, uncomplicated, smear-positive pulmonary TB.
Secondary Objective(s):	1. To assess the early bactericidal activity of increasing doses of rifampicin when administered as a single drug 2. To describe the steady-state pharmacokinetics of increasing doses of rifampicin when administered as a single drug and when combined with isoniazid, pyrazinamide and ethambutol 3. To assess possible relationships between pharmacokinetic parameters of rifampicin on the one hand and adverse events and bactericidal activity on the other hand (pharmacodynamics of rifampicin).
Clinical Trial/Study site(s):	• TASK applied Science (South Africa) • Centre for Clinical Tuberculosis Research University of Stellenbosch, Tygerberg (South Africa) • University of Cape Town Lung Institute, Cape Town (South Africa)
Collaborating site(s):	• Radboud University (The Netherlands) • Ifakara Health Research and Development Centre (Tanzania) • Aurum Institute for Health Research (South Africa) • Stellenbosch University (South Africa) • St Andrews University (UK) • University College London (UK) • Makerere University (Uganda) • Kilimanjaro Christian Medical Centre (KCMC) (Tanzania) • National Institute for Public Health and the Environment (RIVM) (The Netherlands)
Study design:	An open-label, prospective, two-centre, Phase IIA, maximum tolerability dosage (MTD) study conducted in consecutive groups. Study 4: Open-label, one-arm, two-period, and fixed-order pharmacokinetic interaction study
Number of subjects:	68
Product(s):	Rifampicin
Manufacturer/Developer:	Sanofi-Aventis, Paris (France)
Cofunders:	• Netherlands Organisation for Scientific Research (NWO, Netherlands) • Radboud University Nijmegen (Netherlands) • Swiss Tropical and Public Health Institute (Switzerland) • Prince Leopold Institute of Tropical Medicine (Belgium) • Medical Research Council South Africa (MRC, South Africa)
Trial registration number(s):	PACTR201104000281203
Status:	Ongoing
Results and Outcomes:	The group have successfully completed the enrolment of 68 participants in the dose escalation study. The safety results of the patients have been extensively reviewed by the Trial Steering Committee for all dosing steps. With 35 mg rifampicin/kg still being safe and tolerable an important deliverable is obtained, but the search for the maximum tolerated dose of rifampicin has not yet been completed.
Study / Trial 2	
Site Principal	• Gibson Kibiki (Tanzania)

Investigator(s):	• Klaus Reither (Tanzania)
Clinical Trial/Study Sponsor:	Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands
Trial/Study title:	Pharmacokinetics and pharmacodynamics of high versus standard dose rifampicin in patients with pulmonary tuberculosis in Tanzania (High RIF Study).
Goal:	To evaluate the safety/tolerability and pharmacokinetics of 900 mg and 1200 mg of rifampicin combined with other TB drugs during a period of two months. Study 2 is a small exploratory Phase II study to evaluate the safety/tolerability and pharmacokinetics of 900 mg and 1200 mg of rifampicin combined with other TB drugs during a period of two months. This Phase II study reflects a cautious approach for the sake of patients' safety, in which application of high dose rifampicin for 2 months period is first evaluated for rather modest dose increases of rifampicin.
Primary Objective(s):	1. To determine the effect of a higher than standard dose of rifampicin on the pharmacokinetics of rifampicin in patients with smear-positive pulmonary tuberculosis in Tanzania 2. To determine the effect of a higher than standard dose of rifampicin on the occurrence of adverse events in the same population 3. To explore the effect of a higher than standard dose of rifampicin on the bacteriological response of Mycobacterium tuberculosis, evaluated by sputum culture conversion at two months and Serial Sputum Colony Forming Units Count (SSCC), in the same population.
Secondary Objective(s):	1. To compare the accuracy of surrogate markers (SSCC and RNA) with the standard two month sputum conversion marker in patients with smear-positive pulmonary tuberculosis in Tanzania 2. To document the occurrence of mixed Mycobacterium tuberculosis strain infections in the same patient population and its influence on treatment response.
Clinical Trial/Study site(s):	• Kilimanjaro Christian Medical College, Moshi with its field site Kibong'oto National TB Hospital, Sanya Yuu (Tanzania) • Ifakara Health Research and Development Centre, Bagamoyo (Tanzania)
Collaborating site(s):	Kibong'oto National TB Hospital, Sanya Yuu (Tanzania)
Study design:	Double blind, randomised, controlled, three arm, phase II clinical trial
Number of subjects:	150
Product(s):	Rifampicin
Manufacturer/Developer:	Sanofi-Aventis (France)
Cofunders:	• Netherlands Organisation for Scientific Research (NWO, Netherlands) • Radboud University Nijmegen (Netherlands) • Swiss Tropical and Public Health Institute (Switzerland) • Prince Leopold Institute of Tropical Medicine (Belgium) • Medical Research Council South Africa (MRC, South Africa)
Trial registration number(s):	NCT00760149 PACTR2009060001493909
Status:	Ongoing
Results and Outcomes:	Study 1 was completed however is planned to expand based upon the initial trial outcomes. This trial aimed to investigate the maximum tolerable dosage (MTD) of rifampicin compared to standard treatment (10 mg/kg or approximately 600mg daily).

	The MTD study administered 20, 25, 30 and 35 mg/kg of rifampicin. The study team found that despite administering a dose up to 3.5 fold increase in rifampicin compared to standard treatment, the MTD has not yet been found. The primary endpoint was to determine the incidence of adverse events and to identify the MTD. Based upon the common terminology criteria for adverse events (CTCAE) grading scale, only minimal grade 3 and 2 events occurred. No grade 4 or 5 events were reported. A secondary outcome was that the higher dosages of rifampicin (30 and 35 mg/kg) showed improved early bactericidal activity (EBA) over a 14 day period. The conclusion of this study was that the increase from 10 to 35mg/kg was found to be safe and tolerated, with a suggestion that higher dosages were more effective in treating tuberculosis infection. As the MTD for rifampicin has not yet been determined, the study team is now seeking additional funds to continue this study.
PhD studies:	Title: Exploratory phase II study about laboratory analyses Candidate: Charles Mtahbo (Radboud University, Nijmegen, Netherlands) Dates: -December 2013
	Title: Method validation and Pharmacokinetics Candidate: Hadija Semvua (Muhimbili University, Tanzania) Dates: -December 2013
Other/Sub-studies:	Multi-arm multi-stage trial to identify regimens to include in a phase III trial for shorter treatment of tuberculosis. Objectives: The general objective is to identify arms which are significantly more efficient than the control regimen in terms of reducing bacterial load in sputum, measured by time to culture conversion. Secondary objectives are: • to assess the relative efficacy of the experimental four-drug combinations for the treatment of pulmonary tuberculosis within the first twelve weeks of treatment, and select the most efficient experimental treatment regimen for further development, • to assess the frequency of acquired drug resistance among the experimental four-drug combinations. • to assess the frequency, severity, and type of adverse events (AEs), AE-related treatment discontinuations, and changes in ECG, • to describe the steady-state pharmacokinetics of the experimental new drugs and/or doses used in the experimental regimens and to assess possible relationships between pharmacokinetic parameters of the various drugs, and • to describe relationships between pharmacokinetic parameters and pharmacodynamic indices on the one hand and efficacy and safety endpoints on the other hand.
Publications:	1. Jakko van Ingen, Rob E. Aarnoutse, Peter R. Donald, Andreas H. Diacon, Rodney Dawson, Georgette Plemper van Balen, Stephen H. Gillespie, and Martin J. Boeree. Why Do We Use 600 mg of Rifampicin in Tuberculosis

	Treatment?. *Clinical Infectious Diseases* (2011) 52 (9): e194-e199. doi: 10.1093/cid/cir184 2. M. J. Boeree, G. Plemper van Balen, R. A. Aarnoutse. High-dose rifampicin: how do we proceed? *International Journal of Tuberculosis and Lung Disease*. 2011. PMID 21740683 3. Phillips PP, Gillespie SH, Boeree M, Heinrich N, Aarnoutse R, McHugh T, Pletschette M, Lienhardt C, Hafner R, Mgone C, Zumla A, Nunn AJ, Hoelscher M. Innovative Trial Designs Are Practical Solutions for Improving the Treatment of Tuberculosis. *J Infect Dis*. 2012 Mar 23. PubMed PMID: 22448027.

2.1.7 PanACEA-SQ109

EDCTP Project Coordinator:	Michael Hoelscher (Ludwig-Maximilians Universitat Munchen, Germany)
EDCTP Call Title:	Support of phase I, II and III clinical trials on new drugs and improved drug combinations for the treatment of tuberculosis
EDCTP Project Title:	Evaluation of a novel TB drug (SQ109) to shorten and simplify TB treatment
EDCTP Project Code:	IP.2007.32011.013
EDCTP Project Start Date:	16 June 2009
EDCTP Project End Date:	15 June 2014
Collaborators:	• Akim Ayola Adegnika (Leiden University, Netherlands) • Gavin Churchyard (Aurum Institute for Health Research, South Africa) • Rodney Dawson (University of Cape Town Lung Institute, South Africa) • Keertan Dheda (University College London, UK) • Andreas Henri Diacon (Stellenbosch University, South Africa) • Martin Grobusch (University of the Witwatersrand, South Africa) • Sonja Henne (Ludwig-Maximilians Universitat Munchen, Germany) • Grey Horwith (Sequella Inc., USA) • Leonard Maboko (Mbeya Medical Research Programme, Tanzania) • Ulrich Mansmann (Ludwig-Maximilians Universitat Munchen, Germany) • Peter Mwaba (University of Zambia (UNZA), Zambia) • Alphonse Okwera (Makerere University, Uganda) • Michael Ramharter (University of Tübingen, Germany) • Klaus Reither (Ifakara Health Research and Development Centre, Tanzania) • Alimuddin Zumla (University College London, UK)
Study / Trial 1	
Site Principal Investigator(s):	• Andreas Diacon (South Africa) • Michael Hoelscher (Germany)
Clinical Trial/Study Sponsor:	University of Munich (Germany)
Trial/Study title:	**Study 1:** A Phase 2A Trial to evaluate the extended early bactericidal activity, safety, tolerability and Pharmacokinetics of of SQ109 in adult subjects with newly-diagnosed , uncomplicated, smear-positive, pulmonary tuberculosis (N=90) **Study 2:** A phase 2A, dose-ranging study to assess safety, tolerability, and preliminary efficacy of isoniazid, rifampicin, pyrazinamide, and SQ109 (HRZSQ) for intensive-phase treatment of patients with uncomplicated, smear-positive, pulmonary tuberculosis caused by drug-sensitive Mycobacterium tuberculosis (N=150) **Study 3:** A phase 2B, double-blind comparison of isoniazid, rifampicin, pyrazinamide, and SQ109 (HRZSQ) and isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) intensive-phase DOTS regimen for treatment of patients with uncomplicated, smear-positive, pulmonary tuberculosis caused by drug-sensitive Mycobacterium tuberculosis (N=400)
Goal:	The overall objective of the SQ109 trial is to add a novel drug that has the potential to shorten the duration of TB treatment, simplify the treatment regimen, and decrease disease

	recurrence by replacing EMB in the intensive treatment phase.
Primary Objective(s):	1. To evaluate the safety, tolerability, efficacy, and pharmacokinetics of three oral dose levels of SQ109 alone and in combination with standard dose rifampicin 2. To assess safety, rolerability, and preliminary efficacy of isoniazid, rifampicin, pyrazinamide, and SQ109 (HRZSQ) 3. To compare of isoniazid, rifampicin, pyrazinamide, and SQ109 (HRZSQ) with isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE).
Secondary Objective(s):	Rate of change of logCFU in sputum over three time periods, time to sputum culture positivity
Clinical Trial/Study site(s):	• University of Stellenbosch (South Africa) • University of Cape Town (South Africa) • University of Witwatersrand (South Africa) • Aurum Insitute for Health Reserach Studies (Aurum) • Mbeya Medical Research Program (Tanzania) • University of Zambia; Albert Schweitzer Hospital (Gabon)
Collaborating site(s):	• University of Munich (Germany) • University College of London (UK) • University of Stellenbosch (South Africa) • University of Cape Town (South Africa) • University of Witwatersrand (South Africa) • Aurum Insitute for Health Reserach Studies (Aurum) • Mbeya Medical Research Program (Tanzania) • University of Zambia • Albert Schweitzer Hospital (Gabon) • Sequela Inc.(USA)
Study design:	**Study1:** A two-centre, partially blinded, randomised, parallel-group clinical trial. Five groups will receive SQ109 alone or with Rif and a sixth (control) group will receive standard dose RIF for 14 days **Study 2:** A three-arm, double-blind, Phase 2A study to compare activity (qualitative and quantitative sputum culture of M. tuberculosis) during the intensive treatment phase (first 8 weeks) of a “low dose” (150 mg), and a “high dose” (300 mg) SQ109-containing regimen and the standard 4-drug, 2-month, intensive-phase regimen consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE). **Study 3:** A two-arm, double-blind, Phase 2B study to compare activity (quantitative sputum cfu of M. tuberculosis) during the intensive treatment phase (first 8 weeks) of an SQ109 regimen (HRZSQ) selected from Study 2 and the standard 4-drug, 2-month, intensive-phase regimen consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE)
Number of subjects:	Phase IIA: n = 90 MSMA project design: A maximum of 372 adult (≥ 18 years of age) patients with newly diagnosed, smear positive pulmonary TB.
Product(s):	SQ109
Manufacturer/Developer:	Sequella Inc. (USA)
Cofunders:	• Klinikum der Universitat Munchen (Germany) • Institute for Medical Bioinformatics (Germany) • Medical Research Council (UK) • Bill & Melinda Gates Foundation (USA) • Sequella (USA) • Federal Ministry of Education and Research (BMBF, Germany) Netherlands Organisation for Scientific Research (NWO, Netherlands)

Trial registration number(s):	NCT01218217 (The EBA study) PACTR201009000252144
Sub-studies:	Early Bactericidal Activity (EBA)
Status:	Ongoing
Results and Outcomes:	
PhD studies:	Title: Bactericidal assay for therapeutic management of patients with pulmonary tuberculosis from Tanzania. (WBA/PBA Study) Candidate: Stellah Mpagama (KCRI, Tanzania) Dates: February 2012-January 2014
	Title: Direct comparison of different sputum derived biomarkers of antituberculosis drug activity in early bactericidal activity (EBA) studies Candidate: Xavier Abdulkarim Kayifire (Stellenbosch University, South Africa) Dates: March 2012-December 2014
MSc studies:	Title: MSc in Clinical Trials (distance learning) Candidate: Denis Lyakurwa (KCMC/Muhimbili University, Tanzania) Dates: October 2011-August 2013
	Tite: MSc in Clinical Trials (distance learning) Candidate: Jackline Odhiambo (KEMRI, Kenya) Dates: September 2011-October 2013
	Title: Determination of the Mechanism of Action of SQ109 in Mycobacterium tuberculosis (MTB) Candidate: Bayanika Manunu (Stellenbosch University, South Africa) Dates: July 2011-October 2013
	Title: MSc in Infectious Diseases (distance learning) Candidate: Liliana Rutaihwa (IHI-BRTC, Tanzania) Dates: June 2011-July 2014
Publications:	

2.2 Tuberculosis vaccines clinical trials

Project Acronym (Coordinator)	Phase of trial	Product(s)	Manufacturer/ Developer	Study population	Status
THYB-03 (Aseffa)	Phase Ib	Ag85B-ESAT-6	SSI	TST positive healthy adolescents N=39	Completed
Van't Hoog - TB Vac prep Kenya (Van't Hoog)	Prospective Epidemiology Cohort study	N/A	N/A	Neonates and adolescents N=7900	Completed
Musoke-TB Vac prep (Musoke)	Prospective Epidemiology Cohort study	N/A	N/A	Infants and adolescents N=7500	Completed
THYB-04 (Andersen)	II	Ag85B-ESAT-6 + adjuvant (500 nmol KLK and 20 nmol ODN1a)	SSI	TST positive healthy adolescents N= 240	Recruiting
TB-021: Aeras485 MVA85A (McShane)	IIb	MVA85A	Aeras/ OETC	Healthy, HIV-infected adults N=1400	Recruiting
Aeras 402/Crucell Ad35 (Hatherill)	II	AERAS-402	Aeras	BCG vaccinated, HIV-uninfected infants with no evidence of TB N=2200 – 4000 (adaptive). Enrolment stopped by sponsor in accordance with protocol criteria	Stopped
Aurum 102/THYB-05 (Churchyard)	II	Ag85B-ESAT-6 (50 Pg) (SSI H1) + adjuvant (500 nmol KLK and 20 nmol ODN1a)	SSI	HIV-infected, BCG-vaccinated Adults with CD4+ Lymphocyte Counts Greater Than 350 Cells/mm3 N= (48)	Completed

2.2.1 TB Vac prep Ethiopia/THYB-03

EDCTP Project Coordinator:	Abraham Aseffa (Armauer Hansen Research Institute (AHRI), Ethiopia)
EDCTP Call Title:	Capacity building and site development for the conduct of phase III trials of TB vaccines in high risk populations
EDCTP Project Title:	Capacity building for the conduct of ICH-GCP level TB vaccine trials in high risk populations in Ethiopia and East Africa
EDCTP Project Code:	CT.2005.32080.003
EDCTP Project Start Date:	10 August 2007
EDCTP Project End Date:	31 December 2010
Collaborators:	• Markos Abebe (Armauer Hansen Research Institute (AHRI), Ethiopia) • Ripley Ballou (GlaxoSmithKline, UK) • Peter Bang (Statens Serum Institut, (SSI), Denmark) • Joe Cohen (GlaxoSmithKline, UK) • Jaap van Dissel (Leiden University, Netherlands) • Mark Doherty (Statens Serum Institut, (SSI), Denmark) • Patrice Dubois (ImmunoVac Consulting, Belgium) • Howard Engers (AHRI, Ethiopia) • Gibson Kibiki (Kilimanjaro Christian Medical Centre (KCMC), Tanzania) • Opokua Ofori-Anyinam (GlaxoSmithKline, UK) • Tom Ottenhoff (Leiden University, Netherlands) • Herrimanana Henri Ramarokoto (Institut Pasteur de Madagascar) • Voahangy Rasolofo (Institut Pasteur de Madagascar) • John Shao (KCMC, Tanzania) • Ezera Shimeles (AHRI, Ethiopia) • Jean-Louis Soares (Institut Pasteur de Madagascar) • Liya Wassie Dubale (AHRI, Ethiopia) • Lawrence Yamuah (AHRI, Ethiopia)
Study/Trial 1	
Site Principal Investigator(s):	• Abraham Aseffa (Ethiopia) • Jemal Hussein (Ethiopia)
Clinical Trial/Study Sponsor:	SSI (Denmark)
Trial/Study title:	A Safety and Immunogenicity Trial With an Adjuvanted TB Subunit Vaccine (Ag85B-ESAT-6 + IC31) THYB-03
Goal:	4. To evaluate the safety profile of an adjuvanted TB subunit vaccine administered in different antigen/adjuvant formulations at 0 and 2 months 5. To determine the immunogenicity profile of an adjuvanted TB subunit vaccine administered in different antigen/adjuvant formulations at 0 and 2 months.
Primary Objective(s):	Strengthening the capacity of AHRI and its Ethiopian collaborators to carry out the required laboratory and data management activities to satisfy ICH-GCP conduct of Phase I, II and III TB vaccine trials
Secondary Objective(s):	Strengthening the capacity of existing AHRI partners in East Africa (Madagascar and Tanzania) to produce the basic laboratory information and data required for supporting TB vaccine research in their respective countries.
Clinical Trial/Study site(s):	The Armauer Hansen Research Institute (AHRI, Ethiopia)
Collaborating site(s):	• AHRI (Ethiopia) • Institut Pasteur (IPM, Madagascar) • Kilimanjaro Christian Medical College (KCMC, Tanzania) • GlaxoSmithKline Biologicals (GSK, UK)

	• Statens Serum Institute (SSI, Denmark • Leiden University (Netherlands) • Immunovac Consulting (Belgium)
Study design:	Phase I, open labelrandomised ncontrolledtrial to assedd safety and efficacy.
Number of subjects:	39
Product(s):	ESAT-6/Ag85B
Manufacturer/Developer:	• SSI produces ESAT-6/Ag85B • Intercell A/S produces IC31adjuvant
Cofunders:	• Statens Serum Institut (Denmark) • Leiden University (Netherlands)
Trial Registration number(s):	NCT01049282
Status:	Completed
Results and Outcomes:	The project was successful in building capacity for clinical trials at AHRI, Institut Pasteur in Madagascar and at KCMC in Tanzania. At AHRI, the capacity was built with hands on running of a phase I TB vaccine trial (ThyB 03) in collaboration with SSI. Laboratory infrastructure was improved with improved capacity for flow cytometric assays with FACSCanto. The GCP team has developed much experience in the course of the phase I trial and learned to work on a new phase II trial protocol writing. At KCMC, data management capacity was improved and laboratory skills for TB enhanced through training by a team from AHRI. Similarly, IP Madagascar benefited from lab assay training by Immunovac on flow cytometric assays and on GCLP. AHRI organized an ethics training for IP Madagascar staff. Several PhD and Masters students were trained at AHRI, Tanzania and at Madagascar. The links between the institutions were strengthened as a result leading to additional newtowrking in similar projects. At Addis Ababa, AHRI strengthened its links with the Ministry of Health and the regulatory authorities as well as the ethics committees through a number of communications and joint activities. The interaction between the SSI and AHRI scientists has benefitted the site and facilitated skills transfer particularly in the immunogenicity assays for the vaccine trial. Close interaction between Tanzania, Malagasy and Ethiopian laboratory researchers, including a two year stay of two AHRI researchers at KCMC on a Masters project, led to an excellent south-south networking which is now further enriched through additional opportunities of collaboration.
PhD studies:	Immunology project Candidate: Wude Mihret (Addis Ababa University, Ethiopia)
	Candidate: Liya Wassie (Addis Ababa University, Ethiopia)
	Candidate: Kidist Bobsha (Addis Ababa University, Ethiopia)
MSc studies:	MSc in Clinical Research Candidate: Tewodros Tariku (Addis Ababa University, Ethiopia)
	MSc in Clinical Research Candidate: Wassihum Wodajo (Addis Ababa University, Ethiopia)
	MSc in Clinical Research Candidate: Radeye Abeje (Addis Ababa University, Ethiopia)
	MSc Clinical Trials Candidate: Meseret Habtamu (Tumani University, Tanzania)
	MSc in Clinical Trials Candidate: Demis Arga (Tumani University, Tanzania)
	MSc in Clinical Trials Candidate: Tesfamaruam Mebrahtu (Addis Continental School of Public Health/Gondar, Ethiopia)
	MSc in Clinical Trials

	Candidate: Student: Sebe Mamo (Addis Continental School of Public Health/Gondar, Ethiopia)
Publications:	1. Tom H. M. Ottenhoff, T. Mark Doherty, Jaap T. van Dissel, Peter Bang, Karen Lingnau, Ingrid Kromann and Peter Andersen. First in humans: a new molecularly defined vaccine shows excellent safety and strong induction of longlived Mycobacterium tuberculosis-specific Th1-cell like responses. *Human Vaccines*. In Press. December 2010 2. Jaap T. van Dissel, Sandra M. Arend, Corine Prins, Peter Bang, Pernille Nyholm Tingskov, Karen Lingnau, Jan Nouta, Michèl R. Klein, Ida Rosenkrands, Tom H. M. Ottenhoff, Ingrid Kromann, T. Mark Doherty and Peter Andersen. Ag85B-ESAT-6 adjuvanted with IC31® promotes strong and long-lived Mycobacterium tuberculosis specific T cell responses in naïve human volunteers. *Vaccine*. 2010 Apr 30;28(20):3571-81.

2.2.2 Van't Hoog-TB Vac prep Kenya

EDCTP Project Coordinator:	Anja van't Hoog (University of Amsterdam, Netherlands)
EDCTP Call Title:	Capacity building and site development for the conduct of phase III trials of TB vaccines in high risk populations
EDCTP Project Title:	Prospective epidemiological studies of TB in neonates and adolescents in Karemo Division, Siaya district, Western Kenya, in preparation for future clinical trials
EDCTP Project Code:	CT.2005.32080.002
EDCTP Project Start Date:	13 June 2007
EDCTP Project End Date:	31 December 2011
Collaborators:	• Martinus Willem Borgdorff (KNCV Tuberculosis Foundation, Netherlands) • Vicky Cardenas (Aeras Global Tuberculosis Foundation, USA) • Daniela Cirillo, (San Raffaelle del monte Tabor foundation – Milan, Italy) • Parasuram Dhulipalla (Aeras Global Tuberculosis Foundation, USA) • Macaya Julie Douoguih (Aeras Global Tuberculosis Foundation, USA) • Lawrence James Geiter (Aeras Global Tuberculosis Foundation, USA) • Markus Gmeiner (Vienna School of Clinical Research, Austria) • Toni Hawkridge (Aeras Global Tuberculosis Foundation, USA) • Gregory Hussey (University of Cape Town, South Africa) • Kayla Laserson (Centers for Disease Control and Prevention (CDC), USA) • Katherine Leigh Feidler (Aeras Global Tuberculosis Foundation, USA) • Hassan Mahomed (University of Cape Town, South Africa) • Videlis Nduba (Kenya Medical Research Institute (KEMRI), Kenya) • Elizabeth Onyango-Okoth (Ministry of Health, Kenya) • Juliana Otieno (Ministry of Health, Kenya) • Jen Page (Aeras Global Tuberculosis Foundation, USA) • Suzanne Verver (KNCV Tuberculosis Foundation, Netherlands)
Study / Trial 1	
Site Principal Investigator(s):	• Videlis Nduba (Kenya) • Anja van't Hoog (Netherlands) • Kayla Laserson (USA)
Trial/Study title:	A Prospective Epidemiological Cohort Study to Evaluate the Incidence of Tuberculosis in Infants in Western Kenya A Prospective epidemiological study of TB in adolescents in Siaya district, Western Kenya, in preparation for future vaccine trials
Goal:	Cohort studies to develop capacity and prepare for TB vaccine trials
Primary Objective(s):	Neonates study aims to: 1. Estimate the one year incidence of tuberculosis disease as diagnosed by two sputum smears positive for AFB and/or a positive Mycobacterial culture 2. Determine all-cause and TB-specific mortality, through vital events monitoring and verbal autopsies; out-

	migration and cohort retention 3. Develop a system of reporting home deliveries and provision of BCG vaccination within 96 hours of birth 4. Monitor incidence of BCG-related adverse events 5. Assess community knowledge and attitudes about current practices regarding BCG vaccination. The adolescent study aims to: 1. Determine the optimal way to access an adolescent population 2. Determine one-year incidence of TB disease as diagnosed by two sputum smears positive for AFB and/or a positive Mycobacterial culture 3. Determine the prevalence of TB infection and disease 4. Estimate the annual risk of infection with M. tuberculosis as evidenced by the tuberculin skin test (TST) 5. Assess community knowledge and attitudes about current practices regarding BCG vaccination and TB 6. Determine the rate of hospitalization and mortality events through record review and verbal autopsy 7. Determine out-migration and cohort retention.
Secondary Objective(s):	To build capacity to: 1. Develop a system of reporting home deliveries and provision of BCG vaccination within 96 hours of birth 2. Monitor incidence of BCG-related adverse effects 3. Assess community knowledge and attitudes about current practices regarding BCG vaccination 4. Determine all cause mortality and TB specific mortality, through vital events monitoring and verbal autopsies.
Clinical Trial/Study site(s):	Karemo Division, Siaya district (Kenya)
Collaborating site(s):	• KNCV Tuberculosis Foundation (Netherlands) • Ministry of Health (Kenya) • KEMRI, Kenya • University of Cape Town (South Africa) • Center for Disease Control and Prevention (CDC, USA) • Vienna School of Clinical Research (Austria) • San Raffaelle del monte Tabor foundation (Italy)
Study design:	Prospective cohort study
Number of subjects:	5004 adolescents and 2900 infants
Cofunders:	• Netherlands Organisation for Scientific Research (NWO, Netherlands) • KNCV Tuberculosis Foundation (Netherlands) • San Raffaelle del monte Tabor foundation (Italy) • Austrian Federal Ministry of Science (Austria)
Status:	Completed
Results and Outcomes:	**Infant Cohort Study:** Followin screeing of 3223 infants, 2900 infants were enrolled in the study and BCG vaccinated. 60% of infants were born at home and 40% were born at health facilities. 401 (16.3%) were born to HIV infected mothers, and 2.6% tested HIV+ve at 6 weeks of age. Disclosure counselling was done and 47/73 (64%) infants referred and followed up to begin ART as per WHO and National recommendations; 26 out of 73 had died before disclosure. Through four monthly follow up visits and unscheduled (sick visits) 922 (31.8%) TB suspects were identified. 128 (13.9%) had a history of contact, 590(64%) had a hospitalisation criteria and 196 (21.3%) had TB symptoms. Of these 732 (79.6%) were

	investigated for TB in the newly renovated Case Verification Ward. Two early morning gastric aspirates and two induced sputum samples were collected on consequent mornings. Chest radiographs, Mantoux tests, HIV testing and Clinical assessments were done to determine TB cases. 45 TB cases were started on anti TB treatment in conjunction with the National Programme. This gives an incidence rate of 1.0 per 1000 person years (95% CI 0.75-1.36) for definite, probable and possible TB combined. 160 (5.5%) participants were identified to have Latent TB infection based on positive mantoux test, negative culture and normal chest radiographs. 24990 ancillary or unscheduled visits were conducted where free health care was provided at the study clinic. There were 203/2900(57/1000 person years) deaths. This is almost half the infant mortality in the study area (119/1000 live births) 10.8% were neonatal deaths. Pneumonia, malaria, diarreal disease were the leading immediate causes of death accounting for 43.1% of deaths. Study closeout visits have been completed. **Adolescent Cohort Study:** A total of 5541 adolescents were approached to participate in the study of which 5004 (90.3%) were enrolled. Out of 5004 adolescents enrolled, 2579 (51.5%) were male, mean age 14 years (SD 1.9). Based on screening criteria at enrolment, 1775 (35.5%) were identified as TB suspects due to either a household contact 144 (2.9%), symptoms of TB 515 (10.3%) and/or a positive TST 1544/4808 (32.1%); with 87.3% of TB suspects having only one criterion for investigation. All the TB suspects were offered and agreed to a HIV test and 21/1775 (1%) tested HIV positive. Fifteen culture confirmed PTB cases were identified and 24 probable PTB based on clinical and radiological criteria reflecting a prevalence estimate of 300/100,000 (definite) and 779/100,000 (definite and probable) PTB respectively. Of the 5004 adolescents, 4965 adolescents without TB at baseline were followed up for incident TB. During follow up 23 TB cases were found with a corresponding incidence density of 3.9 (95% CI, 2.4-5.8) events per 1000 person years of observation (PYO). After adjustments were done, being male (P=0.0045, HR 0.91 95% CI, 0.86-0.96), having a BCG scar (P=<.0001, HR 2.04 95% CI, 1.88-2.21) and school going (P=<.0001, HR 1.70 95% CI, 1.51-1.92) remained the strongest predictors of TB incidence
PhD studies:	Title: Epidemiology of tuberculosis in adolescents in western Kenya Candidate: Videlis Nduba (University of Amsterdam, Netherlands)
	Title: Tuberculosis incidence among HIV-infected adults and overall health care utilization among target populations in the Health and Demographic Surveillance Population in western Kenya: Implications for TB vaccine trials Candidate: Godfrey Bigogo (University of Amsterdam, Netherlands)
	Title: Infectious disease modeling/epidemiology of tuberculosis in infants and care seeking in self reported adult TB patients in western Kenya Candidate: Lazarus Odeny (University of Amsterdam, Netherlands)

MSc studies:	MA Project Planning and Management Candidate: Joseph Opole (University of Nairobi, Kenya)
	MSc in Clinical Trials Candidate: Walter Mchembere (Maseno University, Kenya)
	Msc in Clinical Trials Candidate: Peter Myamthimba (LSHTM, UK)
Publications:	

2.2.3 TB Vac prep Uganda

EDCTP Project Coordinator:	Philippa Musoke (Makerere University, Uganda)
EDCTP Call Title:	Capacity building and site development for the conduct of phase III trials of TB vaccines in children under 1 year of age
EDCTP Project Title:	Towards conducting phase III trials of novel TB vaccines in Ugandan infants and adolescents
EDCTP Project Code:	CT.2005.32090.003
EDCTP Project Start Date:	28 August 2007
EDCTP Project End Date:	31 January 2012
Collaborators:	• Sabrina Bakeera-Kitaka (Makerere University, Uganda) • Robert Colebunders (Prince Leopold Institute of Tropical Medicine (ITM), Belgium) • Vinod K. Diwan (Karolinska Institute, Sweden) • Willem Hanekom (University of Cape Town, South Africa) • Moses Lutaakome Joloba (Ministry of Health, Uganda) • Gunilla Kallenius (Karolinska Institute, Sweden) • Noah Kiwanuka (Medical Research Council Programme on AIDS - Uganda Virus Research Institute (MRC/UVRI), Uganda) • Asli Kulane (Karolinska Institute, Sweden) • Markus Maeurer (Karolinska Institute, Sweden) • Arnaud Marchant (Université Libre de Bruxelles, Belgium) • Harriet Mayanja-Kizza (Makerere University, Uganda) • Keith McAdam (Makerere University, Uganda) • Joris Menten (ITM, Belgium) • Philippa Musoke (Makerere University) • Patrick Nabongo (Makerere University) • Margaret Nakakeeto Kijambu (Makerere University) • Stefan Peterson (Karolinska Institute, Sweden) • Stefan Svenson (Swedish Institute for Infectious Disease Control (SMI), Sweden) • Suzanne Verver (KNCV Tuberculosis Foundation, Netherlands) • Anne Wajja (Makerere University, Uganda)
Study / Trial 1	
Site Principal Investigator(s):	Philippa Musoke (Uganda)
Clinical Trial/Study Sponsor:	Infectious Diseases Institute (IDI), Makerere University (Uganda)
Trial/Study title:	Epidemiological cohort study
Goal:	To build capacity in Uganda to ultimately conduct phase III trials of novel tuberculosis (TB) vaccines, in infants <1 year of age and adolescents.
Primary Objective(s):	1. To determine the incidence of TB disease in infants. Endpoint: Proportion of infant population with clinical TB disease over a 1 year period 2. To determine the prevalence and the 18 months incidence of TB disease among adolescents 12-16year old. The endpoint of the study is to determine the proportion of the adolescent population with clinical incident TB disease over the 18 month period.
Secondary Objective(s):	1. To determine the longitudinal kinetics of the immune response induced by newborn BCG vaccination. Endpoint: Longitudinal changes in multiple markers of the BCG-induced T cell response 2. To determine the annual risk of infection among adolescent 12-16 year old. Endpoint: Proportion of the

	adolescent population with a positive TST in the different age groups 3. To compare tuberculin skin testing (TST) to novel immunological assays to diagnose TB. Endpoint: Proportion of the adolescent population with clinical TB disease and positive TST and/or positive immunological assays 4. To determine infant and adolescent mortality rates and causes of mortality. Endpoint: Proportion of infant and adolescent population (12 -16 years) that dies, over a period of 2 years, and proportional cause of mortality 5. To determine knowledge, attitudes and practices (KAP) about TB, and willingness to participate in TB vaccination trials, and to increase TB awareness in the community. Endpoint: Qualitative community concepts and quantification of pertinent qualitative findings 6. To determine rates of cohort retention, and causes of loss to follow up. Endpoint: Proportion of enrolled infant and adolescent population that have completed 1 year follow-up of observation, and proportional causes of loss to follow-up.
Clinical Trial/Study site(s):	Iganga/Mayuge Demographic Surveillance Site in Eastern Uganda
Collaborating site(s):	• Infectious Diseases Institute (IDI), Makerere University College of Health Sciences (Uganda) • Mycobacteriology (BSL-3) Lab (MYCO-LAB) – Department of Medical Microbiology, Makerere University College of Health Sciences (Uganda) • The School of Public Health, Makerere University College of Health Sciences (Uganda) • The National TB Reference Laboratory (NTRL)-Wandegeya (Uganda) • South African Tuberculosis Vaccine Initiative (SATVI, South Africa) • Swedish Institute for Infectious Disease Control (SMI, Sweden) • Karolinska Institute (Sweden) • Prince Leopold Institute of Tropical Medicine (Belgium) • The Institute for Medical Immunology (Belgium) • The KNCV Tuberculosis Foundation (Netherlands)
Study design:	Prospective cohort Study
Number of subjects:	2500 subjects in the Infant Cohort Study 5000 subjects in the Adolescent Cohort Study 100 subjects in the immunology study
Cofunders:	• Swedish International Development Cooperation Agency (SIDA, Sweden) • Karolinska Institute (Sweden) • Prince Leopold Institute of Tropical Medicine (Belgium) • Aeras Global TB Vaccine Foundation (USA)
Status:	Completed
Results and Outcomes:	Primary outcomes of the study were: 1. To determine the incidence of TB disease in infants. Endpoint: Proportion of infant population with clinical TB disease over a 1 year period – The study showed a low incidence of TB disease in this population. Only one (1) culture positive case of MTB (definite TB) was found throughout the study follow up. However using the SATVI algorithm which classifies cases into definite, probable and possible TB, there

	were 27 probable TB cases and therefore the incidence rate (combining 1 definite and 27 probable cases) is 62 per 10,000 person years. Another 35 cases were classified as possible TB. Overall, 38 participants were treated for TB mostly based on clinical or radiological assessment.and these included 1 definite case, 2 probable TB cases and 35 possible TB cases 2. To determine the prevalence and the 18 months incidence of TB disease among adolescents 12-16 year old: Endpoint: Proportion of the adolescent population with clinical incident TB disease over the 18 month period – Eight culture confirmed cases of TB were found among adolescents at baseline resulting in a prevalence of 160/100,000 (95% CI, 69-315). During follow up, a total of 14 cases of TB of which one was clinical extra-pulmonary TB and the 13 culture confirmed MTB cases of TB in an average of 1.1 person years of follow up was found resulting in an incidence
Total number of subjects (cohort/epidemiological/ other studies):	2500 subjects in the Infant Cohort Study 5000 subjects in the Adolescent Cohort Study 100 subjects in the immunology study
PhD study:	Title: Vaccine induced immunity in nine-month old infants following BCG vaccination at birth or at 6 weeks of age Candidate: Fredrick Lutwama (University of Cape Town, South Africa)
Publications:	1. Esther Buregyeya, Asli Kulane, Robert Colebunders, Anne Wajja, Juliet Kiguli, Harriet Mayanja, Philippa Musoke, George Pariyo and Ellen M.H. Mitchell. Knowledge, attitudes and health seeking behavior towards tuberculosis in rural Uganda. *International Journal of TB and Lung Diseases Int J Tuberc Lung Dis*. 2011 Jul;15 (7):938-42 2. Benon B Asiimwe, Godwins B Bagyenzi, Willy Ssengooba, Francis Mumbowa, Gerald Mbowa, Anne Wajja, Harriet Mayanja-Kiiza, Philippa Musoke, Gunilla Kallenius and Moses L Joloba, Species and genotypic diversity of non-tuberculous mycobacteria isolated from children investigated for pulmonary tuberculosis in rural Uganda. *BMC Infectious Diseases* 2013, 13:88, doi:10.1186/1471-2334-13-88.

2.2.4 THYB-04

EDCTP Project Coordinator:	Peter Andersen (Statens Serum Institut, (SSI), Denmark)
EDCTP Call Title:	Call for support of clinical trials, capacity building and networking in tuberculosis vaccines development
EDCTP Project Title:	Conduct of ICH-GCP level phase II TB vaccine trials in high risk populations in Africa
EDCTP Project Code:	IP.2007.32080.001
EDCTP Project Start Date:	25 March 2009
EDCTP Project End Date:	24 March 2014
Collaborators:	• Peter Aaby (Bandim Health Project, Guinea-Bissau) • Markos Abebe (Armauer Hansen Research Institute (AHRI), Ethiopia) • Abraham Aseffa (AHRI, Ethiopia) • Peter Bang (SSI, Denmark) • Ahmed Bedru (AHRI, Ethiopia) • Jaap van Dissel (Leiden University, Netherlands) • Mark Doherty (SSI, Denmark) • Howard Engers (AHRI, Ethiopia) • Asfawossen Gebreyohannis (AHRI, Ethiopia) • Victor Gomes (Bandim Health Project, Guinea Bissau) • Jemal Hussain (AHRI, Ethiopia) • Ingrid Kromann (SSI, Denmark) • Ruth Leekassa (AHRI, Ethiopia) • Tom Ottenhoff (Leiden University, Netherlands) • Liya Wassie Dubale (AHRI, Ethiopia) • Christian Wejse (University of Aarhus, Denmark) • Lawrence Yamuah (AHRI, Ethiopia)
Study / Trial 1	
Site Principal Investigator(s):	Hennie Geldenhuys (South Africa)
Clinical Trial/Study Sponsor:	Statens Serum Institute (SSI, Denmark)
Trial/Study title:	A phase II, randomised, double-blind, trial to evaluate the immunogenicity and safety of 2 doses of an adjuvanted TB subunit vaccine (Ag85B-ESAT-6 + IC31) using 2 different vaccination schedules in healthy adolescents (THYB-04)
Goal:	To test the hypothesis that the vaccine is safe and immunogenic at a dose and in a human population resembling that in which the final product will be used.
Primary Objective(s):	To evaluate the immunogenicity and safety of a TB subunit vaccine administered in volunteers at 0 and 2 months. The description of the immunogenicity profile will be based on the magnitude of production of IFN after stimulation with mitogen or antigen. The relative change from baseline will be visualised using plots. The relative change from baseline to the end of the study will be quantified using regression techniques allowing for within subject correlation.
Clinical Trial/Study site(s):	1. Armauer Hansen Research Institute (AHRI) Addis Ababa, Ethiopia (no longer THYB-04 clinical trial site as per September 2011) 2. Nazaret/Adama Regional Hospital(Nazaret/Ethiopia) (no longer THYB-04 clinical trial site as per September 2011) 3. Debre Zeit Hospital (Debre Zeit/Ethiopia) (no longer THYB-04 clinical trial site as per September 2011) 4. SATVI South Africa
Collaborating site(s):	• Statens Serum Institute (SSI, Denmark) • Armauer Hansen Research Institute (AHRI, Ethiopia)

	• Leiden University Medical Centre (LUMC, Netherlands) • Projecto de Saúde de Bandim/SSI (Guinea-Bissau) • Bandim Health Project/ Aarhus University Hospital, Århus (Denmark)
Study design:	Phase II multicentre double-blinded randomised controlled trial
Number of subjects:	240
Product(s):	• ESAT-6/Ag85B • adjuvant IC31
Manufacturer/Developer:	• SSI produces ESAT-6/Ag85B and IC13 • Intercell A/S developed IC31adjuvant
Cofunders:	• Danish International Development Agency (Denmark) • Leiden University Medical Centre (Netherlands)
Trial registration number(s):	DOH-27-0612-3947 (SANCTR)
Status:	Ongoing
Results and Outcomes:	Recruitment at SATVI started September 2012. As of 28 March 2013, 358 patients were screened and 178 were enrolled.
PhD studies:	Title: Analysis of regulation of immune responses in Tuberculosis Candidate: Martha Zewdie (SSI, Denmark/AHRI, Ethiopia) Dates: 1 January 2011 – 30 November 2013
	Title: PREDicting Tuberculosis among TB suspects, Improving triage and Nutritional support to Alter Mortality, PREDÌNAM Candidate: Frauke Rudolph (Bandim Health Project, Guinea Bissau) Dates: 1 September 2009 – 31 January 2013
	Title: Isoniazid or Rifampicin and Isoniazid Preventive Therapy for children exposed to Tuberculosis – the IRIPT trial Candidate: Grethe Lemvik (Bandim Health Project, Guinea Bissau) Dates:1 March 2010 – 28 February 2014
Post-Doc studies:	Title: Implementation of IPT in an low resource setting Candidate: Victor Gomes (Bandim Health Project, Guinea Bissau) Dates: 1 April 2011 – 31 March 2014
	Title: Evolution of immune response during TB treatment Candidate: Markos Abebe (AHRI, Ethiopia) Dates: 2010 – March 2014
Study / Trial 2	
Site Principal Investigator(s):	Grethe Lemvik (Guinea Bissau)
Clinical Trial/Study Sponsor:	Statens Serum Institute (SSI, Denmark)
Trial/Study title:	Isoniazid or Rifampicin and Isoniazid Preventive Therapy for children exposed to Tuberculosis – the IRIPT trial
Goal:	To determine the best preventive therapy for TB exposed children
Primary Objective(s):	To compare the adherence of 9 months of INH (9I) versus 4 months of INH+RIF (4IR)
Secondary Objective(s):	To assess the TB-incidence and mortality related to TB and TB-exposure among children<15 years of age in an urban area of Guinea-Bissau
Clinical Trial/Study site(s):	Bandim Health Project (Guinea Bissau)
Collaborating site(s):	• SSI (Denmark) • AHRI (Ethiopia) • Leiden University Medical Centre (LUMC) (Netherlands) • Projecto de Saúde de Bandim/SSI (Guinea-Bissau) • Bandim Health Project/Aarhus University Hospital, Århus

	(Denmark)
Study design:	Open-label cluster-randomised clinical trial
Product(s):	Isoniazid and Rifampicin
Manufacturer/Developer:	International Dispensary Association, Holland
Cofunders:	SSI (Denmark)
Trial Registration number(s):	PACTR201101000273931
Status:	Ongoing
Results and Outcomes:	Recruitment is currently ongoing
Study / Trial 3	
Site Principal Investigator(s):	Frauke Rudolf (Guinea Bissau)
Clinical Trial/Study Sponsor:	Statens Serum Institute (SSI, Denmark)
Trial/Study title:	PREDicting Tuberculosis among TB suspects, Improving triage and Nutritional support to Alter Mortality, PREDÌNAM
Goal:	To improve the case management of pulmonary tuberculosis (PTB) suspects and confirmed PTB patients by using simple measures and interventions applicable in low resource settings.
Primary Objective(s):	To lower mortality in PTB suspects by securing early consideration of PTB in the diagnostic process and using a diagnostic algorithm applicable in a low resource setting.
Secondary Objective(s):	To compare risk assessment in the current PTB suspect cohort to identification of high risk patients after implementation of the suPAR quicktest.
Tertiary Objective(s):	To reduce the complexity of the current version of the TBscore by using Principal Component Analysis.
Clinical Trial/Study site(s):	Bandim Health Project (Guinea Bissau)
Collaborating site(s):	• Statens Serum Institute (SSI), Copenhagen, Denmark • Armauer Hansen Research Institute (AHRI), Addis Ababa, Ethiopia • Leiden University Medical Centre (LUMC) Leiden, Netherlands • Projecto de Saúde de Bandim/SSI, Guinea-Bissau • Bandim Health Project/ Aarhus University Hospital, Århus, Denmark
Study design:	Observational follow-up cohort study on PTB suspects
Product(s):	suPARnostic quick test
Manufacturer/Developer:	Virogates
Cofunders:	SSI (Denmark)
Trial Registration number(s):	PACTR201101000273931
Status:	Ongoing
Results and Outcomes:	930 TB suspects enrolled as of March 2012
Study / Trial 4	
Site Principal Investigator(s):	Martha Zewdie (Ethiopia)
Trial/Study title:	Analysis of regulation of immune responses in Tuberculosis
Goal:	Assessment of the “quality” of the memory immune response during TB treatment, latent infection and after vaccination allowing us to compare memory in a failed natural immune response (TB disease) with a rotective natural immune response (control of infection leading to latency) with the immune response generated by vaccination.
Primary Objective(s):	1. Measure magnitude and duration of primary endpoints in vaccine study cohorts (IFN gamma production by ELISA/ELISpot)

	2. Identify the role of effector, memory and Treg cell subsets in the induction of a robust immune response in healthy adults given a new candidate TB vaccine 3. Evaluate the role of different subsets of T cells during latent and active TB infection before and after chemotherapy 4. Evaluate the difference in effector and regulatory immune cells between active TB patients, latently infected individuals, and healthy endemic controls 5. Assess the efficacy of real time PCR in identifying and distinguishing T cell subsets by comparison with flow cytometry.
Clinical Trial/Study site(s):	• Armauer Hansen Research Institute (AHRI, Ethiopia)
Cofunders:	SSI (Denmark)
Status:	Ongoing
Results and Outcomes:	Recruiting
Publications:	

2.2.5 TB-021

EDCTP Project Coordinator:	Helen McShane (University of Oxford, UK)
EDCTP Call Title:	Call for support of clinical trials, capacity building and networking in tuberculosis vaccines development
EDCTP Project Title:	A proof-of-concept Phase IIb clinical trial to evaluate the protective efficacy of a booster MVA85A vaccination administered to healthy, HIV infected adult in South Africa, Senegal and The Gambia
EDCTP Project Code:	IP.2007.32080.002
EDCTP Project Start Date:	27 August 2009
EDCTP Project End Date:	26 August 2014
Collaborators:	• Nathaniel Brittain (University of Oxford, UK) • Christiane A.J. Huygen (Pasteur Institute – Brussels, Belgium) • Farba Karam (University Cheikh Anta DIOP de Dakar (UCAD), Senegal) • Souleymane Mboup (UCAD, Senegal) • Paul Milligan (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Robert Wilkinson (University of Cape Town, South Africa)
Study / Trial 1	
Site Principal Investigator(s):	Robert Wilkinson (South Africa)
Clinical Trial/Study Sponsor:	University of Oxford (UK)
Trial/Study title:	A phase II, proof-of-concept, randomised, double-blind, placebo-controlled study to evaluate the protective efficacy against TB disease, safety, and immunogenicity of MVA85A/AERAS-485 in healthy, HIV-infected adults
Goal:	To evaluate the protective efficacy against TB disease and the safety of MVA85A/AERAS-485 in HIV-positive adults. In addition, the immunogenicity of MVA85A/AERAS-485 will be evaluated.
Primary Objective(s):	To evaluate the efficacy of MVA85A/AERAS-485 in the prevention of TB disease compared to control subjects who receive placebo in HIV-infected, African adult subjects without active TB disease.
Secondary Objective(s):	1. To evaluate the safety of MVA85A/AERAS-485 compared to placebo 2. To evaluate CD4+ lymphocyte counts and HIV-1 viral load before and after administration of MVA85A/AERAS-485 compared to placebo 3. To evaluate the efficacy of MVA85A/AERAS-485 in the prevention of TB disease in subjects who received isoniazid preventive therapy compared to control subjects who also received isoniazid preventive therapy but who receive placebo 4. To evaluate the immunogenicity of MVA85A/AERAS-485 compared to placebo as described by the ex vivo IFN-γ ELISPOT assay. 5. To evaluate the immunogenicity of MVA85A/AERAS-485 compared to placebo as described by flow cytometric intracellular cytokine staining of CD4+ and CD8+ T cells after stimulation with a peptide pool of mycobacterial antigens 6. To identify potential immunological correlates of protection from tuberculosis in subjects vaccinated with

	MVA85A/AERAS-485 7. To evaluate the QuantiFERON (QFN) conversion rate at final study assessment in MVA85A/AERAS-485 recipients compared to control subjects without a diagnosis of tuberculosis during the trial.
Clinical Trial/Study site(s):	• Centre Hospitalier Universitaire Le Dantec, Dakar (Senegal) • Khayelitsha site B and GF Jooste Hospital, Cape Town (South Africa)
Collaborating site(s):	• University of Oxford (UK) • LSHTM (UK) • University of Cape Town (South Africa) • Centre Hospitalier Universitaire Le Dantec, Dakar (Senegal) • Pasteur Institute, Brussels (Belgium)
Study design:	Phase II proof-of-concept double-blinded randomised placebo-controlled trial
Number of subjects:	1400
Product(s):	• Candin (Allermed Labs, USA) - placebo • MVA85A (IDT GmbH / Oxford) / AERAS – 485 (Impfstoffwerk Dessau- • Tornau (IDT) Biologika GmBH, DE
Manufacturer/Developer:	• IDT • UoT OETC
Cofunders:	• DfID UK • Aeras • Scientific Institute of Public Health (SIPH) Belgium
Trial registration number(s):	NCT01151189
Status:	Ongoing
Results and Outcomes:	Recruitment started October 2011.
Total number of subjects (clinical trials only):	650
PhD studies:	Title: Incidence and patterns of TB among HIV-infected participants of MVA85a/AERAS 485 phase II clinical trial in Senegal Candidate: Birahim Pierre Ndiaye (Cheikh Anta Diop University, Senegal) Dates: September 2010 - 2014
	Title: Novel peptide based correlates of protection and diagnosis in TB Candidate: Fadheela Patel (UCT, South Africa) Dates: March 2011 – June 2014
MSc studies:	MSc at LSHTM by distance learning Candidate: Aderonke Odutola
	Title: Clinical epidemiology of HIV associated TB in Khayelitsha, South Africa Candidate: Tolullah Oni (Imperial College London, UK)
Postdoc study:	Candidate: Kerryn Matthews (UCT, South Africa)
Publications:	1. Oni T, Tsekela R, Kwaza B, Manjezi L, Bangani N, Wilkinson KA, Coetzee D, Wilkinson RJ. A Recent HIV Diagnosis Is Associated with Non-Completion of Isoniazid Preventive Therapy in an HIV-Infected Cohort in Cape Town. *PLoS One*. 2012;7(12):e5AE2489. doi: 10.1371/journal.pone.0052489. Epub 2012 Dec 20. 2. Pepper DJ, Marais S, Bhaijee F, Wilkinson RJ, De Azevedo V, et al. Assessment at Antiretroviral Clinics during TB Treatment Reduces Loss to Follow-Up among HIV-Infected Patients. (2012) *PLoS ONE* 7(6): e37634.

doi:10.1371/journal.pone.0037634
3. Vordermeier HM, Hewinson RG, Wilkinson RJ, Wilkinson KA, Gideon HP, et al. Conserved Immune Recognition Hierarchy of Mycobacterial PE/PPE Proteins during Infection in Natural Hosts. (2012) *PLoS ONE* 7(8): e40890. doi:10.1371/journal.pone.0040890

2.2.6 AERAS 402/Crucell Ad35

EDCTP Project Coordinator:	Mark Hatherill (University of Cape Town, South Africa)
EDCTP Call Title:	Call for support of clinical trials, capacity building and networking in tuberculosis vaccines development
EDCTP Project Title:	A Multicentre Phase II Trial of a New TB Vaccine in African Infants
EDCTP Project Code:	IP.2007.32080.003
EDCTP Project Start Date:	25 May 2009
EDCTP Project End Date:	24 May 2014
Collaborators:	• Benon Asiimwe, (Makerere University, Uganda) • Christian Burri (Swiss Tropical Institute, Switzerland) • Robert Colebunders (Prince Leopold Institute of Tropical Medicine (ITM), Belgium) • Vinod K. Diwan (Karolinska Institute, Sweden) • Katrina Downing (University of Cape Town, South Africa) • Bernard Erima (Makerere University, Uganda) • Willem Hanekom (University of Cape Town, South Africa) • Anja van 't Hoog (University of Amsterdam, Netherlands) • Gabriela Schreyer (ienna School of Clinical Research, Austria) • Moses Lutaakome Joloba (Ministry of Health, Uganda) • Gunilla Kallenius (Karolinska Institute, Sweden) • Asli Kulane (Karolinska Institute, Sweden) • Kayla Laserson (Centers for Disease Control and Prevention (CDC), USA) • Markus Maeurer (Karolinska Institute, Sweden) • Hassan Mahomed (University of Cape Town, South Africa) • Harriet Mayanja-Kizza (Makerere University, Uganda) • Jose Muñoz Gutierrez (Hospital Clinic of Barcelona, Spain) • Philippa Musoke (Makerere University, Uganda) • Videlis Nduba (Kenya Medical Research Institute (KEMRI), Kenya) • George Pariyo (Makerere University, Uganda) • Stefan Peterson (Karolinska Institute, Sweden) • Jahit Sacarlal (Manhiça Health Research Center, Mozambique) • Stefan Svenson (Swedish Institute for Infectious Disease Control (SMI), Sweden) • Suzanne Verver (KNCV Tuberculosis Foundation, Netherlands) • Eric Wobudeya (Makerere University, Uganda)
Study/Trial 1	
Site Principal Investigator(s):	• Mark Hatherill(Cape Town) • Jahit Sacarlal (Manhica) • Videlis Nduba (Kenya)
Clinical Trial/Study Sponsor:	Aeras (USA)
Trial/Study title:	A phase II, double-blind, randomised, placebo-controlled, multicentre, proof-of-concept study to evaluate the safety and efficacy of AERAS-402 in BCG-vaccinated, HIV-uninfected infants without evidence of tuberculosis
Goal:	This study will include a dose-finding phase followed by a safety and efficacy phase at a selected dose of AERAS-402. The rationale for the dose selected for use in the safety and efficacy phase will incorporate the safety experience and immunogenicity results from an ongoing phase I trial in infants as well as from the dose-finding phase in this study.

	An exploratory objective of this trial will be to evaluate the efficacy of Crucell Recombinant Ad35 TB vaccine in infants at eight discrete sites in Africa
Primary Objective(s):	1. To evaluate the safety profile of AERAS-402 in infants 2. To evaluate the efficacy of AERAS-402 in the prevention of TB in infants based on TB case definition endpoint #1 as described in the protocol
Secondary Objective(s):	1. To select a dosing regimen of AERAS-402 for testing in infants 2. To evaluate the immunogenicity of AERAS-402 compared to controls as described by flow cytometric intracellular cytokine staining (ICS) of CD4 and CD8 T cells producing one, two or three cytokines (IFN-γ, TNF-α, and/or IL-2) simultaneously after stimulation with a peptide pool of mycobacterial peptides 3. To evaluate the immunogenicity of AERAS-402 in infants compared to controls by whole blood intracellular cytokine assay developed by the University of Cape Town (UCT) 4. To assess potential immune correlates of protection from TB in infants vaccinated with AERAS-402 5. To evaluate the proportion of on-study IFN-γ release assay (IGRA) conversions, measured using QuantiFERON-TB Gold In-Tube test, in infants that received AERAS-402 compared to controls 6. To evaluate the efficacy of AERAS-402 in the prevention of TB in infants based on TB case definition endpoints #2 and #3 as specified in the protocol.
Clinical Trial/Study site(s):	• Kisumu, Siaya district (Kenya) • Manhiça (Mozambique) • Worcester (South Africa) • The NIH funded sites that are taking part in C-029-402 are Perinatal HIV Research Unit (PHRU, South Africa) • Baragwanath, Johannesburg (South Africa) • KID-CRU, Stellenbosch (South Africa) • Sandy Pillay (NIH site in Durban, South Africa)
Collaborating site(s):	• ITM (Belgium) • Swiss Tropical and Public Health Institute (STI, Switzerland) • Swiss Agency for Development and Cooperation (SDC, Switzerland) • Karolinska Institutet (Sweden) • KNCV Tuberculosis Foundation (Netherlands) • University of Cape Town (South Africa) • KEMRI (Kenya) • CRESIB (Mozambique) • Infectious Diseases Institute (IDI) Makarere University, Kampala (Uganda) • Mulago Hospital, Kampala (Uganda)
Study design:	Phase II proof-of-concept multi-centre double-blinded randomised placebo-controlled trial
Number of subjects:	Between 2,200 and 4,000 to be enrolled (Adaptive design).
Product(s):	AERAS-402/Crucell Ad35
Manufacturer/Developer:	• Crucell B.V. • Aeras
Cofunders:	• Instituto de Salud Carlos III, Madrid (Spain) • Aeras (USA) • Vienna School of Clinical Research (VSCR, Austria) • SDC (Switzerland)
Trial registration	NCT 01198366

number(s):	PACTR201203000306280
Status:	Stopped
Results and Outcomes:	From January 2012, the first group of the efficacy phase was enrolled at three sites (group 5): KEMRI/CDC (141), SATVI (118) and PHRU (22; an NIH site). A safety and immunogenicity review of this group was scheduled to take place in August/ September 2012 after which expansion to the full efficacy phase was planned subject to an appropriate safety profile for the vaccine and adequate immune responses. In June, NIH had withdrawn the MUJHU site from the trial since they anticipated that the rates of TB there would be too low to determine efficacy in this trial. In September, all sites were informed that no further enrolments would take place and there would be no expansion into the full efficacy phase due to there being inadequate scientific support for such an expansion. Nevertheless, a third dose would still be given to the last group enrolled (group 5) but for all participants follow up would be shortened from 2 years to 6 months after the last dose was given. Final enrolment status for the sites participating in this trial is: KEMRI/ CDC – 285, SATVI – 166, CISM – 14, MUJHU – none. Given these changes, trial follow up is expected to be completed in mid 2013 and activities to wind down the trial another 3 months.
Total number of subjects (clinical trials only):	Between 2,200 and 4,000 to be enrolled (Adaptive design). 96 from groups 1, 2 and 3 enrolled to date.
Total number of subjects (cohort/epidemiological/ other studies):	Infant TB epidemiological study in Mozambique: 198 enrolled at 14 March 2011 out of a target enrolment of 800-1000.
PhD studies:	Title: Phenotypic analysis of MTB antigen specific T-cells and the evaluation of new point of care TB diagnostic tests Candidate: Helen Buteme (KI, Sweden) Supervisors: Gunilla Kanellius, Moses Joloba, Markus Maeurer
	PhD in Epidemiology Candidate: Steve Wandiga (KEMRI/CDC, Kenya) Supervisor: Prof. Christian Heumann
Post Doctoral studies:	Topic: Identification of immune correlates of risk of childhood TB disease, following BCG vaccination (cont. of Dr Brian Abel's work) Candidate: Adam Penn-Nicholson
MSc studies:	Title: Integration of HIV services in TB treatment in Uganda Candidate: Faith Keneko (deceased)
	Title: Prevalence and factors associated with hepatotoxicity in HIV infected patients on anti-tuberculosis therapy in Mulago Hospital Candidate: Mark Okwir
	Title: Diagnostic accuracy of the Genexpert system among children with possible/probable tuberculosis at Mulago Hospital Candidate: Moorine Sekadde
	MSc in Clinical Trials via distant learning at the LSHTM Candidate: Grace Kiringa
	MSc in Laboratory Science/Microbiology at the Kenya Medical Research Institute, KEMRI/CDC programme Candidate: Benson Muchiri (discontinued)
	MSc in Clinical Trials part time (LSHTM) Candidate: Paul Mwaka
	MSc Clinical Trials part time (LSHTM)

	Candidate: Samuel Gurrion Ouma
	MA Project Planning & Management Candidate: Hyrine Matheka
Other/Sub-studies:	ITHACA study
Study / Trial 2	
Site Principal Investigator(s):	• Jahit Sacarlal • Kizito Gondo • Jose Muňoz
Trial/Study title:	Determination of the minimum incidence rate of tuberculosis in infants and children in Manhiça District, Mozambique
Goal:	This is a prospective study aiming to assess the incidence of TB among children under 3 years in the DSS population during a period of one year
Primary Objective(s):	To estimate the annual minimum incidence rate of TB disease in children under 3 years in the Manhiça area
Secondary Objective(s):	1. To describe the clinical characterisation and outcome of tuberculosis in children under 3 years 2. To describe the timing and coverage of BCG vaccination (including scarring patterns) in TB suspects under 3 years 3. To compare the bacteriologic yield of fluorescence microscopy compared to culture in gastric aspirates and induced sputa samples of TB suspects under 3 years 4. To assess the rate of co-infection with HIV in TB suspects and TB cases under 3 years 5. To assess the rate of co-infection with helminths in TB suspects and TB cases under 3 years.
Clinical Trial/Study site(s):	Manhiça District (Mozambique)
Status:	Ongoing
Results and Outcomes:	Recruitment started 21 June 2010
Publications:	1. Fletcher HA, Keyser A, Bowmaker M, Sayles PC, Kaplan G, Hussey G, Hill AV, Hanekom WA. Transcriptional profiling of mycobacterial antigen-induced responses in infants vaccinated with BCG at birth. *BMC Med Genomics*. 2009 Feb 24; 2:10. doi: 10.1186/1755-8794-2-10 2. Hawkridge T, Mahomed H. Prospects for a new, safer and more effective TB vaccine. *Paediatr Respir Rev*. 2011 Mar;12(1):46-51. doi: 10.1016/j.prrv.2010.09.013. Epub 2010 Oct 14. Review 3. Kagina BM, Abel B, Scriba TJ, Hughes EJ, Keyser A, Soares A, Gamieldien H, Sidibana M, Hatherill M, Gelderbloem S, Mahomed H, Hawkridge A, Hussey G, Kaplan G, Hanekom WA; other members of the South African Tuberculosis Vaccine Initiative. Specific T cell frequency and cytokine expression profile do not correlate with protection against tuberculosis after bacillus Calmette-Guérin vaccination of newborns. *Am J Respir Crit Care Med*. 2010 Oct 15;182(8):1073-9. doi: 10.1164/rccm.201003-0334OC. Epub 2010 Jun 17. 4. Mahomed H, Fourie PB. Clinical trials of TB vaccines: harmonization and cooperation. *Tuberculosis* (Edinb). 2012 Mar;92 Suppl 1:S21-4. doi: 10.1016/S1472-9792(12)70008-2.

2.2.7 Aurum 102/THYB-05

EDCTP Project Coordinator:	Gavin Churchyard (Aurum Institute for Health Research, Denmark)
EDCTP Call Title:	Call for support of clinical trials, capacity building and networking in tuberculosis vaccines development
EDCTP Project Title:	Phase II Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Immunogenicity of H1, an adjuvanted TB subunit vaccine in HIV-infected, BCG-vaccinated Adults With CD4+ Lymphocyte Counts Greater Than 350 Cells/mm3
EDCTP Project Code:	IP.2009.32080.002
EDCTP Project Start Date:	30 September 2010
EDCTP Project End Date:	4 October 2012
Collaborators:	• Andersen, Peter (Statens Serum Institut, (SSI), Denmark) • Bang, Peter (SSI, Denmark) • Borgdorff, Martinus Willem (KNCV Tuberculosis Foundation, Netherlands) • Burri, Christian (Swiss Tropical Institute, Switzerland) • Charalambous, Salome (Aurum Institute for Health Research, South Africa) • Daubenberger, Claudia (Swiss Tropical Institute, Swtizerland) • Doherty, Mark (SSI, Denmark) • Hawkridge*, Toni (Aeras, USA) • Kromann, Ingrid (SSI, Denmark) • Kufa, Tendesayi (Aeras, USA) • Lwilla, Fred Israel (Ifakara Health Research and Development Centre, Tanzania) • Mashamaite, Sello (Aurum Institute for Health Research, South Africa) • Mitchell, Ellen (KNCV Tuberculosis Foundation, Netherlands) • Reither, Klaus (Ifakara Health Research and Development Centre, Tanzania) • Verver, Suzanne (KNCV Tuberculosis Foundation, Netherlands)
Study/Trial 1	
Site Principal Investigator(s):	• Klaus Reither (BRTC/IHI, Tanzania) • Nicolene Gardiner (Aurum, Denmark)
Clinical Trial/Study Sponsor:	Statens Serum Institute (SSI, Denmark)
Trial/Study title:	Phase II double-blind, randomised, placebo-controlled study to evaluate the safety and immunogenicity of H1, an adjuvanted TB subunit vaccine (Ag85B-ESAT-6 + IC31), in HIV-infected, BCG-vaccinated adults with CD4+ lymphocyte counts greater than 350 Cells/mm3
Goal:	To test the hypothesis that the vaccine is safe and immunogenic at a dose and in a human population resembling that in which the final product will be used.
Primary Objective(s):	1. To evaluate the safety of H1/IC31®, an adjuvanted TB subunit vaccine administered to HIV-infected adult subjects with no evidence of active TB disease. 2. To determine the immunogenicity of H1/IC31® in HIV-infected adult subjects with no evidence of TB disease.
Secondary Objective(s):	1. To assess cellular immunity induced by H1 in HIV-infected, BCG-vaccinated adult subjects. 2. Exploratory Objective: To evaluate innate and adaptive immune response to H1/IC31® in HIV-infected adults

	using transcriptomics, multi-colour flow cytometry, multi-plex luminex assays and quantitative real time PCR.
Clinical Trial/Study site(s):	• Ifakara Health Institute/Bagamoyo Research Centre, Bagamoyo Tanzania) • The Aurum Institute (Johannesburg, South Africa
Collaborating site(s):	• The Aurum Institute (South Africa) • Aeras Global TB Vaccine Foundation (South Africa) • KNCV Tuberculosis Foundation (The Netherlands) • Swiss Tropical Institute (Switzerland) • Ifkara Health Institute (Tanzania) • Statens Serum Institut (Denmark) • University of Amsterdam-Academic Medical Centre (The Netherlands)
Study design:	Phase II double-blinded randomised placebo-controlled trial
Number of subjects:	48 (24 each site)
Product(s):	Ag85B-ESAT-6 [50 Pg](H1) + adjuvant [500 nmol KLK and 20 nmol ODN1a] (IC31) Control: Tris buffer (FL), (10mM Tris + 169mM NaCl, pH 7.4)
Manufacturer/Developer:	SSI (Denmark)
Cofunders:	• Swiss Tropical and Public Health Institute, Switzerland • SIDA, Sweden • Swiss National Science Foundation (SNSF), Switzerland
Trial registration number(s):	PACTR201105000289276 DOH-27-0611-3538
PhD studies:	PhD Immunology Title: Flow cytometry based immunomonitoring in TB and malaria vaccine trials Candidate: Maxmillian Mpina (AMC UvA, Netherlands) Dates: January 2011 – December 2013
	PhD Epidemiology Title: Incidence of tuberculosis among HIV-infected persons with CD4 Counts greater than 350 cells/µl attending primary care clinics in Ekurhuleni North Sub-District in South Africa Candidate: Tendesayi Kufa (UvA, Netherlands) Dates: September 2011 – September 2014
	PhD Epidemiology Title: Impact of HIV, malaria and Helminths co-infections on innate and adaptive immune responses in East African volunteers Candidate:Nicole Lenz (Swiss TPH, Switzerland) Dates: January 2011 – December 2013
MSc studies:	MSc Epidemiology (protocol development) Title: Estimating TB incidence among HIV-infected antiretroviral therapy naïve persons with early HIV disease in Tanzania Candidate: Khadija Said (IHI) [Swiss TPH, Switzerland]) Dates: March 2013 – June 2014
	MSc Immunogology Title: Cellular immunogenicity of H1/IC31® tuberculosis vaccine in HIV infected adults Candidate: Teson Lukindo (IHI) [Nelson Mandela African Institute of Science and Technology Arusha Tanzania] Dates: November 2011 – November 2013
	Title: Targeted transcriptome analysis for characterisation of H1/IC31 induced adaptive immune response in HIV infected adults Candidate: Tobias Schindler (Swiss TPH, Switzerland) Dates: April 2013 – March 2014
Sub-studies:	**Bagamoyo** Retrospective cohort study of TB incidence regardless of prior

	IPT use based on review of medical records combined with a prospective assessment of the TB status Approximately 1400 participants will be enrolled (on paper) over 1 year (in 2008) to meet the sample size requirements and will be once followed-up during the observation period of one year. Objectives: • To describe among HIV-infected adults with a CD4 count>350 cells/mm3 living in Bagamoyo district – The incidence of TB overall and restricted to 18 to 45 year olds – The risk factors associated with TB, such as age, sex, CD4 category, history of TB, IPT use Status: Ongoing. Delay as product label had to be redone to conform to enrolment numbers. **Johannesburg** A prospective study of TB incidence among HIV infected participants with CD4 counts >350 cells/Pl. To be eligible participants have to be 18 years or older, had a CD4 count>350 cell/pl within one year preceding enrolment and living within the catchment area of the facilities from which enrolment is taking place. Objectives: • To describe among HIV-infected adults with a CD4 count greater than 350 cells/mm3 living in the Ekurhuleni districts of Johannesburg – The incidence of TB overall and restricted to 18 to 45 year olds – Assess prevalence of TB among this group to determine what proportion would be excluded from a trial – The risk factors associated with TB incidence, such as age, sex, CD4 category, history of TB, IPT use, district, facility, history of diabetes and occupation. Status: Pending protocol approval. GSK to fund GeneXpert tests)
Status:	Ongoing
Results and Outcomes:	THYB-05 recruitment has started in both sites. The first participants were screened on 19 December 2011 at both (sites 1 and 2 in Tanzania and South Africa respectively). A total of 68 potential participants were screened in Tanzania. The target enrolment of 24 participants was met by 14 February 2012 in Tanzania. A total of 99 potential participants were screened in South Africa. The target enrolment of 24 participants was met by 12 March 2012 in South Africa. Each of the 24 participants was followed-up over 10 visits with 47 of the 48 participants receiving a second vaccination at visit 7 (study day 56). One Tanzanian participant fell pregnant during the study and was not revaccinated. As of November 2012 both sites are in the process of cleaning the data on the eCRF database and processes are in place to

	facilitate the study close out.
Publications:	1. Kufa T, Chihota V, Charalambous S, Verver S, Churchyard GJ. Willingness to participate in trials and to be vaccinated with new tuberculosis vaccines. Public Health Action 2013,3(1): 31–37 2. Rustomjee R, McClain B, Brennan MJ, McLeod R, Chetty-Makkan CM, McShane H, et al. Designing an adaptive phase II/III trial to evaluate efficacy, safety and immune correlates of new TB vaccines in young adults and adolescents. Tuberculosis (Edinb) 2013 Mar;93(2):136-42. 3. Rustomjee R, McLeod R, Hanekom W, Steel G, Mahomed H, Hawkridge A, et al. Key issues in the clinical development and implementation of TB vaccines in South Africa. Tuberculosis (Edinb) 2012 Sep;92(5):359-64.

2.3 Tuberculosis diagnostics clinical trials

Project Acronym (Coordinator)	Product(s)	Manufacturer / Developer	Study population	Status
TB NEAT (Dheda) LAM prospective cohort	Optimised smear microscopy with LED-illuminated microscopes Urine LAM lateral flow strip test (Determine TB®)	Carl Zeiss MicroImaging GmbH, Germany Inverness Medical Professional Diagnostics	ADULT (18 and older) HIV-positive patients with suspected TB, 500 recruits per site	Ongoing
TB-NEAT (Dheda) LAM RCT	Optimised smear microscopy with LED-illuminated microscopes Urine LAM lateral flow strip test (Determine TB®)	Carl Zeiss MicroImaging GmbH, Germany); Inverness Medical Professional Diagnostics)	ADULT (18 and older) HIV-positive patients with suspected TB, 300 recruits per site	Ongoing
TB NEAT (Dheda) Xpert/RIF	Point-of-treatment GeneXpert MTB/RIF assay	Cepheid, Sunnyvale, California USA	ADULT 18 years and older. 300 patients per site	Completed
TB-NEAT (Dheda) paediatric study	Xpert MTB/Rif assay	Cepheid, Sunnyvale, California USA.	Children (up to 15 years old), clinically suspected of having pulmonary TB or extrapulmonary TB 500 HIV-infected children compared to 200 HIV-uninfected children with suspected TB (Red Cross War Memorial Hospital and New Somerset Hospital)+ 400 children with suspected TB (Nolungile Clinic)	Ongoing
TB CHILD (Lwilla)	LHSD Rapid test to detect LAM in sputum or urine Loop-mediated isotermal amplification (LAMP) GeneXpert Diagnostic potential of IP10 and other biomarkers in blood and urine	LIONEX Eiken Chemical Co. Ltd Cepheid Not applicable Not applicable Not applicable STMicroelectronics Biotech	Study A: 18 years and older. 180 TB cases (90 smear positive TB cases and 90 smear negative but Xpert MTB positive /culture positive TB cases) 120 healthy cases Study B: Children TB suspects, 6	Completed

	T cell activation markers on Mycobacterium tuberculosis (MTB) specific T cells (TAM-IGRA) Mtb DNA extraction from stool Lab-on-chip based new platform (In-checkTM) for the molecular diagnosis Ustar TB IAD Kit Pari eFlowrapid nebulizer Newly developed TB diagnostics	Pari Pharma Not applicable	weeks - 14 years old. 600 paediatric TB suspects	
AE TBC (Walzl)	QuantiFERON® TB Gold In-Tube T SPOT TB	Cellestis Oxford Immunotec	HIV uninfected adult TB suspects N=800 HIV infected adults TB suspects N=400	Ongoing

2.3.1 TB NEAT

EDCTP Project Coordinator:	Keertan Dheda (University of Cape Town, South Africa)
EDCTP Call Title:	Call for applications to support clinical trials, capacity building and networking in new and improved diagnostics for tuberculosis (TB)
EDCTP Project Title:	Evaluation of multiple novel and emerging technologies for TB diagnosis, in smear-negative and HIV-infected persons, in high burden countries (the TB-NEAT study)
EDCTP Project Code:	IP.2009.32040.009
EDCTP Project Start Date:	17 May 2010
EDCTP Project End Date:	16 May 2014
Collaborators:	• Keertan Dheda (University of Cape Town (UCT), South Africa) • Mark Nicol (National Laboratory Service and UCT, South Africa) • Peter Mwaba (University Teaching Hospital, Zambia) • Lynn Zijenah (University of Zimbabwe, Zimbabwe) • Peter Mason (Biomedical Research and Training Institute, Zimbabwe) • Andrea Rachow (NIMR-MMRP, Tanzania) • Alexander Pym (MRC South Africa, South Africa) • Alimuddin Zumla (University College London (UCL), UK) • Bram van Ginneken (Radboud University, Netherlands) • Michael Hoelscher (Klinikum der Universität München, Germany) • Markus Maeurer (MTC, Karolinska Institute, Sweden) • Catharina Boehme (Foundation for Innovative Diagnostics (FIND), Switzerland)
Study/Trial 1	**Point-of-treatment GeneXpert MTB/RIF Assay**
Site Principal Investigator(s):	• Keertan Dheda (South Africa) • Mark Patrick Nicol (South Africa) • Alexander Pym (South Africa) • Peter Mwaba (Zambia) • Lynn Sodai Zijenah (Zimbabwe) • Andrea Rachow (Tanzania)
Clinical Trial/Study Sponsor:	Institute of Infectious Disease and Molecular Medicine, University of Cape Town (South Africa)
Trial/study title	A randomised controlled trial of point-of-treatment GeneXpert MTB/RIF Assay for the diagnosis of TB at primary care clinics in high HIV prevalence resource limited settings.
Goal	To evaluate whether one sputum GeneXpert MTB/RIF assay performed at point-of-treatment will improve TB diagnosis and the time-to-treatment for HIV-infected and un-infected patients with TB presenting to primary level TB clinics in high HIV prevalent settings.
Primary Objective(s):	1. To determine the differences in time-to-treatment initiation between the point-of-treatment Xpert® MTB/RIF Assay and microscopy-centre based same day smear microscopy 2. To compare the performance outcomes of one point-of-treatment sputum GeneXpert® MTB/RIF Assay compared to two same-day standard fluorescence smear microscopy for TB diagnosis in primary level clinics 3. To determine the incremental diagnostic yield of a single point-of-treatment Xpert® MTB/RIF Assay over two sputum fluorescence smears using MGIT Liquid culture as the reference standard

	4. To examine the feasibility of the point-of-treatment GeneXpert® MTB/RIF Assay performed by non-technical research personnel 5. To evaluate the cost-effectiveness of using a single point-of-treatment GeneXpert® MTB/RIF Assay for primary clinic-based TB diagnosis.
Clinical Trial/Study site(s)	• University of Cape Town (South Africa) • National Health Laboratory Service and University of Cape Town (South Africa) • Medical Research Council (South Africa) • University Teaching Hospital (Zambia) • NIMR-Mbeya Medical Research Programme (MMRP) (Tanzania • University of Zimbabwe College of Health Sciences, Harare, Zimbabwe
Collaborating site(s)	• University College London (UK) • Radboud University (Netherlands) • Klinikum der Universität München (Germany) • MTC, Karolinska Institute (Sweden)
Study design	The study will be a multicentre patient-level randomised controlled trial comparing a single sputum GeneXpert MTB/RIF Assay performed at point-of-treatment with same-day standard fluorescent smear microscopy for TB diagnosis at the primary level of care. Liquid MGIT culture will be used as the “classic” TB reference standard.
Study population and number of expected recruits	ADULT 18 and over, 300 patients per site
Investigational product(s)/Manufacturer/ Developer: (if applicable)	Xpert MTB/Rif assay (Cepheid, Sunnyvale, California USA)
Cofunders	• Foundation for Innovative New Diagnostics (FIND, Switzerland) • Swedish International Development Cooperation Agency (SIDA, Sweden) • German Ministry for Education and Research (BMBF, Germany) • Computer-Aided Detection of Tuberculosis (CAD4TB, Netherlands); • Evaluation of transrenal-DNA detection to diagnose tuberculosis (TB trDNA) - a FP6-funded project from the University College London (UCL, UK) • MRC (UK) • Active Diagnosis of Active TB [ADAT, EU-funded consortium between Zambia, Tanzania, UCL and Ludwig Maximilian University of München (LMU, Germany) • Netherlands-African partnership for capacity development and clinical interventions against poverty-related diseases (NACCAP, Netherlands)
Status:	Completed
Results and Outcomes:	
Study/Trial 2	**Determine TB® Point-of-care urine LAM prospective cohort**
Site Principal Investigator(s):	• Keertan Dheda (South Africa) • Jonny Peter (South Africa) • Grant Theron (South Africa) • Peter Mwaba (Zambia) • Lynn Sodai Zijenah (Zimbabwe) • Andrea Rachow (Tanzania) • Peter Mwaba (Zambia)

	• Duncan Chandra (Zambia) • Lynn Zijenah (Zimbabwe) • Michael Hoelscher (NIMR-MMRP) • Andrea Rachow (NIMR-MMRP)
Clinical Trial/Study Sponsor:	Institute of Infectious Disease and Molecular Medicine, University of Cape Town (South Africa)
Trial/Study title:	A randomized control trial of the point-of-care urine LAM lateral flow strip test – Determine TB® - for HIV co-infected patients at primary care TB clinics
Goal:	To assess the LAM lateral flow strip test when combined with smear microscopy (LAM or smear positive) will significantly improve the rapid diagnosis of TB and the proportion of patients starting TB treatment with 24 hours compared to smear microscopy alone in HIV-infected patients.
Primary Objective(s):	1. To compare the performance outcomes of the Determine TB® urine LAM lateral flow test in combination with same-day sputum smear microscopy (so treatment based on LAM or smear in that order) versus same-day sputum smear microscopy alone, for TB diagnosis in HIV-infected patients in primary care TB clinics 2. To determine the time-specific proportion of patients on TB treatment and differences in time-to-treatment initiation between the Determine TB® urine LAM lateral flow test/ same-day sputum microscopy versus same-day sputum microscopy alone for TB diagnosis in HIV-infected patients 3. To evaluate the cost-effectiveness of each strategy for TB diagnosis in HIV-infected patients at primary TB clinics.
Clinical Trial/study site(s)	• University of Cape Town (South Africa) • South African MRC (South Africa) • University Teaching Hospital (Zambia) • University of Zimbabwe College of Health Sciences (Zimbabwe) • NIMR-MMRP (Tanzania)
Collaborating site(s):	• University College London (UK) • Radboud University (Netherlands) • Klinikum der Universität München (Germany) • MTC, Karolinska Institute (Sweden)
Study design:	The study involves two phases. The 1st phase will be a prospective cohort study to evaluate the Determine TB urine LAM lateral flow test specificity. The 2nd phase will be a multicentre patient-level randomised controlled trial comparing a point-of-care Determine TB® urine LAM lateral flow strip test together with same-day standard fluorescent smear microscopy for TB diagnosis in HIV-infected patients at primary care level. Liquid MGIT culture will be used as the TB reference standard.
Number of subjects:	Adult (18 and older) HIV-positive patients with suspected TB, 600 recruits per site
Product(s):	Urine LAM lateral flow strip test (Determine TB®) Xpert® MTB/RIF Assay
Manufacturer/Developer:	Inverness Medical Professional Diagnostics Cepheid, Sunnyvale, California USA
Cofunders:	• Foundation for Innovative New Diagnostics (FIND; Switzerland) • Swedish International Development Cooperation Agency (SIDA) • Sweden) • German Ministry for Education and Research (BMBF; Germany) • Computer-Aided Detection of Tuberculosis (CAD4TB;

	Netherlands) • Evaluation of transrenal-DNA detection to diagnose tuberculosis (TB trDNA) - a FP6-funded project from the University College London (UCL) UK) • Medical Research Council (MRC) UK • Active Diagnosis of Active TB [ADAT, EU-funded consortium between Zambia, Tanzania, UCL and Ludwig Maximilian University of Munich (LMU; Germany); • Netherlands-African partnership for capacity development and clinical interventions against poverty-related diseases (NACCAP; Netherlands)
Status:	Complete
Results and Outcomes:	This study was a go/no go decision based on the performance of the LAM strip for TB detection when using urine collected from the Xpert RCT. The strip test showed good performance on approximately 600 urines and, based on this, the group have decided to proceed with phase 2, which involves patient recruitment.
Study/Trial 3	**Determine TB® Point-of-care urine LAM RCT**
Site Principal Investigator(s):	• Keertan Dheda (South Africa) • Jonny Peter (South Africa) • Grant Theron (South Africa) • Peter Mwaba (Zambia) • Lynn Sodai Zijenah (Zimbabwe) • Andrea Rachow (Tanzania) • Peter Mwaba (Zambia) • Duncan Chandra (Zambia) • Lynn Zijenah (Zimbabwe) • Michael Hoelscher (NIMR-MMRP) • Andrea Rachow (NIMR-MMRP)
Clinical Trial/Study Sponsor:	Institute of Infectious Disease and Molecular Medicine, University of Cape Town (South Africa)
Trial/Study title:	A randomised controlled trial to evaluate the impact of using a point of-care urine LAM strip test for TB diagnosis amongst hosptialized HIV-infected patients in resource-poor settings
Goal:	The purpose of this study will be to determine the impact of the urine LAM strip test on mortality in hospitalized HIV-infected patients with suspected TB when LAM is used as a POC test to guide rapid treatment initiation
Primary Objective(s):	To examine whether the urine LAM strip test, when combined with standard TB diagnostics (smear microscopy and culture), will significantly improve TB treatment-related outcomes (TB-related mortality, morbidity and length of hospital stay) in HIV-infected hospitalized patients when compared to standard TB diagnostics alone.
Clinical Trial/study site(s)	• University of Cape Town (South Africa) • University Teaching Hospital (Zambia) • University of Zimbabwe College of Health Sciences (Zimbabwe) • NIMR-MMRP (Tanzania)
Collaborating site(s):	• University College London, London, UK; • Radboud University, Nijmegen Medical Center, Nijmegen, Netherlands • Klinikum der Universität München, Department of Infectious Diseases & Tropical Medicine, Munich, Germany • MTC, Karolinska Institute, Stockholm, Sweden
Study design:	Randomised controlled trial (RCT)
Number of subjects:	Adult (18 and older) HIV-positive patients with suspected TB, 600 recruits per site

Product(s):	Urine LAM lateral flow strip test (Determine TB®) Xpert® MTB/RIF Assay
Manufacturer/Developer:	Inverness Medical Professional Diagnostics Cepheid, Sunnyvale, California USA
Cofunders:	• Foundation for Innovative New Diagnostics (FIND, Switzerland) • Swedish International Development Cooperation Agency (SIDA, Sweden) • German Ministry for Education and Research (BMBF, Germany) • Computer-Aided Detection of Tuberculosis (CAD4TB, Netherlands) • Evaluation of transrenal-DNA detection to diagnose tuberculosis (TB trDNA) - a FP6-funded project from the University College London (UCL, UK) • Medical Research Council (MRC, UK • Active Diagnosis of Active TB [ADAT, EU-funded consortium between Zambia, Tanzania, UCL and Ludwig Maximilian University of Munich (LMU, Germany); • Netherlands-African partnership for capacity development and clinical interventions against poverty-related diseases (NACCAP, Netherlands)
Status:	Ongoing
Results and Outcomes:	
Study / Trial 4	**Paediatrics study**
Site Principal Investigator(s):	• Heather Zar (South Africa) • Mark Nicol (South Africa)
Clinical Trial/Study Sponsor:	Institute of Infectious Disease and Molecular Medicine, University of Cape Town (South Africa)
Trial/Study title:	Diagnosis of Tuberculosis in HIV-infected children – development of microbiological and immunological strategies
Goal:	To evaluate the utility of new TB diagnostics in children
Primary Objective(s):	Aim 1: Microbiological approach 1. To improve the rapid diagnosis (within 1 day) of TB disease in HIV-infected children by investigating the sensitivity and specificity of the following diagnostic techniques (using culture-proven TB as the gold-standard): – Loop-mediated isothermal amplification (LAMP, Eiken/FIND, Geneva, Switzerland) of respiratory and non-respiratory samples – A novel fully automated real-time PCR-based test (Xpert™ MTB, Cepheid/FIND) for the detection of MTB DNA and associated rifampicin resistance – Antigen capture ELISA for detection of mycobacterial lipoarabinomannan (LAM, FIND) in urine 2. To improve the yield and speed of microscopy and culture-based diagnosis of TB disease in HIV-infected children – To determine the optimum specimen collection protocol by comparing the yield from repeated induced sputum and nasopharyngeal aspirates (NPA) – To determine whether microscopic observation drug susceptibility (MODS) assay provides more rapid culture and drug-susceptibility results than conventional (mycobacterial growth indicator [MGIT]) culture. Aim 2: Immunological approach 1. To determine the incremental value of the addition of MTB-

	specific enzyme linked immunospot (ELISpot) assay (T-SPOT.TB, Oxford Immunotec, Oxford, U.K.) to clinical diagnostic algorithms for the diagnosis of TB disease in HIV-infected children. Children with culture confirmed TB and a control group in whom TB has been excluded will represent gold standard positive and negative. The effect of age and degree of immune depletion on ELISpot responses and TST will also be investigated 2. To determine whether ELISpot (T-SPOT.TB) using cells from a site-specific clinical specimen (e.g. pleural or cerebrospinal fluid) confers increased sensitivity over ELISpot using peripheral blood for the diagnosis of extrapulmonary TB in HIV-infected children.
Clinical Trial/study site(s)	• Red Cross War Memorial Children's Hospital (RCH), Cape Town (South Africa) • New Somerset Hospital (NSH), Cape Town (South Africa) • Nolungile Clinic, Site C, Khayelitsha (South Africa)
Collaborating site(s):	• Childrens Hospital of Melbourne (Australia) • McGill University (Canada)
Study design:	Prospective study of the diagnostic value of novel tests for TB in HIV-infected children with suspected pulmonary or extrapulmonary TB presenting to pediatric hospitals in Cape Town, South Africa, a high HIV and high TB prevalence area.
Number of subjects:	Children (up to 15 years old), clinically suspected of having pulmonary TB or extrapulmonary TB (TB meningitis or pleural TB or pericardial TB or abdominal TB RCH and NSH: 500 HIV-infected children compared to 200 HIV-uninfected children with suspected TB. Khayelitsha (site C): 400 children with suspected TB
Product(s):	Xpert MTB/Rif assay
Manufacturer/Developer:	Cepheid, Sunnyvale, California USA
Cofunders:	• Foundation for Innovative New Diagnostics (FIND, Switzerland) • Swedish International Development Cooperation Agency (SIDA, Sweden) • German Ministry for Education and Research (BMBF, Germany) • Computer-Aided Detection of Tuberculosis (CAD4TB, Netherlands) • Evaluation of transrenal-DNA detection to diagnose tuberculosis (TB trDNA) - a FP6-funded project from the University College London (UCL, UK) • Medical Research Council (MRC, UK • Active Diagnosis of Active TB [ADAT, EU-funded consortium between Zambia, Tanzania, UCL and Ludwig Maximilian University of Munich (LMU, Germany) • Netherlands-African partnership for capacity development and clinical interventions against poverty-related diseases (NACCAP, Netherlands)
Status:	Ongoing
Results and Outcomes:	
Total number of subjects (cohort/epidemiological/ other studies):	N = 4000
PhD studies:	Title: Predictive value of quantitative T cell responses for progression to active TB in HIV co-infected individuals Candidate: Duncan Chandra (University Teaching Hospital Lusaka, Zambia) Dates: February 2012-December 2015

	Title: Population specific risks for TB infection and the variable performance characteristics of novel diagnostic technologies Candidate: Richard Nellis Van Zyl-Smit (UCT, South Africa) Dates: January 2010-December 2011
	Title: An evaluation of immunodiagnostic tests for tuberculosis infection and determinants of TB infection in a population of healthcare workers in the Western Cape, University of Cape Town, South Africa Candidate: Shahieda Adams (UCT, South Africa) Dates: January 2010-January 2014
	Title: Sputum induction, and novel emerging technologies to improve TB diagnosis, in a high HIV prevalence primary care setting (SINET study) Candidate: Jonny Peter (UCT, South Africa) Dates: January 2010-January 2014
	Development and Evaluation of Point-Of-Care Diagnostics for Tuberculosis Candidate: Veronica Allen (UCT, South Africa) Dates: June 2009-August 2012
	Title: Improvement and development of microbiological TB detection methods in resource constrained settings Candidate: Gabriel Rojas-Ponce (NIMR-MMRP) Dates: September 2010-August 2013
	Title: Automatic detection of tuberculosis in radiographs using active learning Candidate: Laurens Hogeweg (Radboud University, Netherlands) Dates: November 2008-August 2013
	Title: Automatic detection of tuberculosis in radiographs Candidate: Pragnya Maduskar (Radboud University, Netherlands) Dates: November 2010-November 2014
MSc studies:	Title: Evaluation and validation of TB-BEAD Diagnostic assay in both smear positive and negative TB Suspects Candidate: Jennifer Allen (MRC Durban, South Africa) Dates: January 2010-December 2012
	Title: Performance outcomes of LED technology (Lumin) for microscopic detection of mycobacteria in a high HIV seroprevalence setting in Africa Candidate: Cuthbert Musarurwa (University of Zimbabwe College of Health Sciences)
Postdoc studies:	Grant Theron (UCT, South Africa)
	Brandie Young-Gqama (UCT, South Africa)
	Justin O'Grady (UCL, South Africa)
	Samana Schwank (UCL, South Africa)
	Widaad Zemanay (UCT, South Africa)
Other/Sub-studies:	Proteomics study "A mass spectral proteomic analysis of human urine samples for the discovery and qualification of new tuberculosis diagnostic biomarkers – a TB-NEAT substudy" IGRA HCW study "Scientific protocol for a study to evaluate immunodiagnostic tests for Tuberculosis infection and determinants of TB infection in a population of health care workers in the Western Cape of South Africa" Sputum Induction study "Utility of sputum induction, and new and emerging technologies to improve the diagnostic yield, in a high HIV prevalence

	primary care setting (SINET study)" Xpert negative study "Specificity of GeneXpert MTB/RIF® in culture-negative TB suspects"
Publications:	1. Theron, G, Peter, J, van Zyl-Smit, R, Mishra, H, Streicher, E, Murray, S, Dawson, R, Whitelaw, A, Holescher, M, Sharma, S, Pai, M, Warren, R, Dheda, K. (2011) Evaluation of the XpertMTB/RIF Assay for theDiagnosis of Pulmonary Tuberculosis in a High HIV Prevalence Setting. *Am J Respir Crit Care Med*, 184: 132-140, doi: 10.1164/rccm.201101-0056OC 2. Peter, JG, Theron, G, Dheda, K. (2013) Can Point-of-Care Urine LAM Strip Testing for Tuberculosis Add Value to Clinical Decision Making in Hospitalised HIV-Infected Persons? *PloS ONE*, 8(2): e54875. doi: 10.7448/IAS.15.3.17364

2.3.2 TB CHILD

EDCTP Project Coordinator:	Fred Lwilla (Ifakara Health Research and Development Centre, Tanzania)
EDCTP Call Title:	Call for applications to support clinical trials, capacity building and networking in new and improved diagnostics for tuberculosis (TB)
EDCTP Project Title:	Evaluation of new and emerging diagnostics for childhood tuberculosis in high burden countries (TB CHILD)
EDCTP Project Code:	IP.2009.32040.007
EDCTP Project Start Date:	17 May 2010
EDCTP Project End Date:	16 May 2013
Collaborators:	• Klaus Reither (Swiss Tropical and Public Health Institute Switzerland and Ifakara Health Research and Development Centre, Tanzania) • Levan Jugheli (Ifakara Health Research and Development Centre, Tanzania) • Salim Abdoulla (Ifakara Health Research and Development Centre, Tanzania) • Christian Burri (Swiss Tropical and Public Health Institute, Switzerland) • Francesco Aloi (San Raphael of St. Francis Hospital Nsambya, Uganda) • Hans-Peter Beck (Swiss Tropical Institute, Switzerland) • Catharina Boehme (Foundation for Innovative New Diagnostics (FIND), Switzerland) • Claudia Daubenberger (Swiss Tropical and Public Health Institute, Switzerland) • Martin Nsubuga (San Raphael of St. Francis Hospital Nsambya, Uganda) • Petra Clowes (MMRP, Tanzania) • Nyanda Elias (MMRP, Tanzania) • Enrico Girardi (National Institute for Infectious Diseases Lazzaro Spallanzani, Italy) • Delia Goletti (National Institute for Infectious Diseases Lazzaro Spallanzani, Italy) • Angela Cannas (National Institute for Infectious Diseases Lazzaro Spallanzani, Italy) • Daniela Maria Cirillo (San Raphael of St. Francis Hospital Nsambya, Italy) • Christof Gedmacher (LMU München, Germany) • Michael Hoelscher (LMU München, Germany) • Mahavir Singh (Lionex GmbH, Germany) • Francis Drobniewski (Health Sciences Research Ltd, UK)
Study / Trial 1	**Study A: Trial for early evaluation in adults**
Chief Trial investigator	Klaus Reither (Tanzania)
Site Principal Investigator(s):	• Nahya Salim Masoud (Tanzania) • Martin Nusubuga/ Franscesco Aloi (Uganda) • Nyanda Elias/Petra Clowes (Tanzania)
Clinical Trial/Study Sponsor:	Ifakara Health Institute (Tanzania)
Goal:	Developing sustainable, collaborative research capacity for the diagnosis of childhood TB in parts of sub-Saharan Africa and on the effective, efficient conduct of clinical trials on new or improved diagnostics for pediatric tuberculosis
Primary Objective(s):	1. To assess performance characteristics (sensitivity, specificity, positive and negative predictive value, diagnostic likelihood ratios) of new TB diagnostics in

	sputum smear-positive or sputum smear-negative/culture-positive adults and adult controls, and the appropriateness of the new test for further systematic evaluation in children 2. To assess reproducibility of test results 3. To investigate the influence of clinical characteristics on the test performance 4. To establish a specimen bank of adequately stored clinical materials from well-characterised patients for future analysis.
Clinical Trial/Study site(s):	• Bagamoyo Research and Training Centre / Ifakara Health Institute, and • NIMR-Mbeya Medical Research Programme (Tanzania) • San Raphael of St. Francis Hospital Nsambya (Uganda)
Collaborating site(s):	• Swiss Tropical and Public Health Institute (Switzerland) • Klinikum of the University of Munich (LMU) (Germany) • Italian National Institute for Infectious Diseases (Italy) • Fondazione Centro San Raffaele del Monte Tabor (Italy) • Foundation for Innovative New Diagnostics (FIND) (Switzerland) • Stellenbosch University (South Africa) • Health Sciences Research Ltd (UK) • LIONEX GmbH (Germany)
Study design:	Case-control evaluation study Adult patients suspected of having pulmonary TB will be prospectively recruited. The study is expected to recruit: sputum smear-positive and smear-negative/ Xpert MTB positive or culture-positive adult pulmonary TB cases, and additionally healthy non-TB controls. These groups will be utilised for the early evaluation studies on those new emerging diagnostic approaches in order assess test accuracy and reproducibility and probably to refine the methodology for application in children.
Number of subjects	Adults; TB cases: 180; Healthy controls: 120
Product(s):	• LHSD Rapid test to detect LAM in sputum or urine • Diagnostic potential of IP10 and other biomarkers in blood and urine • T cell activation markers on Mycobacterium tuberculosis (MTB) specific T cells (TAM-IGRA) • Lab-on-chip based new platform (In-checkTM) for the molecular diagnosis • Newly developed TB diagnostics
Manufacturer/Developer:	• LIONEX, Braunschweig, Germany • Not applicable • Not applicable • STMicroelectronics, Geneva, Switzerland • Not applicable
Cofunders	• State Secretariat for Education and Research SER / Swiss National Science Foundation (Switzerland) • Bundesministerium für Bildung und Forschung (BMBF, Germany) • FIND (Switzerland) • Italian Ministry of Foreign Affairs – Italian Directorate for Development Cooperation (Italy) • Fondazione Centro San Raffaele del Monte Tabor (Italy) • Aispo-Nsambya Hospital (Uganda/Italy) • LMU-Klinikum Der Universitat Munchen (Germany) • Swiss Agency for Development and Cooperation (SDC, Switzerland)
Status	Completed

Results and Outcomes	
Study / Trial 2	**Study B: New diagnostics for childhood TB**
Chief Trial investigator	Klaus Reither (Tanzania)
Site Principal Investigator(s):	• Nahya Salim Masoud (Tanzania) • Martin Nusubuga/ Franscesco Aloi (Uganda) • Nyanda Elias/Petra Clowes (Tanzania)
Clinical Trial/Study Sponsor:	Ifakara Health Institute (Tanzania)
Trial/Study title:	New diagnostics for childhood TB
Goal:	Developing sustainable, collaborative research capacity for the diagnosis of childhood TB in parts of Sub-Saharan Africa and on the effective, efficient conduct of clinical trials on new or improved diagnostics for pediatric tuberculosis
Primary Objective(s):	1. To assess new TB diagnostic modalities regarding sensitivity, specificity, positive and negative predictive value, as well as diagnostic likelihood ratio, in comparison to well-defined diagnostic classification groups for childhood TB 2. To investigate the influence of clinical characteristics and disease diversity on the test performance 3. To test reproducibility of test results 4. To obtain operational feasibility data and assess staff and training requirements for promising new tests 5. To assess the requirements for quality assurance and safety issues for each new test 6. To explore the identification of a resource-stratified diagnostic algorithm by integrating various clinical variables, risk factors and relevant laboratory results 7. To establish a specimen bank of adequately stored clinical reference materials from well-characterised patients for future analysis.
Clinical Trial/Study site(s):	• Bagamoyo Research and Training Centre / Ifakara Health Institute (Tanzania) • NIMR-Mbeya Medical Research Programme (Tanzania) • Saint Raphael of St. Francis, Nsambya Hospital, Kampala (Uganda)
Collaborating site(s):	• Swiss Tropical and Public Health Institute (Switzerland) • Klinikum of the University of Munich (LMU, Germany) • Italian National Institute for Infectious Diseases (Italy) • Fondazione Centro San Raffaele del Monte Tabor (Italy) • Foundation for Innovative New Diagnostics (FIND, (Switzerland) • Stellenbosch University (South Africa) • Health Sciences Research Ltd (UK) • LIONEX GmbH (Germany)
Study design:	This is the central study of the project. The study will comprehensively assess the ability of new tests/approaches, identified in adult early evaluation studies, to reliably diagnose TB in children. Diagnostic accuracy, operational feasibility and appropriateness of the candidate tests/approaches for routine health care service implementation will be evaluated.
Number of subjects	Children (between 6 weeks and 14 years old) with suspected TB N=600
Product(s):	• LHSD Rapid test to detect LAM in sputum or urine • Loop-mediated isotermal amplification (LAMP) • GeneXpert • Diagnostic potential of IP10 and other biomarkers in blood and urine • T cell activation markers on Mycobacterium tuberculosis

	(MTB) specific T cells (TAM-IGRA) • Mtb DNA extraction from stool • Lab-on-chip based new platform (In-checkTM) for the molecular diagnosis • Ustar TB IAD Kit (Biotech) • Pari eFlowrapid nebulizer • Newly developed TB diagnostics
Manufacturer/Developer:	• LIONEX, Braunschweig, Germany • Eiken Chemical Co. Ltd., Tokyo, Japan • Cepheid, Sunnyvale, USA • Not applicable • Not applicable • Not applicable • STMicroelectronics, Geneva, Switzerland • Biotech, China • Pari pharma, Germany • Not applicable
Cofunders:	• State Secretariat for Education and Research SER / Swiss National Science Foundation (Switzerland) • Bundesministerium für Bildung und Forschung (BMBF, Germany) • FIND (Switzerland) • Italian Ministry of Foreign Affairs – Italian Directorate for Development Cooperation (Italy) • Fondazione Centro San Raffaele del Monte Tabor (Italy) • Aispo-Nsambya Hospital (Uganda/Italy) • LMU-Klinikum Der Universitat Munchen (Germany) • Swiss Agency for Development and Cooperation (SDC, Switzerland)
Status:	Completed
Results and Outcomes	
Total number of subjects (clinical trials only):	Total: 1200 (Study A: 300; Study B: 600; PhD 1 : 300)
PhD studies:	Title: Evaluation of XpertTMTM MTB/RIF (GeneXpert, Cepheid) AND Ustar® IAD TB (Biotech) on cytological aspirates for diagnosis of extrapulmonary tuberculosis in children compared to established FNA methodologies and subsequent genotyping of mycobacterial isolates Candidate: Maira Bholla (Aga Khan Hospital, Kenya) Dates: March 2011-March 2015
	Title: Serum microRNAs as biomarkers for active and latent tuberculosis infection in immunocompetent and immunodeficient hosts Candidate: Grace Mwangoka (Ifakara Health Institute, Tanzania) Dates: October 2010-October 2014
MSc studies:	Title: MSc Applied Microbiology, University Dar es Salaam; Thesis title: Prevalence and Environment sources of Atypical Mycobacteria among Tuberculosis suspects Candidate: Sarah Mswata (Ifakara Health Institute, Tanzania) Dates: June 2010-June 2012
	Title: Active case finding among household contacts of patients with sputum smear positive tuberculosis in Mbeya Tanzania, Liverpool School of Tropical Medicine Candidate: Nyanda Elias Ntinginya (Mbeya Medical Research Programme, Tanzania) Dates: September 2010-September 2011
Other/Sub-studies:	Ancillary study: Molecular characterization of M.tuberculosis strains from Bagamoyo and Dar es Salaam (‘genotyping’)
Publications:	

2.3.3 AE TBC

EDCTP Project Coordinator:	Gerhard Walzl (Stellenbosch University, South Africa)
EDCTP Call Title:	Call for applications to support clinical trials, capacity building and networking in new and improved diagnostics for tuberculosis (TB)
EDCTP Project Title:	The evaluation of Mycobacterium tuberculosis specific host cytokine signatures in whole blood culture supernatants as diagnostic biomarkers for active TB infection
EDCTP Project Code:	IP.2009.32040.011
EDCTP Project Start Date:	16 June 2010
EDCTP Project End Date:	15 December 2013
Collaborators:	• Claudia Giehl (European Reasearch & Project Office GmbH (EURICE), Germany) • Amelia Crampin (Karonga Prevention Study (KPS), Malawi) • Hazel Dockrell (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Rawleigh Howe (Armauer Hansen Research Institute (AHRI), Ethiopia) • Desta Kassa (Ethiopian Health and Nutrition Research Institute (EHNRI), Ethiopia) • Stefan H.E.Kaufmann (Max Planck Institute for Infection Biology (MPIIB), Germany) • Harriet Mayanja-Kizza (CWRU Research Collaboration (UCRC), Uganda) • Jayne Sutherland (MRC, The Gambia) • Tom Ottenhoff (Leiden University Medical Centre (LUMC), Netherlands) • Ida Rosenkrands (Statens Serum Institute (SSI), Denmark) • Marieta Van der Vyver (University of Namibia (UNAM), Namibia)
Study / Trial 1	
Site Principal Investigator(s):	• Gerhard Walzl (South Africa) • Jayne Sutherland (The Gambia) • Rawleigh Howe (Ethiopia) • Desta Kassa (Ethiopia) • Harriet Mayanja-Kizza (Uganda) • Mia Crampin (Malawi) • Marieta Van der Vyver (Namibia)
Clinical Trial/Study Sponsor:	Stellenbosch University (South Africa)
Trial/Study title:	The evaluation of Mycobacterium tuberculosis specific host cytokine signatures in whole blood culture supernatants as diagnostic biomarkers for active TB infection
Goal:	The overall goal of the project is to develop a point of care test for diagnosis of active TB that will be based on an overnight culture of whole blood in the presence of Mtb antigens and the measurement of a combination of up to three markers (EGF, IL-1α and MIP-1β) by lateral flow upconverting phosphor technology.
Primary Objective(s):	To evaluate the performance of the combination of levels of EGF, IL-1α and MIP-1β in WBA supernatants, measured by lateral flow upconverting phosphor test strips to enable the accurate diagnosis of active tuberculosis in a rapid field-friendly assay. Such a test would be a significant improvement over current tests as it would not require advanced laboratory capacity, as it would provide a result within 24 hours and as it

	may enable diagnosis of active disease in patients with paucibacillary or extrapulmonary disease.
Secondary Objective(s):	1. To evaluate improvements of the overnight whole blood assay by: – Investigating WBA supernatants by Luminex multiplex cytokine technology to identify additional host markers with good diagnostic ability to differentiate between active and latent TB – Investigating the performance of novel infection phase specific Mtb proteins – Investigating the performance of the novel tests discussed above to diagnose TB in clinical situations where bacteriologic confirmation is difficult, including in HIV infection and in extrapulmonary TB 2. To establish a comprehensive bio bank for diagnostic marker discovery
Clinical Trial/Study site(s):	• Stellenbosch University (South Africa) • Medical Research Council (The Gambia) • Armauer Hansen Research Institute (Ethiopia) • Makerere University (Uganda) • Karonga Prevention Study/LSHTM, (Malawi) • University of Namibia (Namibia) • Ethiopian Health and Nutrition Research Institute (Ethiopia)
Collaborating site(s):	• Max Planck Society for the Advancement of Science/Max Plank Institute for Infection Biology (Germany) • LUMC (The Netherlands) • LSHTM (UK) • European Research & Project Office GmbH (Eurice) (Germany) • Statens Serum Institute (Denmark)
Study design:	Group I: TB suspects (adult, >14 to 65) will be recruited and followed up for 6 months at primary health care clinics at the African consortium institutions. Confirmation of disease status will be performed by clinical (symptom questionnaire, physical examination), radiological (chest X-rays) and laboratory measures (sputum smear and culture, confirmation by speciation). Participants will be followed up once at month six to ascertain treatment response and thereby increase diagnostic certainty. The project expects to enrol 300 active TB cases and 500 participants without active TB and this group will include people with LTBI and acute and chronic lung infections not due to TB as well as non-infectious conditions, like chronic obstructive pulmonary disease (COPD). Group II: TB suspects (Adult, >14 to 65) as above but with HIV infection. The study expects to enrol 200 active TB cases and 200 participants without active TB and this group will include people with LTBI and acute and chronic lung infections not due to TB, all with HIV infection. Database and sample bank: All clinical and laboratory data will be entered into i) site-specific databases and ii) a central consortium database. Samples will be stored at site-specific bio banks but sample information will also be entered into the central database. Samples will be collected to establish a bio bank for future discovery of diagnostic biomarkers.
Number of subjects	Group I: 800 HIV uninfected TB suspects Group II: 400 HIV infected TB suspects

Product(s):	Commercial in vitro interferon gamma (IFN-γ) release assays (IGRAs): QuantiFERON® TB Gold In-Tube T SPOT.TB
Manufacturer/Developer:	• Cellestis, Victoria (Australia) • Oxford Immunotec, Abington (UK)
Cofunders:	• Stellenbosch University (South Africa) • Makarere University (Uganda) • Max Planck Institute (Germany) • Leiden University (Netherlands) • LSHTM (UK) • European Research and Project Office GmbH (Germany) • BMBF (Germany) • NACCAP (Netherlands) • MRC (UK)
Status:	Ongoing
Results and Outcomes	First patient in: 9 November 2010
Total number of subjects (cohort/epidemiological/ other studies):	N = 1200
PhD studies:	Gene expression and cytokine pattern of pulmonary tuberculosis patients and their contacts in Ethiopia Candidate: Adane Mhiret Bekele (Stellenbosch University, South Africa) Dates: April 2009-December 2012
	Title: pending Candidate: Wegene Tamene (pending) Dates: pending
MSc studies:	Title: Innate immune responses in protection against MTB infection Candidate: Khutso Phalane (Stellenbosch University, South Africa) Dates: January 2011-December 2012
	Title: Diagnostic potential of memory T cell subtypes in MTB infection Candidate: Paulin Essone Ndong (Stellenbosch University, South Africa) Dates: January 2011-December 2012
	Title: The evaluation of MTB specific host cytokine signatures in whole blood culture supernatants as diagnostic biomarkers Candidate: Josephina Nolongo (University of Namibia) Dates: March 2011-October 2012
	Title: The profile of antiretroviral drug resistance mutations at baseline and at time of failure of antiretroviral therapy in tuberculosis co-infected Human Immunodeficiency Virus-1 patients in Ethiopia Candidate: Gebremedhin Gebremichael (LSHTM, UK) Dates: pending
	Title: Mycobacterium tuberculosis specific cytokine profile in childhood Tuberculosis in Ethiopia Candidate: Yodit Alemayehu (LSHTM, UK) Dates:
	Title: Cytokines as markers to detect active tuberculosis in patients attending the tuberculosis clinic at Mulago Hospital Candidate: Anna Ritah Namuganga (Makerere University, Uganda) Dates: pending
	Title: Evaluation of clinical and radiological predictors of TB disease recurrence Candidate: Grace Muzanye (LSHTM, UK) Dates: August 2011-August 2014

Post-doc studies:	Novel Chegou (Stellenbosch University, South Africa) Maria Esterhuyse (Max Planck Institute for Infection Biology, Germany)
Other/Sub-studies:	Global transcriptome analyses of blood leukocytes Maria Esterhuyse (post-doctoral fellowship)
Publications:	1. Chegou, NN, Hoek, KG, Kriel, M, Warren, RM, Victor, TC, Walzl, G. (2011) Tuberculosis assays: past, present and future. *Expert Rev Anti Infect Ther*. 9(4):457-469, doi: 10.1586/eri.11.23. 2. Walzl, G, Ronacher, K, Hanekom, W, Scriba, TJ, Zumla, A. (2011) Immunological biomarkers of tuberculosis. *Nat Rev Immunol*. 11(5):343-54, doi: 10.1038/nri2960.

3 Malaria

3.1 Malaria treatment clinical trials

Project Acronym (Coordinator)	Phase of trial	Product(s)	Manufacturer / Developer	Study population	Status
4ABC (D'Alessandro)	IIIb	Amodiaquine-artesunate Dihydroartemisinin-piperaquine Artemether-lumefantrine Lapdap (Chlorproguanil-Dapsone) + artesunate	Sanofi-Aventis Sigma-Tau Glaxo SmithKline Novartis	CHILDREN with uncomplicated malaria (6-59 months) N=4,112	Completed
SMAC-II (Kremsner)	II	Artesunate (iv)	WRAIR Sigma-Tau	CHILDREN with severe malaria (6 months to 10 years) N=197	Completed
SMAC-III (Kremsner)	III	Artesunate (iv and im)	Guillin Pharm.	CHILDREN with severe malaria (≤14 years) – N=1,047	Completed
PREGACT (D'Alessandro)	IIIb	Artesunate-amodiaquine Dihydroartemisinin-piperaquine Artesunate-mefloquine Artemether-lumefantrine	Sanofi-Aventis Sigma-Tau Farmanguinhos Novartis	PREGNANT WOMEN+INFANTS (>15 years old) & their newborns N=3480	Ongoing
MiPPAD (Menéndez)	IV	Mefloquine Sulphadoxine-pyrimethamine	Hoffman-La Roche UCB Pharma Carreras/Bonals	PREGNANT WOMEN+INFANTS (>15 years old) & their newborns N=5783	Ongoing
MiPPAD (Menéndez)	IIIb/IV	Mefloquine Sulphadoxine-pyrimethamine Cotrimoxazole Placebo	Hoffman-La Roche UCB Pharma Carreras/Bonals	PREGNANT WOMEN (HIV-positive)+INFANTS (>15 years old) & their newborns N=5783	Ongoing
IPTp – SP (ter Kuile)	IIIb/IV	Sulfadoxine-pyrimethamine Dihydroartemisinin-piperaquine Artemether-lumefantrine Artesunate-amodiaquine	Durbin PLC Sigma-Tau	PREGNANT WOMEN+INFANT (>16 years old) N=1,675	Ongoing

		mefloquine-artesunate			
IPTp – SP (ter Kuile)	IIIb/IV	Sulfadoxine-pyrimethamine Artemether-lumefantrine	Novartis	PREGNANT WOMEN+INFANT (>16 years old) N=5,000	Ongoing
WANECAM (Djimde)	IIIb/IV	Amodiaquine-artesunate Dihydroartemisinin-piperaquine Artemether-lumefantrine Artesunate-pyronaridine	Sanofi-Aventis Sigma-Tau Novartis Shin Poong Pharm.	CHILDREN with uncomplicated malaria (6 months-5 years old) & ADULTS N=4,032	Ongoing
ADAPT (Mwapasa)	IIIb	Amodiaquine-artesunate Dihydroartemisinin-piperaquine Artemether-lumefantrine Antiretroviral drug combinations [3TC-d4T-NVP, Trioimune, Cipla; 3TC-AZT-EFV (combivir plus efavirenz); 3TC-AZT-NVP (combivir plus NVP); TDF-3TC-AZT-LPV/r (tenofovir, combivir plus lopinavir/ritonavir)]	Sanofi-Aventis Sigma-Tau Novartis	ADULTS HIV+ individuals (step 1 study, half-dose ACTs) N= 66 ADULTS HIV+ individuals (step 2 study, full-dose ACTs) N= 40 (To be updated, step 2 study now ongoing)	Ongoing (step 1 & step 2, enrollment completed)

3.1.1 4ABC study

EDCTP Project Coordinator:	Umberto D'Alessandro (Prince Leopold Institute of Tropical Medicine, Belgium)
EDCTP Call Title:	Support of phase II-III drug trials for uncomplicated malaria using novel artemisinin-based combination drugs
EDCTP Project Title:	Evaluation of 4 artemisinin-based combinations for treating uncomplicated malaria in African children
EDCTP Project Code:	CT.2004.31060.001
EDCTP Project Start Date:	5 December 2005
EDCTP Project End Date:	30 June 2010
Collaborators:	• Abdel Babiker (Medical Research Council (MRC), UK) • Francis Bajunirwe (Mbarara University of Science and Technology, Uganda) • Quique Bassat (Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain) • Julia Critchley (University of Liverpool, UK) • Carrol Gambie (University of Liverpool, UK) • Paul Garner (University of Liverpool, UK) • Jean Pierre van Geertruyden (Prince Leopold Institute of Tropical Medicine (ITM), Belgium) • Raquel Gonzales (Manhiça Health Research Center (CISM), Mozambique) • Philippe Jean Guerin (Epicentre, France) • Robert T Guiguemdé (Centre Muraz, Burkina Faso) • Jean Paul Guthmann (Epicentre, France) • Moses Kamya (Makerere University, Uganda) • Corine Karema (Programme National de Lutte contre le Paludisme, Rwanda) • Bertrand Lell (University of Tübingen, Germany) • Eusebio Macete (CISM, Mozambique) • Sónia Machevo (CISM, Mozambique) • Pierre Blaise Matsiegui (Albert Schweitzer Hospital, Gabon) • Clara Menendez (Hospital Clinic of Barcelona, Spain) • Martin Meremikwu (University of Calabar, Nigeria) • Modest Mulenga (Tropical Diseases Research Centre, Zambia) • Theonest Mutabingwa (National Institute for Medical Research (NIMR), Tanzania) • Lawrence Mwananyanda (Tropical Diseases Research Centre, Zambia) • Carolyn Nabasumba (Mbarara University of Science and Technology, Uganda) • Nathan Bakyaita Nsubuga (Makerere University, Uganda) • Piola, Patrice (Epicentre Uganda, Uganda) • Claude Rwagacondo (Programme National de Lutte contre le Paludisme, Rwanda) • Caroline Sabin (University College London, UK) • Francisco Saute (CISM, Mozabique) • Ambrose Talisuna (Ministry of Health, Uganda) • Halidou Tinto (Centre Muraz, Burkina Faso) • Innocent Valea (Centre Muraz, Burkina Faso) • Paula Williamson (University of Liverpool, UK) • Adoke Yeka (Makerere University, Uganda)
Site Principal Investigator(s):	• Umberto D'Alessandro (Antwerpen, Belgium) • Halidou Tinto (Bobo Dioulasso, Burkina Faso) • Pierre Matsiegui (Libreville, Gabon)

	• Sonia Machevo (Manhiça, Mozambique) • Martin Meremikwu (Cross River State, Nigeria) • Corine Karema (Kigali, Ruanda) • Patrice Piola (Kampala, Uganda) • Moses Kamya (Kampala, Uganda) • Carolyne Nabasumba (Mbarara, Uganda) • Modest Mulenga (Ndola, Zambia)
Clinical Trial/Study Sponsor:	Prince Leopold Institute of Tropical Medicine, Antwerp (Belgium)
Trial/Study title:	Evaluation of 4 artemisinin-based combinations for treating uncomplicated malaria in African children
Goal:	The main objective is to compare the safety and efficacy of 4 artemisinin-based combinations (ACT) [amodiaquine-artesunate (AQ+AS), dihydroartemisinin-piperaquine (DHAPQ), artemether-lumefantrine (AL) and chlorproguanil/dapsone plus artesunate (CDA) for single and repeat treatments of uncomplicated malaria in children. Safety was determined by registering and grading adverse events and by laboratory, and vital signs evaluations. Their incidence was compared between the different study arms.
Primary Objective(s):	3. PCR unadjusted treatment failure (TF28U): all treatment failures detected during the active follow up, regardless of genotyping (time frame: day 28) 4. PCR adjusted treatment failure up to day 28 (TF28A): all early failures before day 14 plus the recurrent parasitaemias detected at day 14 or later and classified by genotyping as recrudescence (time frame: day 28).
Secondary Objective(s):	5. PCR unadjusted treatment failure up to day 63 (TF63U): TF28U plus all cases of recurrent parasitaemia (symptomatic or asymptomatic) detected between day 29 and day 63 by passive follow up, regardless of genotyping (time frame: day 63) 6. PCR adjusted treatment failure for the whole period of passivesurveillance (TFAPS): TF28A plus all episodes of recurrent parasitaemia identified as recrudescence by genotyping (time frame: day 28) 7. Fever clearance time 8. Asexual parasite clearance time 9. Gametocytaemia (prevalence and density) at day 7, 14, 21 and 28 after treatment (for both active follow-ups) (time rame: 28 days) 10. Hb changes day 3, 7, 14 and 28 (first and second follow up) (time frame: 28 days) 11. Clinical malaria after first active follow-up (time frame: 28 days) 12. Clinical malaria after second active follow-up (time frame: Up to 7 months) 13. Time frame (TF) second clinical episode (D28 and D63) (time frame: 63 days) 14. Changes in the frequency of mutations in the dihydrofolate reductase (DHFR) gene at day 0 first follow-up and day re-appearance of parasitaemia (for patients treated with CDA - Note that CDA arm was discontinued on 17.02.2008 because of safety concerns). 15. Safety profiles including significant changes in relevant laboratory values (time frame: up to 7 months).
Clinical Trial/Study site(s):	• Nanoro (Burkina Faso) • Afokang and Pamol (Nigeria) • Fougamou and Lambaréné (Gabon)

	• Mbarara, Jinja and Tororo (Uganda) • Rukara and Mashesha (Rwanda) • Ndola (Zambia) • Manhiça (Mozambique)
Collaborating site(s):	• Institute of Tropical Medicine, Antwerp (Belgium) • Liverpool School of Tropical Medicine and University of Liverpool (UK) • Centre Muraz/IRSS, Bobo-Dioulasso (Burkina Faso) • University of Calabar, Calabar (Nigeria) • Tropical Diseases Research Centre, Ndola (Zambia) • University Hospital Tuebingen, Tübingen (Germany) Albert Schweitzer Hospital, Lambaréné (Gabon) • Uganda Malaria Surveillance Project (Uganda) • Mbarara University of Science and Technology, Mbarara (Uganda) • Programme National Lutte contre le Paludisme, Kigali (Rwanda) • Center for International Health Research, University of Barcelona, Barcelona (Spain) • Manhiça Health Research Centre, Manhiça (Mozambique)
Study design:	Phase III randomised, controlled, open-label study Randomised controlled trial, comparing 4 combinations of artesunate derivatives: **Arm 1:** Intervention with amodiaquine-artesunate (ASAQ) consisting of a fix-dose combination tablet containing artesunate-amodiaquine in three different dosages, to be used according to patient age and weight: 25mg/67.5mg; 50mg/135mg; 100mg/270mg (other name of ASAQ is Coarsucam by Sanofi-Aventis). **Arm 2:** Intervention with dihydroartemisinin-piperaquine (DHAPQ) consisting of DHAPQ tablets contain either 20/160mg or 40/320mg of dihydroartemisinin (DHA) and piperaquine phosphate (PQ) respectively. TO BE NOTED: since the batches of the study drug DHAPQ expired at the end of October 2008 and the unavailability of a new batch of DHAPQ from the manufacturer, the recruitment in the DHAPQ arm had to be discontinued on 30 October 2008. A formal amendment was submitted to all the concerned ECs and competent authorities (other names for DHAPQ is Eurartekin by Sigma-Tau). **Arm 3:** Intervention with artemether-lumefantrine (AL) consisting of tablets containing 20 mg of Artemether and 120 mg of Lumefantrine (other names for AL are Coartem and Riamet by Novartis) **Arm 4:** Intervention with Lapdap (Chlorproguanil-Dapsone) + artesunate (AS) consisting of Lapdap tablets contain 15/18.75mg or 80/100mg of Chlorproguanil Hydrochloride and Dapsone, respectively. Arsumax® tablets contain 50mg Artesunate (other names of CDA are Lapdap by GSK and Arsumax by Sanofi-Aventis and Guilin Pharmaceutical). TO BE NOTED: following GlaxoSmithKline decision to discontinue the clinical development of the fixed-doses combination of Lapdap (Chlorproguanil-Dapsone) and artesunate, the Lapdap plus Artesunate arm was immediately discontinued in this study, on 17 February 2008. A formal amendment was approved by several ethics and regulatory

	authorities by June 2008.
Product(s):	• Amodiaquine-artesunate (ASAQ) • Dihydroartemisinin-piperaquine (DHAPQ) • Artemether-lumefantrine (AL) • Lapdap (Chlorproguanil-Dapsone) + artesunate (AS) (CDA)
Manufacturer/Developer:	• Sigma-Tau • Sanofi-Aventis • Glaxo SmithKline • Novartis
Cofunders:	• Medicines for Malaria Venture [MMV] (Switzerland) • Carlos III Health Institute (Spain) • Medical Research Council [MRC] (UK) • Prince Leopold Institute of Tropical Medicine, (Belgium) • GlaxoSmithKline Foundation, Department for International Development [DFID] (UK)
Trial Registration number(s):	NCT 00393679
Status:	Completed
Results and Outcomes:	The results from this study have shown that AL, ASAQ, and DHAPQ had excellent efficacy up to day 63 post-treatment. However, the risk of recurrent infections was significantly lower, even in areas of high transmission, for DHAPQ, followed by ASAQ, and then AL. CDA treatment was withdrawn early in course of the study for safety reasons (high risk of developing severe anaemia in glucose-6 phosphate dehydrogenase deficient individuals). Furthermore, the study showed that CDA had the lowest efficacy of the four ACTs. This large multicentre trial covered seven African countries with different malaria endemicities and has generated information that will assist national malaria control programmes in sub-Saharan Africa in choosing the most appropriate ACTs for their specific setting. AL and ASAQ are already included in the antimalarial drug policies of many sub-Saharan African countries. Importantly, the data also showed that DHAPQ is a new option for the treatment of uncomplicated malaria with the added value of its long lasting prophylaxis in comparison to the other two ACTs. These results have contributed to the recent registration of DHAPQ by EMEA. This project is an excellent model of a strong North-South partnership, involving 10 sites in 7 African countries (Burkina Faso, Gabon, Mozambique, Nigeria, Rwanda, Uganda and Zambia) in partnership with 5 European institutions (Belgium, United Kingdom, Germany, France and Spain) as well as the product development partnership, Medicines for Malaria Venture (MMV).
Total number of subjects (clinical trials only):	4,116 children 6-59 months old with uncomplicated *P. falciparum* malaria
PhD studies:	Title: The best approach for retreating patients with recurrent malaria in the era of ACT Candidate: Adoke Yeka (Uganda) Dates: End 2012
	Title: Antimalarial treatment policies in Africa: How to improve the existing strategies? The experience of Burkina Faso Candidate: Innocent Valéa (Burkina Faso) Dates: End 2012

	Title: The value of individual patient data for mixed treatment comparison meta-analysis Candidate: Sarah Donegan (University of Liverpool, UK) Dates: January 2006 - 23 September 2011
Other/Sub-studies:	Efficacy of quinine, artemether-lumefantrine and dihydroartemisinin-piperaquine for recurrent uncomplicated malaria in Ugandan children
Publications:	1. D'Alessandro U on behalf of The Four Artemisinin-Based Combinations (4ABC) Study Group. A Head-to-Head Comparison of Four Artemisinin-Based Combinations for Treating Uncomplicated Malaria in African Children: A Randomised Trial. *PLoS Med* 2011, 8(11): e1001119 2. Donegan, S; Williamson, P; D'Alessandro, U; Smith, CT. Assessing the consistency assumption by exploring treatment by covariate interactions in mixed treatment comparison meta-analysis: individual patient-level covariates versus aggregate trial-level covariates. (2012). *Statistics in Medicine* 31(29) 3840-3857. 3. Donegan, S; Williamson, P; D'Alessandro, U; Garner, P; Smith, CT. Combining individual patient data and aggregate data in mixed treatment comparison meta-analysis: Individual patient data may be beneficial if only for a subset of trials. (2012). *Statistics in Medicine*. Doi: 10.1002/sim.5584.

3.1.2 SMAC-II and III (Dose Optimisation Study)

EDCTP Project Coordinator:	Peter G. Kremsner (University of Tübingen, Germany)
EDCTP Call Title:	Support of Phase II-III (dose optimization) drug trials for the treatment of severe malaria using artemisinin compounds
EDCTP Project Title:	Artesunate for severe malaria in African children
EDCTP Project Code:	CT.2004.31070.001
EDCTP Project Start Date:	3 July 2006
EDCTP Project End Date:	5 April 2013
Collaborators:	• Tsiri Agbenyega (University of Science and Technology-Kwame Nkrumah, Ghana) • Kalifa Bojang (Medical Research Council Laboratories, The Gambia) • Markus Gmeiner (Vienna School of Clinical Research, Austria) • Saadou Issifou (Albert Schweitzer Hospital, Gabon) • Christa Janko (Vienna School of Clinical Research, Austria) • Maryvonne Kombila (Cambodian University of Health Sciences, Gabon) • Sanjeev Krishna (St. George's University of London, UK) • James Mwenechanya (Queen Elizabeth Central Hospital, Malawi) • Charles Newton (Kenya Medical Research Institute (KEMRI), Kenya) • Gabriele Schreyer (Vienna School of Clinical Research, Austria) • Terrie Taylor (Queen Elizabeth Central Hospital, Malawi)
Study / Trial 1	**SMAC-II (artesunate study in severe malaria)**
Site Principal Investigator(s):	• Peter Kremsner (Tuebingen, Germany & Lambaréné, Gabon) • Saadou Issifou (Lambaréné, Gabon) • Maryvonne Kombila (Libreville, Gabon) • Terrie Taylor (Blantyre, Malawi)
Clinical Trial/Study Sponsor:	Medicines for Malaria Venture, Geneve (Switzerland)
Trial/Study title:	Phase II Randomised, Double-Blind Study of the Efficacy, Safety, Tolerability, and Pharmacokinetics of Intravenous Artesunate in Children With Severe Malaria
Goal:	The overall goal of the study is to compare the efficacy, safety and tolerability of the standard 5-dose iv regimen with a simplified 3-dose iv regimen of Artesunate in children with severe malaria.
Primary Objective(s):	To evaluate the effectiveness of 2 intravenous artesunate dosing regimens (2.4 mg/kg initially and at 12, 24, 48, and 72 hours or 4.0 mg/kg initially and at 24 and 48 hours) in clearing *P. falciparum* parasites in children with severe malaria.
Secondary Objective(s):	1. To compare the tolerability and safety of the 2 intravenous artesunate dosing regimens 2. To evaluate differences in the pharmacokinetic profile of intravenous artesunate by patient age and clinical presentation.
Clinical Trial/Study site(s):	• Albert Schweitzer Hospital, Lambaréné (Gabon) • Université de Medecine et Science de la Santé, Libreville (Gabon) • Queen Elizabeth Central Hospital, Blantyre (Malawi)
Collaborating site(s):	• School of Medical Sciences, University of Sciences and Technology, Kumasi (Ghana) • Kenya Medical Research Institute (KEMRI), Kilifi (Kenya) • MRC Laboratories, Banjul (The Gambia)

	• University of Tübingen, Tübingen (Germany) • Vienna School of Clinical Research, Vienna (Austria) • St George's Hospital Medical School, London (UK)
Study design:	A double-blind, multicentre, randomised, parallel-group study of the antimalarial activity and safety of 2 intravenous artesunate regimens (2.4 mg/kg initially and at 12, 24, 48, and 72 hours or 4.0 mg/kg initially and at 24 and 48 hours) in children with severe *P. falciparum* malaria. The study will also evaluate the pharmacokinetic profile of artesunate in pediatric patients. Patients will be randomised to 1 of 2 cohorts. Cohort 1: artesunate 2.4 mg/kg on admission, and at 12, 24, 48, and 72 hours (12 mg/kg total dose); or Cohort 2: artesunate 4 mg/kg on admission, and at 24 and 48 hours (12 mg/kg total dose), normal saline will be administered as a placebo at 12 and 72 hours in order to maintain the study blind. As soon as the patient is able to receive oral medication and no signs and symptoms of severe malaria are present, but not before the last pharmacokinetic sample is taken (approximately 50 hours after the start of therapy), a single dose of sulfadoxine/pyrimethamine will be administered to ensure parasitological cure. Randomisation will be balanced at each study site in a 1:1 ratio for each artesunate regimen. Patient participation will be for at least 28 days following the first dose of study drug. Patients will be hospitalized for at least 4 days (day 0, 1, 2, and 3). The patient will return to the study site for study visits on days 7, 14, and 28. If adverse events reported during the study are unresolved by day 28, patients will be followed for an additional 30 days or until resolution of the event or determination that no further medical management is deemed necessary. Similarly, the investigator will instruct the patient to return to the study site if any untoward event occurs within 30 days of completing the study drug.
Product(s):	Artesunate
Manufacturer/Developer:	WRAIR
Cofunders	• Medicines for Malaria Venture (MMV, Switzerland) • Federal Ministry of Education and Research (BMBF, Germany)
Trial Registration number(s):	NCT00522132
Status:	Completed
Results and Outcomes:	The results of the phase II studies showed that treatment of severe malaria can be simplified to a 3-dose regimen (given at 0, 24 and 48 h) with a total dose of 12 mg/kg artesunate intravenously administered instead of the conventional 5-dose regimen of intravenous artesunate (given at 0, 12, 24, 48 and 72 hours). If outcome is positive, the results of the ongoing phase III studies investigating further simplification of the treatment of severe malaria by administering artesunate in a simplified 3-

	dose regimen intramuscularly rather than intravenously have potential for cost saving and improved severe malaria management in resource limited settings. These results will inform policy and evidence-based future changes in malaria treatment guidelines by WHO for malaria endemic countries. The study timelines were from September 2007 to December 2008.
Total number of subjects (clinical trials only):	200 patients planned, 182 patients analysed (ITT population)
Total number of subjects (cohort/epidemiological/ other studies):	93 patients analysed in cohort 1 89 patients analysed in cohort 2
PhD study	Title: Efficacy, Safety and Tolerability of two different regimen of intravenous Artesunate therapy in children with severe malaria Candidate: Matthias Duscha (Germany)
Publications:	3. A simplified intravenous artesunate regimen for severe malaria. Kremsner, PG, Taylor T, Issifou S, Kombila M, Chimalizeni Y, Kawaza K, Bouyou Akotet MK, Duscha M, Mordmuller B, Kösters K, Humberg A, Scott Miller R, Weina P, Duparc S, Möhrle J, Kun JFJ, Planche T, Teja-Isavadham P, Simpson J, Köhler C, Krishna S. *Journal of Infectious Diseases* 2012; 205:312-9
Study / Trial 2	**SMAC-Dose Optimization Study (Artesunate Follow-Up Study for severe malaria in children)**
Site Principal Investigator(s):	• Peter Kremsner (Tuebingen, Germany & Lambaréné, Gabon) • Saadou Issifou (Lambaréné, Gabon) • Maryvonne Kombila (Libreville, Gabon) • Terrie Taylor (Blantyre, Malawi) • Tsiri Agbenyega (Kumasi, Ghana) • Charles Newton (Kilifi, Kenya) • Bernhards Ogutu (Kisumu, Kenya) • Kalifa Bojang (Banjul, The Gambia) • Sanjeev Krishna (London, UK)
Clinical Trial/Study Sponsor:	Universitätsklinikum Tübingen, Tübingen (Germany)
Trial/Study title:	Phase III Comparative, Open-Label, Dose and Regimen Optimisation Follow-up Study of Intravenous and Intramuscular Artesunate in African Children With Severe Malaria
Goal:	The overall goal of the study is to compare the efficacy, safety and tolerability of 3-dose regimens: iv artesunate and im artesunate simplified dosing regimens (4 mg/kg artesunate at 0, 24 and 48 hours; 12 mg/kg total dose) and the standard iv treatment dosing regimen (2.4 mg/kg artesunate at 0, 12, 24, 48 and 72 hours; 12 mg/kg total dose).
Primary Objective(s):	The primary objective of the study is to evaluate the non-inferiority of iv artesunate and im artesunate simplified dosing regimens (4 mg/kg artesunate at 0, 24 and 48 hours; 12 mg/kg total dose) to the standard im treatment dosing regimen (2.4 mg/kg artesunate at 0, 12, 24, 48, 72 hours; 12 mg/kg total dose) in clearing parasitaemia in children with severe malaria.
Secondary Objective(s):	1. To compare the tolerability and safety of the 3 artesunate dosing regimens 2. To evaluate differences in the pharmacokinetic profile of parenteral artesunate by patient age and clinical presentation (total of 300 patients to be studied). Exploratory Analysis:

	3. To assess non-invasive oto-acoustic tests linked to disease 4. To assess predictability of fatal malaria by means of the Lambaréné-Organ-Dysfunction Score (LODS) 5. To analyze genetic polymorphisms in humans and parasites linked to disease and treatment 6. To assess in vitro drug sensitivity of clinical study isolates.
Clinical Trial/Study site(s):	• Albert Schweitzer Hospital, Lambaréné (Gabon) • Université de Médecine et Science de la Santé, Libreville (Gabon) • Queen Elizabeth Central Hospital, Blantyre (Malawi) • School of Medical Sciences, University of Sciences and Technology, Kumasi (Ghana) • Kenya Medical Research Institute (KEMRI), Centre for Geographical Medicine (Coast), Kilifi (Kenya) • Kenya Medical Research Institute (KEMRI), Kondele Childrens Hospital, Kisumu (Kenya) • MRC Laboratories, Banjul (The Gambia)
Collaborating site(s):	• Vienna School of Clinical Research, Vienna (Austria) • St George's Hospital Medical School, London (UK) • Institut für klinische Pharmakologie, Stuttgart (Germany) • University of Innsbruck (Austria)
Study design:	An open label, multicenter, parallel-group, three arm follow-up study to compare the antimalarial activity and safety of 3 artesunate dosing regimens in children with severe *P. falciparum* malaria: iv artesunate 4 mg/kg initially, and at 24 and 48 (12 mg/kg total dose); im artesunate 4 mg/kg initially, and at 24 and 48 hours (12 mg/kg total dose), im artesunate 2.4 mg/kg initially, and at 12, 24, 48 and 72 hours (12 mg/kg total dose). The study will also evaluate the pharmacokinetic profile of artesunate in pediatric patients. Patients will be randomised to 1 of 3 cohorts. Cohort 1: iv artesunate 4 mg/kg initially, and at 24 and 48 hours (12 mg/kg total dose); or Cohort 2: im artesunate 4 mg/kg initially, and at 24 and 48 hours (12 mg/kg total dose), or Cohort 3: im artesunate 2.4 mg/kg initially, and at 12, 24, 48, and 72 hours (12 mg/kg total dose). Patient participation will be for at least 28 days following the first dose of study drug. Patients will be hospitalized for at least 3 days. The patient will return to the study site for study visits on Days 7, 14, and 28. If adverse events reported during the study are unresolved by day 28, patients will be followed for an additional 30 days or until resolution of the event or determination that no further medical management is deemed necessary. Similarly, the investigator will instruct the patient to return to the study site if any untoward event occurs within 30 days of completing the study drug. Artesunate treatment will be completed with another antimalarial, e.g. sulfadoxine-pyrimethamine (25 mg/kg and 1.25 mg/kg) at discharge. Adjunctive therapy, including fluids, glucose and blood will follow SMAC standards based on WHO guidelines for the treatment of severe malaria. In case of initial treatment failure with intravenous or

	intramuscular artesunate or a severe drug reaction to artesunate, parenteral quinine will be given to treat severe malaria, if patients had previous quinine therapy (within 12 hours), continue administering 8mg quinine base/kg every 8 hours, if no previous quinine therapy, give loading dose of 16 mg/kg and continue with normal regimen). Recurrent malarial infection within 28 days will be treated with artemether/lumefantrine. The study timelines were from December 2010 to April 2013 (Recruitment period from July 2011 until September 2012).
Product(s):	Artesunate
Manufacturer/Developer:	Guillin Pharmaceuticals, Shanghai (China)
Cofunders:	Federal Ministry of Education and Research (BMBF, Germany)
Trial Registration number(s):	PACTR201102000277177
Status:	Ongoing
Results and Outcomes:	All study sites completed recruitment in early October 2012 (Lambaréné, Libreville, Kumasi, Banjul, Kisumu and Kilifi). Study is in close-out phase, analysis expected for March 2013
Total number of subjects (clinical trials only):	1,046 patients enrolled (vs the 1,044 planned)
Total number of subjects (cohort/epidemiological/ other studies):	348 patients planned per cohort approx. 300 patients to be included in PK-& genetic polymorphism-analysis approx. 200 patients to be included in auto-acoustic tests approx. 200 patients to included in in vitro-sensitivity assay
Other/Sub-studies:	• PK- and exploratory analysis will not be performed on the whole study population but only in selected centers on a limited number of patients: – PK: 300 patients to be analysed from the population recruited in Lambaréné, Kumasi and Kisumu. – Genetic Polymorphisms: 300 patients to be analysed from the population recruited in Lambaréné, Kumasi and Kisumu. – Oto-acoustic tests: 200 patients to perform these tests from the populations recruited in Lambaréné, Kumasi and Kisumu. – In vitro-sensitivity: 200 patients to be analysed from the population recruited in Lambaréné.
Publications:	

3.1.3 PREGACT

EDCTP Project Coordinator:	Umberto D'Alessandro (Prince Leopold Institute of Tropical Medicine, Belgium)
EDCTP Call Title:	Support of clinical trials, capacity building and networking in malaria in pregnancy
EDCTP Project Title:	Safe and Efficacious Artemisinin-based Combination Treatments for African Pregnant Women With Malaria
EDCTP Project Code:	IP.2007.31080.001
EDCTP Project Start Date:	6 February 2009
EDCTP Project End Date:	30 September 2014
Collaborators:	• Sharleen Braham (Prince Leopold Institute of Tropical Medicine (ITM), Belgium) • Victor Chalwe (Tropical Diseases Research Centre, Zambia) • Yves Claeys (ITM, Belgium) • Jean Pierre van Geertruyden (ITM, Belgium) • Jenny Hill (University of Liverpool, UK) • Christa Janko (Vienna School of Clinical Research, Austrial) • Gertrude Kalanda (University of Malawi) • Linda Kalilani-Phiri (University of Malawi) • Charles Mangani (University of Malawi) • Christine Manyando (Tropical Diseases Research Centre, Zambia) • Joris Menten (ITM, Belgium) • Modest Mulenga (Tropical Diseases Research Centre, Zambia) • Theonest Mutabingwa (National Institute for Medical Research (NIMR), Zambia) • Reuben Ndindi (University of Malawi) • Vysaul Nyirongo (Malawi-Liverpool-Wellcome Trust Research Programme, Malawi) • Rafaella Ravinetto (ITM, Belgium) • Stephen Rulisa (University Central Hospital of Kigali, Rwanda) • Henk Schallig (Royal Tropical Institute (KIT), Netherlands) • Gabriele Schreyer (Vienna School of Clinical Research, Austria) • Harry Tagbor (University of Science and Technology-Kwame Nkrumah, Ghana) • Christian Tahita (Institut de Recherche en Sciences de la Santé, Burkina Faso) • Feiko ter Kuile (University of Liverpool, UK) • Halidou Tinto (Centre Muraz, Burkina Faso) • Maminata Traore (Centre Muraz, Burkina Faso) • Peter J de Vries (ICRH-International Centre of Reproductive Health, Netherlands)
Site Principal Investigator(s):	• Umberto D'Alessandro (Antwerpen, Belgium) • Halidou Tinto, Marc Tahita, Maminata Traoré (Bobo Dioulasso, Burkina Faso) • Harry Tagbor (Kumasi, Ghana) • Linda Kalilani-Phiri & Victor Mwapasa (Blantyre, Malawi) • Modest Mulenga & Michael Nambozi (Nchlenge, Zambia)
Clinical Trial/Study Sponsor:	Institute of Tropical Medicine, Antwerp (Belgium)
Trial/Study title:	Safe and Efficacious Artemisinin-based Combination Treatments for African Pregnant Women With Malaria
Goal:	To determine the safety and efficacy of 4 ACTs (amodiaquine-

	artesunate or AQAS, dihydroartemisinin-piperaquine or DHAPQ; artemether-lumefantrine or AL, Mefloquine-artesunate or MQAS) when administered to pregnant women with *P. falciparum* infection during the second and the third trimester and collect explanatory variables for treatment failure (PCR-corrected) and for recurrent parasitaemia. Safety will be determined by registering adverse events and grading, laboratory, and vital signs evaluations. Their incidence will be compared between the different study arms. The primary hypothesis tested is the clinical equivalence (pair-wise non-inferiority) of the 4 treatment regimens with clinical equivalence defined as difference in treatment failure rates (PCR corrected) of 5% or less.
Primary Objective(s):	1. To compare the efficacy of AL, AQAS, MQAS and DHAPQ in terms of – Treatment failure (see definition below) by 63 days after start of treatment with or without genotyping – Time to treatment failure (PCR adjusted and unadjusted) during 63 days of active follow-up after treatment – Asexual parasite clearance time – Gametocytaemia (prevalence and density) at day 7, 14, 21, 28 and 63 after treatment, and gametocyte carriage (gametocyte-weeks) – Haematological recovery by 14, 28, 42 and 63 days post-treatment and at delivery – Preventing placenta *P. falciparum* malaria – Birth weight measured within 72 hrs of delivery 2. To describe the safety profile of AL, AQAS, MQAS and DHAPQ in terms of – Tolerability – Incidence of serious and non-serious adverse events until delivery
Secondary Objective(s):	1. To determine the relation between drug pharmacokinetics (partner drug) and response to treatment 2. To assess the in-vitro susceptibility of *P. falciparum* isolates collected before treatment and at time of recurrent infection to several drugs, including the partner drug tested, and to correlate their IC50 to treatment response.
Clinical Trial/Study site(s):	• Nanoro & Nazoanga (Burkina Faso) • Ejisu Sekyere East & Juaben Government Hospital, and Effiduase Government Hospital in the Sekyere East district, Ashanti Region (Ghana) • Madziabango & Mpemba Health Centers, Blantyre (Malawi) • St. Paul's' Hospital, Nchelenge Kashikishi & Kambwali Health Centers (Zambia)
Collaborating site(s):	• Institute of Tropical Medicine, Antwerp (Belgium) • Liverpool School of Tropical Medicine, Liverpool (UK) • Centre Muraz/IRSS, Bobo-Dioulasso (Burkina Faso) • Kwame Nkrumah University of Science and Technology, Kumasi (Ghana) • University of Malawi College of Medicine, Blantyre (Malawi) • Central University Hospital of Kigali, Kigali (Rwanda) • Tropical Diseases Research Centre, Ndola (Zambia) • Seattle Institute for Biomedical and Clinical Research & National Institute for Medical Research, Morogoro (Tanzania) • Vienna School of Clinical Research (Austria)

	• Institute of Tropical Medicine (KIT) & Academic Medical Center, Amsterdam (Netherlands)
Study design:	Phase IIIb randomised, controlled, open label study Randomised controlled trial, comparing 4 combinations of artesunate derivatives (DHAPQ, MQAS, AQAS and AL), to be tested in each country by a 3-arm trial using a "balanced incomplete block design". **Arm 1 (experimental): three-day treatment with dihydroartemisinin-piperaquine (DHAPQ)** DHAPQ tablets are green film coated intended for oral use and contain 20/160mg or 40/320mg of dihydroartemisinin (DHA) and piperaquine phosphate (PQ) respectively. In this trial the 40/320mg for adults will be used (other name of DHAPQ is Eurartesim and was developed by Sigma Tau in partnership with Medicines for Malaria Venture). **Arm 2 (experimental): three-day treatment with artesunate-mefloquine (MQAS)** MQAS will be provided as a fixed-dose ACT. There are 2 strengths (AS25+MQ55mg and AS100+MQ220mg) and dosing regimen is calculated according to 12 mg/kg AS and 24mg/kgMQ total dose over three days. Pregnant women will receive 2 tablets/day for 3 days. It is developed by Farmanguinhos with the Drugs for Neglected Diseases Initiative (DNDi). **Arm 3 (active comparator): three-day treatment with artesunate-amodiaquine (AQAS)** AQAS, developed by DNDi with Sanofi-Aventis and manufactured by Sanofi-Aventis, has been pre-qualified by the WHO in 2008 and is available in several African countries, including those involved in this trial. AQAS tablets are round, yellow on one side and white-slightly yellow on the other, with a breaking bar, AS engraved on one side and either 25, 50 or 100 on the other side. Tablets to be used in this trial are those 100mg/270mg AS/AQ, containing 100 mg of artesunate, 352.640 mg of amodiaquine hydrochloride corresponding to 270mg of amodiaquine base (other name of AQAS is Winthrop®). **Arm 4 (active comparator): three-day treatment with artemether-lumefantrine (AL)** AL (tablets containing a FDC of 20 mg of artemether and 120 mg of lumefantrine) is manufactured by Novartis and has been extensively used in Africa for the treatment of uncomplicated malaria. AL was registered in Switzerland in 1999, has since received marketing authorisation in several endemic and non-endemic countries and it is WHO pre-qualified (other name of AL is Coartem®, Riamet).
Product(s):	• Dihydroartemisinin-piperaquine • Artesunate-mefloquine • Artesunate-amodiaquine • Artemether-lumefantrine
Manufacturer/Developer:	• Sigma-Tau • Farmanguinhos (with the mediation from DNDi) • Sanofi-Aventis • Novartis

Cofunders:	• Medical Research Council (MRC, UK) • Austrian Federal Ministry of Science (Austria) • Netherlands Organisation for Scientific Research (NWO, (Netherlands) • Liverpool School of Tropical Medicine (UK) • Prince Leopold Institute of Tropical Medicine (Belgium) • Bill & Melinda Gates Foundation (USA)
Trial Registration number(s):	NCT 00852423 PACTR 201008000248160
Status:	Ongoing
Results and Outcomes:	Summary of achievements (from February 2010 until March 2013) 1. In Clinical trials: • Phase III studies (main trial): – Recruitment is completed in 3 out of the 4 recruiting sites, i.e. Malawi, Zambia and Burkina Faso and in Ghana is about 65% of their total sample size. So far, 3,205 patients have been enrolled from a total sample size of 3,480 (and 2,664 deliveries have been recorded) – The delay in recruitment in Ghana during this reporting period is mainly due to the temporary suspension of the trial by the local Food and Medicine Board (from April to October 2012, coinciding with the peak of the malaria season in the area). Therefore, the recruitment period for this collaborating centre will need to be extended until August/September 2013, which in consequence the last follow-up visit of the last newborn will take place by August/September 2014. An additional recruitment center has been identified in order to allow completion of the trial within the NCE period (September 2014). • Three sub-studies: – Sub-study 1: Malaria signs and symptoms in pregnancy (Nanoro, BF). Six hundred pregnant women have been enrolled, 200 with suspected clinical malaria and 400 as controls. Analysis is in progress; however, active screening to early detect and treat malaria infection should be performed in all pregnant women attending a health facility – Sub-study 2: Malaria endemicity in Nchelenge District (ZM). This ancillary study was done between February 2012 and March 2012 and 782 children (under 10 years old meeting the inclusion/exclusion criteria) were enrolled in the study – Sub-study 3: Malaria in pregnancy in Rwanda (RW). Study site(s) preparations completed. Recruitment is scheduled to start in April 2013. 2. In capacity development: – There have been minor infrastructure upgrades during this period. Infrastructure upgrade, including a dedicated space was created for the performance of the trial in Ruhuha (Rwanda) – GCLP workshop, Antwerp, Belgium, February 2012. – Placenta histopathology, individual training for Dr Mubikayi, Barcelona August 2012 – GCP course (19-21 September 2012, Malawi) was attended by one study nurse – Project Management in Clinical and Epidemiological

	Research (24-26 September 2012, Malawi) was attended by two study nurses – One MSc student completed his master in February 2012. The second master student is expected to complete in July 2014 – Two PhDs are expected to finish by November 2013 and the other two are expected to finish by July/December 2014. 3. In networking: – Biweekly Trial Steering Committee meetings (TSC) and 3 DSMB meetings in February, June and October 2012 – PREGACT investigator's meeting was held at ASTMH, Atlanta, November 2012 – Malaria in pregnancy Consortium meeting was also held at ASTMH, Atlanta, November 2012 – One article published at AJTMH (2012) JAMA and one publication at International Innovation Journal (2011). Setbacks: 1. The major setback of these studies is the accumulated delays in starting and temporarily interrupting recruitment in Ghana; firstly, because difficulties in obtaining the ethical approval and secondly, because the GCP inspection from the Ghanaian Food and Medicine Board (FMB), from April to October 2012. As consequence, completion of the follow up until delivery will be only possible by August 2014. Thereafter, they will need to finalise the database and the statistical analysis.
Total number of subjects (clinical trials only):	3,480 pregnant women and their infants
PhD studies:	Title: Antimalarial treatment safety and efficacy in pregnant women (Registered at the University of Antwerp, Belgium) Candidate: Michael Nambozi (Zambia) Dates: July 2010-July 2014
	Title: Antimalarial treatment safety and efficacy in pregnant women (Registered at the University of Antwerp, Belgium) Candidate: Marc Tahita (Burkina Faso) Dates: June 2010-December 2014
	Title: The role of drugs in the control of malaria in pregnancy (Registered at the University of Ghent, Belgium & Zambia) Candidate: Christine Manyando (Zimbabwe) Dates: 2012-2013
MSc studies:	Title: How does the risk of morbidity and mortality in HIV-exposed infants who are breast fed compare with morbidity and mortality in HIV-exposed infants who receive replacement feeding? Candidate: Sebastian Hachizovu (MPH, Diseases Control, Institute of Tropical Medicine, Antwerp, Belgium) Dates: 2009-2010
	Title: Master in Public Health: Epidemiology and Clinical Research Candidate: Biébo Bihoun (Burkina Faso) (Registered at the Université Catholique Louvain, UCL, Belgium) Dates: September 2012-July 2014
Other/Sub-studies:	**Malaria signs and symptoms in pregnancy** Site Principal Investigator: Halidou Tinto Title: Clinical signs and symptoms of P. falciparum malaria infection (patent and sub-patent) in pregnant women living in

	an area of high seasonal transmission Purpose: Determine the clinical presentation of malaria during pregnancy Study site: Nanoro (Burkina Faso) Synopsis: A hospital-based descriptive study aiming at describing the clinical presentation of P. falciparum malaria among pregnant women will be carried out in rural Burkina Faso. All women attending Nanoro Hospital, either the routine ANC or the outpatient will be asked to participate to the study. After having obtained the informed verbal consent, age, parity, gestational age and signs and symptoms suggestive of malaria will be recorded by the maternity staff onto a standardized questionnaire. The axillary temperature and a blood sample (capillary) for parasitaemia, PCV and later genotyping will be collected on all included women. Women with a positive blood slide for malaria will be treated with oral quinine for 7 days for those in the first trimester and with ACT in the second and third trimester. Women with complicated malaria will be admitted to the maternity ward and treated with parenteral quinine followed by SP. Anaemia will be treated according to the national guidelines with oral ferrous sulphate and folic acid for one month. This study will provide information on the clinical presentation of malaria during pregnancy. Therefore, it may identify signs and symptoms in women to be treated with an ACT. **Malaria endemicity in Nchelenge District** Site Principal Investigator: Michael Nambozi Title: Defining the Malaria Burden in Nchelenge District using the WHO Malaria Indicators Survey Purpose: To characterise the malaria endemicity in Nchelenge district Primary Objective(s): To assess the prevalence of malaria infection and anaemia in among children less than 10 years Secondary Objective(s): To assess: 1. The knowledge of children's care takers on malaria and relative control measures; 2. The relationship between individual knowledge and interventions' use and the risk of infection and anaemia. Study site: Nchelenge (Zimbabwe) Synopsis: This is a cross-sectional survey to be carried out in the rural communities of Kashikishi and Nchelenge (total population of 43,105); the sampling unit will be the household (defined as all the persons who occupy a housing unit) where all children < 10 will be included in the survey. A blood sample for Hb measurement and detection of malaria infection will be collected by finger prick on each study individual. Households will be selected according to pre-defined, computer-generated list of random numbers. This study will provide information on

	the malaria endemicity in the site where PREGACT is carried out. **Malaria in pregnancy in Rwanda** Site Principal Investigator: Steven Rulisa Title: Placental malaria in an area of low transmission, effects on incidence, diagnostic procedures and immune status Purpose Primary Objective(s): To determine the burden of malaria in pregnancy, either acute or placental infection, and to establish the best method to identify pregnancy-related malaria in Rwanda and to establish the degree of protective immunity against malaria in pregnancy over successive pregnancies. Secondary Objective(s): 1. To determine the incidence of placental malaria via placental biopsy. 2. To determine if there are any immunological markers present in pregnant women that might give an indication of protection in subsequent pregnancies. 3. To determine the association between low birth weight and pre-maturity to maternal malaria. Study sites: Muhima Hospital (Kigali) and Bugesera Hospital and Ruhuha Health Centre in Bugesera District located in eastern Province (Rwanda) Synopsis: In Rwanda, not much is known about malaria in pregnancy. A report from 2005 has described a 13.5% prevalence of malaria in pregnant women but up to date data on the prevalence of placental malaria is not available. However, in recent years malaria transmission has changed (it has decreased) and therefore it can be expected that the incidence of placental malaria has also changed, but this has not been documented yet. In addition, the protective immunity against malarial infections may have decreased, possibly resulting in more acute illness to the mother. It is not known if Rwandese women still have immunity against malaria in pregnancy or that even in this relatively low malaria transmission country immunity can still be build up during successive pregnancies or that immunity has totally weaned. Regardless of the immune status of the women and the prevalence of malaria in pregnancy, it is important to diagnose it because of the potential negative effects that can be expected in both women and their offspring. We seek to document malaria burden including proportion of pregnant mothers with anaemia and the immune status of the mothers as well as the effect of maternal malaria on foetal outcomes. This data is required to effectively plan interventions to improve maternal and foetal health.
Publications:	1. D'Alessandro U. Combating malaria in pregnancy. *International Innovation Journal* (2012). June Issue, 41-43 2. Kattenberg, JH; Tahita, CM; Versteeg, IAJ; Tinto, H; Coulibaly, MT; D'Alessandro, U; Schallig, HDFH; Mens, PF. Evaluation of Antigen Detection Tests, Microscopy, and Polymerase Chain Reaction for Diagnosis of Malaria in Peripheral Blood in Asymptomatic Pregnant Women in Nanoro, Burkina Faso (2012). *AJTMH* 87(2), 251-256.

3.1.4 MiPPAD

EDCTP Project Coordinator:	Clara Menéndez Santos (Hospital Clinic of Barcelona, Spain)
EDCTP Call Title:	Support of clinical trials, capacity building and networking in malaria in pregnancy
EDCTP Project Title:	Evaluation of alternative antimalarial drugs to sulfadoxine-pyrimethamine for intermittent preventive treatment in pregnancy (IPTp) in the context of insecticide treated nets
EDCTP Project Code:	IP.2007.31080.002
EDCTP Project Start Date:	28 November 2008
EDCTP Project End Date:	31 August 2014
Collaborators:	• Salim Abdulla (Ifakara Health Research and Development Centre, Tanzania) • Azucena Bardaji Alonso (Hospital Clinic of Barcelona, Spain) • Valerie Briand (Institut de Recherche pour le Développement (IRD), France) • Michel Cot (IRD, France) • Gilles Cottrell (IRD, France) • Meghna Desai (Centers for Disease Control and Prevention (CDC), USA) • Andre Garcia (IRD, France) • Raquel González Álvarez (Hospital Clinic of Barcelona, Spain) • Abdunoor Mulokozi Kabanywanyi (Ifakara Health Research and Development Centre 2, Tanzania) • Simon Kariuki (Kenya Medical Research Institute (KEMRI), Kenya) • Abraham Katana (KEMRI, Kenya) • Ghislain Koura (Université d'Abomey-Calavi, Benin) • Eusebio Macete (Manhiça Health Research Center, Mozambique) • Sonia Machevo (Hospital Clinic of Barcelona, Spain) • Inacio Mandomando (Manhiça Health Research Center, Mozambique) • Ahlin Achille Massougbodji (Université d'Abomey-Calavi, Benin) • Kephas Otieno (KEMRI, Kenya) • Smaila Ouedraogo (IRD, France) • Peter Ouma (KEMRI, Kenya) • Golbahar Pahlavan (Hospital Clinic of Barcelona, Spain) • Ian Pattison (Vienna School of Clinical Research (VSCR), Austria) • Michael Ramharter (University of Tübingen, Germany) • Gabriele Schreyer (VSCR, Austria) • Esperança Sevene (Eduardo Mondlane University, Mozambique) • Laurence Slutsker (CDC, USA) • Muriel Vray (Institut Pasteur, France)
Study / Trial 1	**IPTp-SP versus IPTp-MQ (in HIV non-infected women receiving LLITNS)**
Site Principal Investigator(s):	• Clara Menéndez Santos (Barcelona, Spain) • Achille Massougbodji (Cotonou, Benin) • Ghyslain Mombo -Ngoma(Lambaréné, Gabon) • Eusebio Macete (Manhiça, Mozambique) • Salim Abdulla (Ifakara, Tanzania) • Michel Cot (Paris, Fance) • Michael Ramharter (Tuebingen, Germany)

Clinical Trial/Study Sponsor:	Fundació Clínic per a la Recerca Biomèdica (FCRB), Barcelona (Spain)
Trial/Study title:	Evaluation of the Safety and Efficacy of Mefloquine as Intermittent Preventive Treatment of Malaria in Pregnancy
Goal:	The study aims to evaluate the safety, tolerability and efficacy of Mefloquine (MQ) as an alternative to Sulfadoxine-Pyrimethamine (SP) in Intermittent Preventive Treatment in pregnancy (IPTp) in the context of Insecticide Treated Nets (ITN) used in different malaria endemic settings in Africa.
Primary Objective(s):	To compare the safety, tolerability and efficacy of MQ to SP as IPTp for the prevention of malaria in pregnancy for the mother and her infant.
Secondary Objective(s):	1. To compare MQ tolerability given as full dose with a split dose administered over 2 days 2. To evaluate the efficacy of CTX in the prevention of malaria infection in pregnant women 3. To compare immune status of HIV infected women receiving CTX + IPTp-MQ to those receiving CTX + IPTp-placebo 4. To assess the safety of study drugs in the development of infants.
Clinical Trial/Study site(s):	• Allada, Sekou and Attogon (Benin) • Fougamou and Lambaréné (Gabon) • Manhiça and Maragra (Mozambique) • Makole and Chambwino (Tanzania)
Collaborating site(s):	• Barcelona Centre for International Health Research (CRESIB) & Hospital Clinic de Barcelona, Barcelona (Spain) • Université d'Abomey-Calavi, Cotonou (Benin) • Albert Schweitzer Hospital, Lambaréné (Gabon) • Manhiça Health Research Centre, Manhiça (Mozambique) • Ifakara Health Institute (IHI) • Ifakara (Tanzania) • Vienna School of Clinical Research (VSCR) • Vienna (Austria) • Institut de Recherche pour le Developpement, Paris (France) • Institute of Tropical Medicine & University of Tuebingen, Tuebingen (Germany)
Study design:	Trial 1: phase IV randomised, controlled, open-label study Comparing IPTp-SP versus IPTp-MQ in HIV non-infected women receiving LLITNS. This is a randomised open-label superiority 3 arms trial to compare 2-dose MQ versus 2-dose SP for IPTp in the prevention of the adverse effects of malaria during pregnancy and to compare MQ tolerability of 2 different MQ administration regimens. The three arms of the study will be: 1. IPTp with SP + LLITNs (Active Comparator) HIV-negative pregnant women receiving 2 doses of IPTp (500mg of sulfadoxine and 25 mg of pyrimethamine) at the 1st and 2nd Antenatal Clinic visit in the context of long lasting Insecticide Treated Nets (LLITNs). 2. 2. IPTp with MQ given as full dose + LLITNs (Experimental) HIV-negative pregnant women receiving 2 full doses of IPTp (15 mg/Kg) on 1 day at the 1st and 2nd Antenatal Clinic visit in the context of LLITNs. 3. 3. IPTp with MQ given as a split dose + LLITNs

	(Experimental) HIV-negative pregnant women receiving 2 doses of MQ as IPTp split dose over 2 days (15mg/kg) at the 1st and 2nd ANC visit in the context of LLITNs. This trial is being conducted in four sites in Benin, Gabon, Tanzania and Mozambique. It thus involves regions from Western, Eastern, Central and Southern sub-Saharan Africa where malaria transmission is stable but displays distinctly varying characteristics according to the site.
Product(s):	• Mefloquine (MQ) • Sulfadoxine-pyrimethamine (SP)
Manufacturer/Developer:	• Hoffman-La Roche • Sterop • UCB Pharma (GSK manufacturer)
Status:	Ongoing
Results and Outcomes:	In progress, recruitment phase completed.
Study/Trial 2	**IPTp-MQ versus IPTp- placebo (in HIV infected women receiving CTX and LLITNs)**
Site Principal Investigator(s):	• Eusebio Macete (Manhiça, Mozambique) • Meghna Desai and Peter Ouma (Kisumu, Kenya) • Salim Abdulla (Ifakara, Tanzania)
Clinical Trial/Study Sponsor:	Fundació Clínic per a la Recerca Biomèdica (FCRB), Barcelona (Spain)
Trial/Study title:	Evaluation of the Safety and Efficacy of Mefloquine as Intermittent Preventive Treatment of Malaria in Pregnancy
Goal:	The study aims to evaluate the safety, tolerability and efficacy of Mefloquine (MQ) as Intermittent Preventive Treatment in pregnancy (IPTp) in HIV-infected women receiving cotrimoxazole in the context of Insecticide Treated Nets (ITN).
Primary Objective(s):	To determine the safety and efficacy of IPTp with mefloquine among HIV infected women receiving cotrimoxazole (CTX) prophylaxis for opportunistic infections.
Secondary Objective(s):	1. To compare MQ tolerability given as full dose with a split dose administered over 2 days 2. To evaluate the efficacy of CTX in the prevention of malaria infection in pregnant women 3. To compare immune status of HIV infected women receiving CTX + IPTp-MQ to those receiving CTX + IPTp-placebo 4. To assess the safety of study drugs in the development of infants.
Clinical Trial/Study site(s):	• Kisumu (Kenya), Manhiça and Maragra (Mozambique) • Dodoma, Makole and Chambwino (Tanzania)
Collaborating site(s):	• Barcelona Centre for International Health Research (CRESIB) & Hospital Clinic de Barcelona, Barcelona (Spain) • Kenya Medical Research Institute & Centers for Disease Control and Prevention (CDC), Kisumu (Kenya) • Manhiça Health Research Centre, Manhiça (Mozambique) • Ifakara Health Institute (IHI), Ifakara (Tanzania).
Study design:	Trial 2: phase IV randomised, double-blind Comparing IPTp-MQ versus IPTp- placebo in HIV-infected women receiving CTX and LLITNs. This is a randomised double-blind superiority clinical trial to compare the efficacy of MQ as IPTp with placebo-IPTp in HIV-infected pregnant women receiving CTX prophylaxis.

	1. CTX+IPTp-Placebo+LLITNs (Experimental) HIV-positive pregnant women receiving 3 doses of IPTp (placebo) at the 1st, 2nd and 3rd Antenatal Clinic visit in the context of LLITNs. 2. CTX + IPTp-MQ+ LLITNs (Experimental) HIV-positive pregnant women receiving 3 doses of IPTp (15 mg/Kg MQ) at the 1st and 2nd Antenatal Clinic visit in the context of LLITNs. This trial is being conducted in 3 sites from south eastern sub-Saharan Africa (Kenya, Mozambique and Tanzania), where HIV prevalence in pregnant women ranges from 10 to 30%.
Product(s):	• Mefloquine (MQ) • MQ Placebo • Cotrimoxazole (CTX)
Manufacturer/Developer:	• Hoffman-La Roche • Carreras/Bonals • UCB Pharma (GSK manufacturer)
Cofunders:	• Carlos III Health Institute (Spain), University of Tübingen (Germany) • German Aerospace Center [Deutsches Zentrum fuer Luft- und Raumfahrt – DLR] (Germany) • Institut de Recherche pour le Développement [IRD] (France) • Austrian Federal Ministry of Science (Austria) • Malaria in Pregnancy Consortium (UK)
Trial Registration number(s):	NCT 00811421 PACTR 2010020001813440 PACTR 2010020001429343
Status:	Ongoing
Results and Outcomes:	Summary of the major achievements (from November 2008 until February 2013): 3. In Clinical trials: • Both trials finalised recruitment and mother follow-up during Y4 (for details in recruitment numbers at each individual study site, please refer to pages 10 & 15). • For Trial 1: Evaluation of the Safety and Efficacy of Mefloquine as Intermittent Preventive Treatment of Malaria in Pregnancy (in HIV non-infected women receiving LLITNS): – During the current reporting period all study sites finalised mother follow-up and in the case of Benin (Q4, Y3) also child follow-up – Monitoring visits have been planned in order to maximize data-collection and shall be finalised in this period (Q4, Y5) leaving only the close-out visits for Y6 – Data management which is centralised in Manhiça, Mozambique has entered to date 80% and 42% of Trial 1 and 2 data, respectively. Data cleaning is ongoing actively in collaboration with the sites – A preliminary analysis of Mother 1 data is planned for Q2 of 2013, and the complete analysis in Q3 of 2013 with input from both the MiPPAD Statistics Working Group and the site PIs at the Annual Investigators Meeting planned in June 2013 – Child data will be ready for analysis approximately early Y6 (Q1, Y6). • For Trial 2: Evaluation of the Safety and Efficacy of

	Mefloquine as Intermittent Preventive Treatment of Malaria in Pregnancy (in HIV infected women receiving CTX and LLITNs): – Mother (Q4, Y4) and child (Q1, Y5) follow-up have been finalised in all sites – Data entry and cleaning shall be finalised with sites' active input by Q3, Y5. Analysis is estimated to take place with the analysis of the Trial 1 data – Ancillary studies: 25 sub-studies have been listed in annex J, for which more detail will be provided – Monitoring activities are carried out by an internal monitor (D Iñiguez) and by Quintiles as the independent monitor. 4. In Capacity Development, Training and Infrastructure: • There have not been any infrastructure upgrades during this final period. A CRF storage unit has been budgeted for the next period • Three short training courses have been held during this reporting period, being all of them carried out by the VSCR, Vienna, Austria • The MSc student is expected to be completed by December 2014 • The PhD is expected to finish by December 2014. 5. In Networking: • The outcome following the WHO Malaria Policy Advisory Committee (MPAC) meeting in September 2012 was the release of the updated "*WHO Policy Recommendation Intermittent Preventive Treatment of malaria in pregnancy using Sulfadoxine Pyrimethamine (IPTp-SP)*" in October 2012 • One DSMB meeting took place during this reporting period (February 2012, Barcelona, ES) • Meeting MiPPAD Statistical Working Group Meeting was held in Barcelona in April 2012 • Four publications were accepted by different international journals during the reporting period under evaluation. The major setbacks of these studies have been the long regulatory processes in several study sites which has had a knock on effect in starting recruitment and the need to request for a no-cost extension to MiP Consortium and EDCTP. In particular, in the case of Kenya and Mozambique, the creation of new regulatory bodies, respectively the Kenya Pharmacy and Poison Board and the Ministry of Health Departamento Farmacéutico, have caused additional delays in securing import permit for study drugs. As consequence the new planned timelines for recruitment initiation were set to Q1-Q2 of 2010.
Total number of subjects (clinical trials only):	Trial 1: 4,716 subjects Trial 2: 1,070 subjects
PhD study:	Title: Safety profile of antimalarial drugs during pregnancy in the evaluation framework of alternative antimalarial drugs to sulfadoxine-pyrimethamine in Sub-saharan Africa (registered at the University of Basel, the Swiss Tropical Institute, Basel, Switzerland) Candidate: Dominic Mosha (Tanzania) Dates: Q1 2012-Q2 2014
MSc study:	Title: Effect of cotrimoxazole alone or in combination with mefloquine on antibodies to variant surface antigens (VSAs) in pregnant women in Western Kenya (Kenya Medical Research

	Institute/Center for Global Health Research, Kisumu, Kenya) Candidate: Kephas Otieno (Kenya) Dates: March 2011-December 2015
Other/Sub-studies:	Ancillary studies The Ancillary studies approved to date by the MiPPAD ExCom are listed below: 1 Benin — Aetiology of anemia in pregnancy and consequences on the infants in a malaria 2 Gabon — Immunological changes related to Helminth co infections and association with 3 Gabon — HHV-8 infection in pregnant women and the potential for in utero transmission to 4 Gabon — Mefloquine pharmacogenetics 5 Gabon — Effects of IPTp with mefloquine and sulfadoxine pyrimethamine on sexually 6 Gabon — Effect of mefloquine on urinary 7 Gabon — Infection biology and epidemiology of Staphylococci and Staphylococcal Diseases 8 Gabon — Population pharmacokinetics of mefloquine as IPTp 9 All sites — Molecular markers of antimalarial drug resistance in the context of the intermittent preventive treatment trials for 10 Mozambique — Role of maternal immuno-endocrine factors on delivery outcomes of malaria-exposed pregnant women in the context of 11 Mozambique — Malaria decline in the context of pregnancy (MiPredux) 12 Mozambique — Perceptions and behaviours related to prevention of MiP in Manhiça District, 13 Kenya — Antibodies to P. falciparum variant surface antigens (VSAs) in pregnant women receiving cotrimoxazole alone or in 14 Kenya — Determine the effect of daily cotrimoxazole prophylaxis on genital-tract bacterial carriage and postpartum morbidity in HIV- 15 Kenya — Pharmacokinetics of IPTp with mefloquine and its effect on steady-state concentrations of sulfamethoxazole and 16 Tanzania — The contribution of dual infection with malaria and HPV virus on pregnancy 17 Tanzania — Safety profile of antimalarial drugs used for prevention and treatment of malaria among pregnant mothers: malaria in 18 All sites — Effect of P. falciparum submicroscopic infections on maternal or fetal health 19 Mozambique — Impact of HIV infection on maternal and neonatal health and pregnancy outcomes 20 Mozambique — Risk factors for HIV Mother to Child Transmission in MiPPAD study participants 21 Kenya — Comparison of the performance characteristics of different placental malaria diagnostic tests across sites that 22 Benin — Birth weight as a predictor for child health

	23 Benin	Environmental, biological and genetic factors involved in the immune tolerance related to malaria:
	24 Benin	Anemia in pregnancy in Benin and impact on cognitive function in childhood
	25 Mozambique	Pregnancy-specific serology
Publications:	1. Smaïla Ouédraogo, Florence Bodeau-Livinec1, Valérie Briand, Bich-Tram Huynh, Ghislain K Koura, Manfred MK Accrombessi, Nadine Fievet, Achille Massougbodji, Philippe Deloron and Michel Cot. Malaria and gravidity interact to modify maternal haemoglobin concentrations during pregnancy. *Malaria Journal* 2012, 11:348. 2. Ouédraogo Smaïla, Ghislain K Koura, Florence Bodeau-Livinec, Manfred MK Accrombessi, Achille Massougbodji and Michel Cot. Maternal anaemia at first antenatal visit: prevalence and risk factors in a malaria endemic area in Benin. *American Journal of Tropical Medicine & Hygiene* 2012, 87(3):418-24. 3. Smaïla Ouédraogo, Ghislain K Koura, Florence Bodeau-Livinec, Manfred MK Accrombessi, Achille Massougbodji and Michel Cot. Maternal Anemia in Pregnancy: Assessing the Effect of Routine Preventive Measures in a Malaria-Endemic Are. *American Journal of Tropical Medicine & Hygiene* 2013, 88(2): 292-300. 4. Arti Basra, Ghyslain Mombo-Ngoma, Meskure Capan Melser, Daisy Akerey Diop, Heike Würbel, Jean-Rodolphe Mackanga, Moritz Fürstenau, Rella Manego Zoleko, Ayola A. Adegnika, Raquel Gonzalez, Clara Menendez, Peter G. Kremsner and Michael Ramharter. Efficacy of Mefloquine Intermittent Preventive Treatment in Pregnancy Against Schistosoma haematobium Infection in Gabon: A Nested Randomized Controlled Assessor-Blinded Clinical Trial. *Clinical Infectious Diseases 2013* (DOI: 10.1093/cid/cis976)	

3.1.5 IPTp-SP

EDCTP Project Coordinator:	Feiko ter Kuile (University of Liverpool, UK)
EDCTP Call Title:	Support of clinical trials, capacity building and networking in malaria in pregnancy
EDCTP Project Title:	Scheduled intermittent screening and treatment in pregnancy (ISTp) versus intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) in women protected by insecticide treated nets for the control of malaria in pregnancy in west Africa and Malawi
EDCTP Project Code:	IP.2007.31080.003
EDCTP Project Start Date:	18 December 2008
EDCTP Project End Date:	17 December 2013
Collaborators:	• Francis Akor (Medical Research Council (MRC) Laboratories, The Gambia) • Kalifa Bojang (MRC Laboratories, The Gambia) • Chandramohan, Daniel (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Manuela Claite (LSHTM, UK) • Christine Clerk (Navrongo Health Research Centre, Ghana) • Sheick Oumar Coulibaly (University of Ouagadougou, Burkina Faso) • Stephanie Dellicour (Liverpool School of Tropical Medicine, UK) • Ogobara Doumbo (University of Bamako, Mali) • Annemieke van Eijk (University of Liverpool, UK) • Brian Faragher (University of Liverpool, UK) • Exnevia Gomo (University of Malawi) • Brian Greenwood (LSHTM, UK) • Jenny Hill (University of Liverpool, UK) • Abraham Hodgson (Navrongo Health Research Centre, Ghana) • Gertrude Kalanda (University of Malawi) • Linda Kalilani-Phiri (University of Malawi) • Kassoum Kayentao (University of Bamako, Mali) • Pascal Magnussen (University of Copenhagen, Denmark) • Paul Milligan (LSHTM, UK) • Gerarld Mwapasa (University of Malawi) • Ian Pattison (Vienna School of Clinical Research (VSCR), Austria) • Sanie Samuel Sogoyan Sesay (MRC Laboratories, The Gambia) • Esperança Sevene (Eduardo Mondlane University, Mozambique) • Jacek Skaribnski (Centers for Disease Control and Prevention (CDC), USA) • Steve Ward (University of Liverpool) • John Williams (Navrongo Health Research Centre)
Study design:	This grant involves two clinical trials and a SP drug resistance sub-study: A phase IIIb, two arm multi-centre randomised controlled superiority trial conducted at three sites in southern Malawi with high levels of SP resistance and high ITN coverage. Phase IV, two-arm, multi-centre, open, randomised, controlled, non-inferiority trial comparing two malaria control strategies in pregnancy in West Africa. A sub-study that explores the relationship between the level of SP resistance in the population (of pregnant women) and the

	effectiveness of IPTp-SP in reducing adverse effect of malaria at birth.
Study/Trial 1	**IPTp-Mon study**
Site Principal Investigator(s):	• Kassoum Kayentao (Malaria Research and Training Centre, Mali) • Sheick O. Coulibaly and B. Kayoute (Université de Ouagadougou CNRFP, Burkina Faso) • Pascal Magnussen (University of Copenhagen, Denmark) • Linda Kalilani (College of Medicine, Malawi) • Daniel Chandramohan and Brian Greenwood (LSHTM, UK) • Harry Tagbor (LSHTM, UK/Ghana) • Feiko ter Kuile (LSTM, UK)
Clinical Trial/Study Sponsor:	• Liverpool School of Tropical Medicine (LSTM, UK) • London School of Hygiene & Tropical Medicine (LSHTM, UK)
Trial/Study title:	Monitoring the impact of Sulphadoxine-Pyrimethamine Resistance on the the Effectiveness of Intermittent Preventive Treatment (IPT) for the Control of Malaria in Pregnancy
Goal:	To explore the relationship between the level of SP resistance in the population (of pregnant women) and the effectiveness of IPTp-SP in reducing the adverse effects of malaria at birth.
Primary Objective(s):	1. To determine the relationship between the degree of SP resistance in the population as assessed by molecular markers and its impact on the ability of IPTp with SP to clear existing infections, prevent new infections and prevent the adverse malaria associated morbidity 2. To design a practical operational tool to monitor SP effectiveness that can be used outside of research settings.
Secondary Objective(s):	1. To characterize the degree of resistance of P. falciparum to SP in the population using molecular markers in dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) 2. To determine the efficacy of SP IPTp in clearing peripheral parasitaemia in asymptomatic parasitaemic pregnant women 3. To determine the effectiveness of SP IPTp in preventing placental malaria, maternal anaemia and low birth weight, by comparing these among women who have received 2 or more versus less than 2 doses of IPTp based on their antenatal clinic records 4. To determine which parasite genotypes recrudesce, cause new infections, and persist in the placenta in women receiving IPTp-SP 5. To model the pharmacodynamic relationship between drug levels, parasite SP resistance genotype, recrudescence, and new infection and to validate the model using the pooled data from the different study sites 6. To use the pooled experience and 'rich' *in-vivo* data from the weekly follow-up to determine the potential validity of a 'sparse' 'population' sampling methodology for future therapeutic *in-vivo* follow-up studies.
Clinical Trial/Study site(s):	• Blantyre district (Malawi) • Ziniare (Burkina Faso) • Navrongo (Ghana) • San and Kita (Mali)
Collaborating partners(s):	• Liverpool School of Tropical Medicine (LSTM, UK) • London School of Hygiene & Tropical Medicine (LSHTM, UK)

	• University of Copenhagen (Denmark) • Université de Ouagadougou (Burkina Faso) • Navrongo Health Research Centre (Ghana) • College of Medicine (Malawi) • Medical Research and Training Centre (Mali) • Manhica Health Research Centre (Mozambique) • Centres for Disease Control and Prevention (CDC, USA) • University of Melbourne (Australia)
Study design:	A multi-centre, multi-country study conducted in several sites in sub-Saharan Africa where malaria is endemic and where IPTp with SP is used in the control of malaria in pregnancy. The study is designed to determine the frequency of molecular markers and the in-vivo response in each site. It is also designed to determine the effect of different doses of IPTp on the presence of placental malaria. In each study site, there will be three parts to this study, each of which will be conducted simultaneously, in the same study area: 1. Molecular markers of SP resistance To characterize the degree of resistance to SP in the population, the prevalence of molecular markers of SP resistance (DHFR and DHPS anti-folate resistance mutations in P. falciparum) will be measured in parasites collected from both pregnant women and a random sample of patients with clinical malaria attending outpatient clinics 2. In vivo assessment of parasitological response to IPTp-SP To determine the efficacy of IPTp-SP in pregnant women in clearing existing infections or preventing new infections, a prospective in vivo study will be conducted in women presenting for antenatal care (ANC). Women will receive IPTp-SP according to national guidelines and be followed weekly for 42 days to assess the parasitological response (therapeutic efficacy) and their ability to prevent new infections. Parasites will be genotyped to distinguish between recrudesce and reinfection and for markers of SP resistance. Drug levels will be measured using nested populations pharmacokinetics studies 3. Assessment of IPTp-SP effectiveness on birth parameters A cross-sectional study at delivery of the impact of IPTp-SP on the prevalence of peripheral malaria, placental malaria, maternal anaemia and low birth weight in primi- and secundigravidae. Diagnostic and speciating PCR will be conducted to determine sub-patent infections, and PCR will be conducted to characterise the presence of molecular markers of SP resistance.
Product(s):	Sulfphadoxine-pyrimethamine (SP)
Manufacturer/Developer:	Durbin PLC (UK)
Cofunders	• Liverpool School of Tropical Medicine (UK) • London School of Hygiene & Tropical Medicine (LSHTM, UK) • MRC (UK), University of Copenhagen (Denmark) • Austrian Federal Ministry of Science (Austria) • Bill & Melinda Gates Foundation (USA)
Status:	Ongoing
Results and Outcomes:	Field work completed, molecular assays ongoing.
Total number of subjects (clinical trials only):	256 per site (in-vivo module), and up to 1,100 deliveries per site (3 study sites)

Study / Trial 2	**ISTp-Malawi**
Site Principal Investigator(s):	• Linda Kalilani-Phiri (Blantyre, Malawi) • Feiko ter Kuile (LSTM, UK)
Clinical Trial/Study Sponsor:	Liverpool School of Tropical Medicine (LSTM, UK)
Trial/Study title:	Scheduled intermittent screening and treatment in pregnancy (ISTp) versus intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) in women protected by insecticide treated nets (ITNs) for the control of malaria in pregnancy in Malawi: a randomised controlled trial
Goal:	To evaluate whether Scheduled intermittent screening and treatment in pregnancy is a suitable alternative strategy to Intermittent Preventive Therapy for the control of malaria in pregnancy in areas with high SP resistance.
Primary Objective(s):	To compare the efficacy of scheduled intermittent screening with malaria rapid diagnostic tests (RDTs) and treatment of RDT-positive women with dihydroartemisinin-piperaquine (ISTp-DP) with intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) in the second and third trimesters on adverse birth outcome and malaria infection at term among HIV-negative women protected by insecticide–treated bed nets.
Secondary Objective(s):	To determine if ISTp-DP has greater efficacy than IPTp-SP in terms of placental malaria (in G1 and G2), maternal malaria infection at delivery, mean birth weight, low birth weight (<2,500 grams), gestational age, mean gestational age at birth, pre-term birth (<37 weeks), small for gestational age, mean maternal haemoglobin at birth; anaemia (Hb ≤ 11 g/dL) at birth, moderate to severe anaemia (Hb ≤ 8g/dL); stillbirths; neonatal deaths; clinical malaria episodes during the second and third trimesters of pregnancy; third trimester mean maternal haemoglobin, anaemia (Hb ≤ 11 g/dL) and moderate to severe anaemia (Hb ≤ 8g/dL); severe cutaneous skin reaction in the mothers; other serious adverse events in the mothers; minor adverse events in the mothers by day three after study drugs given; congenital malformation at birth and by day 28; neonatal jaundice at day one or day seven; incidence of anaemia, and clinical malaria in babies up to the age of eight weeks.
Clinical Trial/Study site(s):	Three trial sites in Blantyre District (Malawi)
Collaborating partner(s):	• Liverpool School of Tropical Medicine (LSTM, UK) • London School of Hygiene & Tropical Medicine (LSHTM, UK) • Vienna School of Clinical Research (VSCR, Austria) • College of Medicine (Malawi) • Manhiça Health Research Centre (Mozambique)
Study design:	Phase IIIb, two arm multi-centre randomised controlled superiority trial to be conducted at three sites in southern Malawi with high levels of SP resistance and high ITN coverage. • Arm 1 (IPTp-SP): 3 or 4-dose regimen of IPTp with SP. • Arm 2 (ISTp-DP): 3 or 4-scheduled doses of ISTp and treatment with ACTs if participants are found to be positive by a rapid diagnostic test (RDT). Participants are randomly allocated to receive either at least three doses of IPTp with SP or at least three scheduled screenings with an RDT and treatment with DHA-PQ if they are RDT-positive. All participants are given an insecticide-treated bed net if they do not already have one. Women enrolled in the trial make at least three scheduled visits

	to the clinic spread over the second and third trimesters at least four weeks apart to receive the study intervention approximately mirroring the appointment schedule for 'focussed antenatal care' in Malawi which consists of four scheduled visits. Newborns are seen at approximately seven days and six weeks after delivery, to assess the health of the infant. The study is open label as it will not be possible to blind the participants to their allocation, although where possible laboratory staffs undertaking trial-related diagnostic tests are blinded. Participants are HIV-negative pregnant women. They are screened for eligibility and enrolled at 16 to 29 weeks gestation. The study aims to recruit 1655 participants and started in the 2nd quarter of 2011 and will recruit for a period of 18 to 24 months, with a further six months follow-up.
Product(s):	• Sulphadoxine-pyrimethamine (SP) • Dihydroartemisinin-piperaquine (DHA-PQ or DP) • Artemether-lumefantrine • Artesunate-amodiaquine • mefloquine-artesunate
Manufacturer/Developer:	• Durbin PLC (UK) (SP) • Sigma-Tau, Italy (DHA-PQ)
Cofunders:	• Liverpool School of Tropical Medicine (UK) • Austrian Federal Ministry of Science (Austria) • Bill & Melinda Gates Foundation (USA)
Trial Registration number(s):	ISRCTN69800930 PACTR201103000280319
Status:	Ongoing
Results and Outcomes:	39% recruited, expected completion Q4 2013.
Total number of subjects (clinical trials only):	1,665
Study/Trial 3	**IST – IPTp study West Africa**
Site Principal Investigator(s):	• Harry Tagbor (Ghana) • Abraham Hodgson (Ghana) • Kassoum Kayentao (MRTC, Mali) • Sheick O. Coulibaly (Université de Ouagadougou CNRFP, Burkina Faso) • Kalifa Bojang (The Gambia) • Daniel Chandramohan and Brian Greenwood (LSHTM, UK) • Feiko ter Kuile (LSTM, UK) • Pascal Magnussen (University of Copenhagen, Denmark)
Clinical Trial/Study Sponsor:	London School of Hygiene & Tropical Medicine (LSHTM, UK)
Trial/Study title:	A trial of intermittent preventive treatment with sulfadoxine-pyrimethamine versus intermittent screening and treatment of malaria in pregnancy in west Africa
Goal:	The goal of this project is to determine whether in pregnant women who sleep under a long lasting insecticide treated bed net, screening and treatment at each scheduled antenatal clinic visit is as effective in protecting them from anaemia, low birth weight and placental infection as SP-IPTp.
Primary Objective(s):	To determine the optimum method of controlling malaria in pregnancy in women who sleep under an LLIN in areas of seasonal malaria transmission.
Secondary Objective(s):	1. To determine if scheduled screening and treatment during antenatal clinic visits is as effective in protecting against low birth weight, anaemia and malaria infection of the placenta as a standard SP-IPTp in primigravidae and

	secundigravidae who sleep under a long lasting ITN. 2. To evaluate the cost-effectiveness of delivering the two strategies measured as the cost per cases of maternal anaemia and antenatal malaria averted.
Clinical Trial/Study site(s):	• Ziniare (Burkina Faso) • Navrongo (Ghana) • San and Kita (Mali) • Basse (The Gambia)
Collaborating partner(s):	• London School of Hygiene & Tropical Medicine (LSHTM, UK) • Liverpool School of Tropical Medicine (LSTM, UK) • Vienna School of Clinical Research (VSCR, Austria) • University of Copenhagen (Denmark) • Université de Ouagadougou (Burkina Faso) • Medical Research Council Laboratories (The Gambia) • Navrongo Health Research Centre (Ghana) • College of Medicine (Malawi) • Medical Research and Training Centre (Mali) • Manhiça Health Research Centre (Mozambique)
Study design:	Phase IV, two-arm, multi-centre, open, randomised, controlled, non-inferiority trial comparing two malaria control strategies in pregnancy is proposed. The study groups are as follows: • Arm 1 (SP-IPTp SP according to WHO recommendations): women receive at least two doses of SP during their pregnancy, one at each of the recommended ante-natal visits during the 2nd and 3rd trimester. Women in this arm are the reference group • Arm 2 (IST using RDTs): scheduled intermittent screening by RDT and treatment of those who are RDT positive during ante-natal clinic visits in the 2nd and 3rd trimester. All study women are provided with an LLIN at their first attendance at the ANC and given instructions on how to use it. Random home visits are made to check on net usage during the pregnancy.
Product(s):	• Sulphadoxine-pyrimethamine (SP) • Artemether-lumefantrine
Manufacturer/Developer:	Novartis (Switzerland)
Cofunders:	• Liverpool School of Tropical Medicine (UK) • London School of Hygiene & Tropical Medicine (LSHTM, UK) • MRC (UK) • University of Copenhagen (Denmark) • Austrian Federal Ministry of Science (Austria) • Bill & Melinda Gates Foundation (USA)
Trial Registration number(s):	NCT 01084213
Status:	Ongoing
Results and Outcomes:	Recruitment completed; last follow-up end of May 2012. Summary of major achievements (from 18 December 2008 until 17 December 2012) 3. In Clinical Trials • SP-resistance studies (Observational study): – All field work for the in vivo and delivery module components is completed in Malawi, Mali and Burkina Faso, totalling 4,383 pregnancies. Molecular assays are ongoing (70% completed)

- Preliminary analysis was presented to WHO-ERG in July 2012
- Results indicated sustained effectiveness of IPTp-SP in Burkina Faso and Mali, but reduced effectiveness in Malawi where saturation of the quintuple DHFR/DHPS mutations has occurred, confirming high-grade SP resistance. There was no indication that the additional DHPS-581 mutation was associated with harm (which was a concern raised by previous NIH funded research from high-grade resistance region in north Tanzania). Two manuscripts in preparation.
- The country specific clinical impact analysis and meta-analysis are ongoing.

- Trial 1b ISTp-Malawi:
  - An additional recruitment center was identified in order to allow completion of the trial; therefore three recruitment sites, two in Blantyre District and one in Chikwawa District, Malawi
  - 100% of multigravidae and 98% of G1/G2 recruited by 1 Mar 2013. At current rate, last patient-in will be completed by March 2013. Last follow-up will be completed by October 2013. Success rate of follow-up consistently of 90%. From these, 70% have delivered
  - Data analysis plan has been discussed with DSMB and is now finalised. Approximately, half of the data is cleaned completed (pending PCR results), the other half involved active participants and is ongoing.
- Trial 2 ISTp-west Africa:
  - ISTp Economics (Malawi Trial 1b)
  - ISTp Acceptability (Malawi Trial 1b)
  - Econ ISTp-IPTp west Africa (Trial 2)
  - Data analysis approved by DSMB. Lab work to be completed by mid-2013 and all data analysis expected to be completed by the end of 2013.
- Three sub-studies:
  - Follow-up of all study women is completed; 5,356 women were recruited into the trial and 4,559 followed until delivery.
  - Success rate of follow-up consistently of 85%.
  - Data analysis approved by DSMB. Lab work to be completed by mid-2013 and all data analysis expected to be completed by the end of 2013.

4. In capacity Development, Training and Infrastructure:

- There have been minor infrastructure upgrades during this period. Two extensions to the Chikwawa antenatal facilities have constructed, one of which is completed (please see provided pictures).
- GCP refresher course (24-26 September 2012, Malawi) attended by two nurses and one data officer.
- Support course for the data managers.
- Two MSc students completed their masters in February 2012. However, an additional MSc student, Mwayi Madanitsa, has registered and begun an online Masters in Epidemiology at the LSHTM, UK (due for completion in June 2014).
- One PhD is expected to finish by December 2013 and a second PhD student is expected to finish by March 2014.

	Preliminary results of the SP resistance study and the above meta-analysis were shared with the WHO ERG meeting in July 2012. In addition, the results of the 2 vs. 3 dose meta-analysis have been communicated via press releases from LSTM and JAMA journal. One article published at JAMA and two manuscripts in preparation. Setbacks: • For Trial 1b, recruitment was planned to be completed by December 2012; however, this is now to be happening in March 2013 • For Trial 2, the team detected that the quality of placental histology slides prepared at 3 of the 4 centers were poor. Thus, placenta blocks from these sites had to be sent to Ghana for new slides to be prepared. This is now ongoing but has caused a delay in completing the database for analysis. • In capacity building, the expected completion dates for the third MSc and for one PhD students will be after the end date of the grant, which is end of December 2013.
Total number of subjects (clinical trials only):	4,500 + 1,655
Total number of subjects (cohort/epidemiological/ other studies):	512 *in-vivo* follow-up of women receiving SP for IPTp
PhD studies:	Title: Optimisation of the existing regimen of intermittent preventive treatment with sulfadoxine-pyrimethamine for the prevention of malaria in pregnancy and assessing the impact of sulfadoxine-pyrimethamine resistance in west-Africa (Liverpool School of Tropical Medicine, Liverpool, UK & Medical Research and Training Centre, University of Bamako, Mali) Candidate: Kassoum Kayentao (Mali)
	Title: The Diagnosis of malaria in pregnancy in west-Africa (London School of Hygiene and Tropical Medicine, London, UK & Navrongo Health Research Centre, Navrongo, Ghana) Candidate: John Williams (Ghana)
MSc studies:	MBA (distance learning) Candidate: Mamkumba Sanneh (The Gambia)
	Master Clinical trials (distance learning) Candidate: Gerald Mwapasa (Malawi)
Other/Sub-studies:	Economic: to determine the cost-effectiveness of ISTp-DP versus IPTp-SP from a societal perspective and to use the cost data to populate a model of the economic burden of malaria in pregnancy. To model the economic cost of scale-up and affordability. Acceptability and implementability: to explore the implementability, acceptability, feasibility and potential for scale-up of ISTp in Malawi.
Publications:	1. Kayentao K, Garner P, van Eijk AM, Naidoo I, Roper C, Mulokozi A, MacArthur JR, Luntamo M, Ashorn P, Doumbo OK, ter Kuile FO. Intermittent preventive therapy for malaria during pregnancy using 2 vs. 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *JAMA* 2013 309: 594-604.

3.1.6 WANECAM

EDCTP Project Coordinator:	Abdoulaye Djimdé (Malaria Research & Training Center, Mali)
EDCTP Call Title:	Support of clinical trials, capacity building and networking in malaria treatment
EDCTP Project Title:	An integrated approach to clinical trials, capacity building and networking in West Africa treatment in pregnancy (IPTp) in the context of insecticide treated nets (WANECAM)
EDCTP Project Code:	IP.2007.31060.002
EDCTP Project Start Date:	15 September 2009
EDCTP Project End Date:	15 March 2013
Collaborators:	• Akim Ayola Adegnika (Leiden University, Netherlands) • Abdoul Habib Beavogui (Centre National de Formation et de Recherche en Santé Rurale (CNFRSR) Jean SENECAL de Mafèrinyah, Guinea) • Anders Björkman (Karolinska Institute, Sweden) • Steffen Borrmann (University of Heidelberg, Germany) • David Joseph Conway (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Esperance Coulibali (Centre national de recherche de Formation sur le Paludisme (CNRFP), Burkina Faso) • Adama Dao (University of Bamako, Mali) • Alexandre Delamou (CNFRSR Jean SENECAL de Mafèrinyah, Guinea) • Mamadou Malal Diallo (CNFRSR Jean SENECAL de Mafèrinyah, Guinea) • Dapa Diallo (University of Bamako, Mali) • Alassane Dicko (University of Bamako, Mali) • Ogobara Doumbo (University of Bamako, Mali) • Kassoum Kayentao (University of Bamako, Mali) • Aminatou Kone (University of Bamako, Mali) • Issa Ouedraogo Nebie (CNRFP, Burkina Faso) • Oumou Niare (University of Bamako, Mali) • Jean-Bosco Ouedraogo (Institut de Recherche en Sciences de la Santé, Burkina Faso) • Stephane Picot (University of Lyon, France) • Issaka Sagara (University of Bamako, Mali) • Sodiomon Sirima (CNRFP, Burkina Faso) • Colin Sutherland (LSHTM, UK) • Mahamadou Aly Thera (University of Bamako, Mali) • Alfred Tiono (CNRFP, Burkina Faso) • Boubacar Traore (University of Bamako, Mali) • Jean Baptiste Yaro (Medical Research Council Laboratories, The Gambia)
Site Principal Investigator(s):	• Sodiomon B. Sirima (Ouagadougou, Burkina Faso) • Issiaka Soulama (Ouagadougou, Burkina Faso) • Jean-Bosco Ouedraogo (Bobo-Dioulasso, Burkina Faso) • Issaka Sagara (Bamako, Mali) • Abdoul H. Beavogui (Conakry, Republic of Guinea)
Clinical Trial/Study Sponsor:	University of Bamako (Mali)
Trial/Study title:	A phase IIIb/IV randomised, multi-centre, open label, parallel 3-arm clinical study to assess the safety and efficacy of repeated administration of pyronaridine-artesunate, dihydroartemisinin-piperaquine or artemether-lumefantrine or artesunate-amodiaquine over a two-year period in children and adult patients with acute uncomplicated Plasmodium sp. Malaria
Goal:	The aim of this study are to compare the efficacy and the

	safety of repeated ACT therapy over a period of 2 years (pyronaridine-artesunate or dihydroartemisininpiperaquine are compared to either artesunate-amodiaquine or artemetherlumefantrine) in children and adults.
Primary Objective(s):	The primary objective of this clinical study is to compare the incidence rate of uncomplicated malaria episode in children and adults treated with repeated ACT therapy over a period of 2 years. In this 3 arm study PA and DHA-PQP is compared to either ASAQ or AL (depending on the site location). PA and DHA-PQP will not be formally compared.
Secondary Objective(s):	1. To compare PCR corrected and uncorrected ACPR at D28 and D42 (as defined by WHO 2009 protocol) between the ACT treatment arms 2. To compare re-infection and recrudescence rates over 42 days between the ACT treatment arms 3. To compare FCT and PCT between the ACT treatment arms 4. To compare gametocytes carriage and density between the ACT treatment arms 5. To compare time to the second infection and re-infections between treatments arms 6. To assess and compare safety of the three ACTs in repeated therapy.
Clinical Trial/Study site(s):	• Bougoula Hameau and Kolle (Mali) • Niankoloko-Banfora and Sakaby-Bobo Dioulasso (Burkina Faso), Maferinyah (Republic of Guinea)
Collaborating site(s):	• University of Bamako & Malaria Research and Training Center, Bamako (Mali) • Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Ouagadougou (Burkina Faso) • IRSS, Bobo-Dioulasso (Burkina Faso) • Centre National de Formation et de Recherche en Santé Rurale (CNFRSR) de Mafèrinyah, Conakry (Republic of Guinea) • Medical Research Council (MRC) Gambia, Fajara (The Gambia) • University of Heidelberg (Germany) • Université Claude Bernard Lyon 1, Lyon (France) • Karolinska University Hospital, Stockholm, (Sweden) • London School of Hygiene & Tropical Medicine (LSHTM), London (UK)
Study design:	The study is designed as a comparative, randomised, multicentre, open label, parallel 3 arm study to assess the safety and efficacy of repeated ACT therapy over a period of 2 years in uncomplicated Plasmodium sp. malaria in children and adults. Patients are to be followed for 2 years starting from the first enrolment with the randomised study drug. In each site, eligible subjects are randomised into 3 treatments arms: • Arm 1: dihydroartemisinin-piperaquine (DHA-PQP), • Arm 2: pyronaridine tetraphosphate/artesunate (pyramax, PA), • Arm 3: either artemether-lumefantrine (AL) or artesunate-amodiaquine (ASAQ) (as first line ACT treatment). The total number of patients to be randomised per country is

	448. Depending on the study site, DHA-PQP on one hand and PA on the other hand will be compared to either ASAQ (Bougoula-Hameau in Mali; Niankoloko-Banfora in Burkina Faso and Maferinyah in Guinea) or AL (Kolle in Mali and Sakaby-Bobo Dioulasso in Burkina Faso). The total number of patients being randomised in each study drug (PA, DHA-PQP) will be 1344. The estimated total number of patients being randomised in the comparator drug (AL or ASAQ) is 1,344. The comparator is regarded in this study as one although for Mali and Burkina Faso the comparator is either ASAQ or AL depending on the study site. This is because, in these 2 countries, both drugs are used as the first line treatments for uncomplicated malaria. No direct comparison will be conducted between DHA-PQP and PA.
Product(s):	Pyramax: pyronaridine tetraphosphate/artesunate (PA) combined tablet or granule for oral administration. Eurartesim: dihydroartemisinin-piperaquine (DHA-PQP) combined tablet for oral administration. ASAQ-Winthrop/Coarsucam: artesunate-amodiaquine (ASAQ) combined tablet for oral administration. Coartem or Coartem-D: artemether-lumefantrine (AL) combined tablet or dispersible tablet for oral administration.
Manufacturer/Developer:	• Novartis • Sanofi-Aventis • Sigma Tau • Shin Poong Pharmaceutical
Cofunders:	• MRC (UK) • SIDA (Sweden) • BMBF (Germany) • University Claude Bernard Lyon (France) • MRTC (Mali) • CNRFP (Burkina Faso) • IRSS (Burkina Faso) • CNFRSR (Republic of Guinea) • Medicines for Malaria Venture (MMV, Switzerland)
Trial Registration number(s):	PACTR201105000286876
Status:	Ongoing
Results and Outcomes:	This project will develop a sub-region composed of Burkina Faso, Guinea and Mali capable of state of the art clinical studies. Recruiting started on 25 October 2011 in Mali and is now ongoing in all three collaboting countries, i.e Mali, Burkina Faso and Republic of Guinea. Summary of major achievements (from 15 September 2009 until 15 December 2012) 1. In Clinical Trials • Study subjects recruitment started in Sotuba, Mali, in October 2011 and is currently ongoing in all 6 trial sites, i.e. 3 study sites in Mali, 2 in Burkina Faso and 1 in the Republic of Guinea. The sample size was increased from 4,032 to 5,376 subjects (i.e. 448 patients in each study arm) because safety requirements, i.e. inclusion criteria of only recruit adults for the Pyramax arm and to

	evaluate a minimum of 20 patients receiving at least one repeat dose of Pyramax before enrolling children (≥ 2 years-old with a weight of at least 15 Kg) in the study. • A database for the clinical trials has been implemented and data entry is ongoing. 2. In capacity Development, Training and Infrastructure • Several ethics and GCP refresher courses, microscopy certification training, training in data management, training in financial management, etc. were provided in an ongoing basis either on-site or during network-wide meetings. Site upgrades have been completed in all trial participating sites. Details are provided below: – Mali: the study site in Kolle is now fully powered with solar panels, which has considerably minimised the consumption of petrol in the site. A new building facility funded by Vac4all (lead by Prof. O. Doumbo) shares the infrastructure with the WANECAM team and vice versa. The vaccine project also equipped three sister sites in villages around the Bougoula study site of the WANECAM project, which are being used by the WANECAM team for patient recruitment – as the vaccine recruitment is completed. As consequence, and using MMV funding, the WANECAM purchased an additional Toyota Pick-up that is used to shuttle patients from these 3 villages to Bougoula-Hameau, the main WANECAM site. Therefore, the Bougoula-Hameau centre has now 3 Toyota Pick-ups (each one funded by the different funding agencies, i.e. EDCTP, MMV and Va4all). Refurbishment of a new dispensary in the village of Samanko, which is 4 Km from the Kolle site in Mali. A Nissan pick-up was purchased from MMV's funding to shuttle patients from Samanko to the main study site in Kolle – Burkina Faso (CNRFP): renovation of an insectarium in Niangoloko/Banfora field site is ongoing. Complementary clinical, laboratory and pharmacy procedures were written and implemented in the study site. An external quality control program was also established with the WWARN through the Malaria Molecular External Quality Assessment Program (M2EQAP) for molecular biology laboratory analysis – Burkina Faso (IRSS): in Sakaby, the rooms where the clinicians receive the study participants have been refurbished with installation of air conditioners. The inpatient department has been extended with the building of a new hall containing 3-4 beds. The hall contains a new consultation room (for the patients under follow up) and a space for the slides reading. In between, a large space is dedicated for a waiting space for children & parents and can occasionally serve as a meeting space (weekly meeting). In August 2012, the team in IRSS received the biochemistry machine and the UPS – Guinea: all laboratory and clinical equipment was successfully installed and tested. The Guinean Ministry of Health provided 12 desktop computers to the Centre in Maferinyah. The

	installation of solar panels in the Maferenya site is underway (with financial support from MMV). 3. Networking activities • Several Networking activities including North-South, South-South and North-North Networking activities have been carried out during this reporting period, including the Second Investigators Meeting held in Conakry (Guinea, 31 May-3 June 2012), where overall 44 participants from Heidelberg, Switzerland, Gambia, Guinea, Mali and Burkina Faso and MMV were present at this meeting. In addition, a Principal Investigators Meeting was held in Philadelphia in December 2011 at the 60th Annual Meeting of American Society of Tropical Medicine & Hygiene (ASTMH) • Establishment of various 'Interest Groups' to address specific research topics and the terms of reference within the Network. These are the following: – Group 1: Infectivity and transmission, led by Colin Sutherland (LSTMH, UK) – Group 2: Pharmacogenomics, molecular markers, led by Pedro Gill (KI, Sweden) – Group 3: Pharmacokinetics and Parasite genotyping, led by Steffen Borrmann (Heidelberg, Germany) – Group 4: In vitro/Ex-vivo studies, led by Stephane Picot (Lyon, France) – Group 5: Immunology, led by Issa Nebie (CNRFP, Burkina-Faso) Two publications were accepted by the Am. J. Trop. Med. Hyg. during the reporting period under evaluation. Seven oral/poster presentations and/or abstracts were presented in international conferences and included in books abstracts. WANECAM network website is under development (www.wanecam.org) Network memberships: West African Network for Clinical Trials of Anti Malarial drugs (Kick-off meeting 23-25 Feb 2010) and World Wide Antimalarial Drug Resistance Network (WWARN).
Total number of subjects (clinical trials only):	5,376
Total number of subjects (cohort/epidemiological/other studies):	600
PhD studies:	Title: Phase IIIb Comparative, Open, Randomised, Multi-Centre, Study of the Efficacy, Safety and Impact on malaria incidence of repetitive treatment with four artemisinin based combination therapies for uncomplicated falciparum malaria: Artesunate-Pyronaridine Dihydroartemisinin-Piperaquine, Artesunate-Amodiaquine, and Artemether-Lumefantrine. Candidate: Issaka Sagara (Mali) Training University: Universite de Marseille, France Dates: September 2009-December 2014
	Title: A pilot study of the efficacy of artesunate in the treatment of uncomplicated malaria in Bougoula-Hameau, Sikasso, Mali Candidate: Aminatou Kone Dates: September 2009-December 2014

	Title: Pharmacodynamic-pharmacokinetic analysis of the effect of artemisinin-based combination therapies on recurrent episodes of uncomplicated *P. falciparum* malaria Candidate: Mamadou Tekete (Mali) Start date: September 2009-December 2014
MSc studies:	Title: Epidemiology, Clinical Research Candidate: Esperance Ouedraogo (Burkina Faso) Dates: February 2011-July 2012
	Title: International Master of Medical & Veterinary Entomology Candidate: Moussa Sylla (Guinea) Supervisor: Abdoul H. Beavogui Dates: September 2009-December 2012
	Title: Molecular Parasitology and Medical Entomology Candidate: Elizabeth Diawara (Guinea) Training Institution: University of Bamako, Mali Dates: July 2009-December 2013
Other/Sub-studies:	Baseline malaria epidemiology and normal references ranges for biological parameters in Maferya, Guinea. Objectives: The primary objective of this study is to measure the age specific incidence disease in children during the two consecutive years to estimate the malaria burden and provide data for sample size calculation for future trials in these age groups. The secondary objectives are to monitor the efficacy of first line antimalarial treatment (ASAQ), to determine the normal references values for biological parameters in this population and to assess the year to year variation in frequency of infection and disease and transmission intensity. Study Design: This is an observational study to determine the burden of malaria in children of 3 months to 45 years of age. Subjects will be identified during a census. After obtaining community consent, eligible subjects will be invited to participated and screened after informed consent is obtained. A total of three cross sectional surveys will be carried out each year for two consecutive years (at the beginning and end of the transmission season and middle of the dry season). During these surveys, blood will be collected for malaria smears and haemoglobin measurement using Hemocue. Subjects will be enrolled at the beginning of transmission season each year and will be followed passively for 12 months. During the follow up, subjects with fever of history or fever will receive a clinical examination and finger pricks for malaria smears and determination of haemoglobin, cases diagnosed with malaria will be treated according to National Malaria Control Program (NMCP) guidelines. Diagnosis and treatment of other conditions will be performed as determined by the treating clinician.
Publications:	1. Khalid B Beshir, Rachel L Hallett, Alice C Eziefula, Robin Bailey, Julie Watson, Stephen G Wright, Peter L Chiodini, Spencer D Polley, Colin J Sutherland. Measuring the efficacy of anti-malarial drugs in vivo: quantitative PCR measurement of parasite clearance. *Malaria Journal* 2010, 9:312 2. Pedro Eduardo Ferreira, Gabrielle Holmgren, Maria Isabel Veiga, Per Uhlen, Akira Kaneko, Jose Pedro Gil. PfMDR1: Mechanisms of Transport Modulation by Functional Polymorphisms. *PLOS One* 2011, 6(9) e23875 3. Amelia W. Maiga, Bakary Fofana, Issaka Sagara, Demba

	Dembele, Antoine Dara, Oumar Bila Traore, Sekou Toure, Kassim Sanogo, Souleymane Dama, Bakary Sidibe, Aminatou Kone, Mahamadou A. Thera, Christopher V. Plowe, Ogobara K. Doumbo, and Abdoulaye A. Djimde. No Evidence of Delayed Parasite Clearance after Oral Artesunate Treatment of Uncomplicated Falciparum Malaria in Mali. *Am. J. Trop. Med. Hyg*. 2012, 87(1), 23–28 4. Issaka Sagara, Bakary Fofana, Jean Gaudart, Bakary Sidibe, Amadou Togo, Sekou Toure, Kassim Sanogo, Demba Dembele, Alassane Dicko, Roch Giorgi, Ogobara K. Doumbo, and Abdoulaye A. Djimde. Repeated Artemisinin-Based Combination Therapies in a Malaria Hyperendemic Area of Mali: Efficacy, Safety, and Public Health Impact. *Am. J. Trop. Med. Hyg*. 2012, 87(1), 50–56 5. PXR Variants and Artemisinin Use in Vietnamese Subjects: Frequency Distribution and Impact on the Interindividual Variability of CYP3A Induction by Artemisinin. Rita Piedade, Elke Schaeffeler, Stefan Winter, Sara Asimus, Matthias Schwab, Michael Ashton, Oliver Burk, and José P. Gil. Antimicrobial Agents and Chemotherapy 2012, 56(4), 2153-2157 6. Aminatou Kone, Jianbing Mu, Hamma Maiga, Abdoul H. Beavogui, Omar Yattara, Issaka Sagara, Mamadou M. Tekete, Oumar B. Traore, Antoine Dara, Souleymane Dama, Nouhoum Diallo, Aly Kodio, Aliou Traoré, Anders Björkman, Jose P. Gil, Ogobara K. Doumbo, Thomas E. Wellems, and Abdoulaye A. Djimde. Quinine Treatment Selects the pfnhe–1 ms4760–1 Polymorphism in Malian Patients with Falciparum Malaria. *The Journal of Infectious Diseases* 2013;207:520–7.

3.1.7 ADAPT

EDCTP Project Coordinator:	Victor Mwapasa (Malawi-Liverpool-Wellcome Trust Research Programme, Malawi)
EDCTP Call Title:	Support of clinical trials, capacity building and networking in malaria treatment
EDCTP Project Title:	Special populations and label expansion studies with the fixed dose combinations artemether-lumefantrine, amodiaquine-artesunate, and dihydroartemisinin-piperaquine in Zambia, Malawi and Mozambique
EDCTP Project Code:	IP.2007.31060.003
EDCTP Project Start Date:	14 July 2009
EDCTP Project End Date:	13 July 2014
Collaborators:	• Michael Boele van Hensbroek (University of Amsterdam, Netherlands) • Mike Chaponda (Tropical Diseases Research Centre, Zambia) • Umberto D'Alessandro (Prince Leopold Institute of Tropical Medicine (ITM), Belgium) • Fraction Dzinjalamala (University of Malawi) • Brian Faragher (University of Liverpool, UK) • Jean Pierre van Geertruyden (ITM, Belgium) • Exnevia Gomo (University of Malawi) • Raquel González Álvarez (Hospital Clinic of Barcelona, Spain) • Nayra Gutierrez (Manhiça Health Research Center, Mozambique) • Gertrude Kalanda (University of Malawi) • Neelam Kaul (Vienna School of Clinical Research (VSCR), Austria) • Saye Khoo (University of Liverpool, UK) • Heinrich Klech (VSCR, Austria) • David Lalloo (University of Liverpool, UK) • José Machado Almeida (Manhiça Health Research Center, Mozambique) • Jane Mallewa (Malawi-Liverpool-Wellcome Trust Research Programme, Malawi) • Inacio Mandomando (Manhiça Health Research Center, Mozambique) • Clara Menendez (Hospital Clinic of Barcelona, Spain) • Modest Mulenga (Tropical Diseases Research Centre, Zambia) • Denise Suzanne Naniche (Hospital Clinic of Barcelona, Spain) • Feiko ter Kuile (University of Liverpool, UK) • Dianne Terlouw (University of Liverpool, UK) • Steve Ward (University of Liverpool, UK) • Sarah Ann White (Malawi-Liverpool-Wellcome Trust Research Programme, Malawi)
Study / Trial 1	**ARV – ACT trial**
Site Principal Investigator(s):	Victor Mwapasa (Malawi)
Clinical Trial/Study Sponsor:	Liverpool School of Tropical Medicine, Liverpool (UK)
Trial/Study title:	Pharmacokinetic studies of interactions between Artemisinin-based Combination Therapies and Antiretroviral Therapies in Malawi - ARV – ACT trial (Theme 1)
Goal:	To reduce malaria-associated morbidity and mortality in HIV

	positive individuals by determining the most appropriate ACT treatment in this group of individuals based on safety and efficacy.
Primary Objective(s):	To identify and describe any pharmacokinetic interactions between ACTs and ARVs and assess the safety of co-administering these drugs in malaria-negative HIV-infected adults.
Secondary Objective(s):	1. To compare the pharmacokinetic parameters (Area Under time-concentration Curve [AUC0-t], maximum concentration [Cmax], time to maximum concentration [tmax], terminal elimination half life [t1/2]) of lumefantrine and dihydroartemisinin in HIV-infected adults taking artemether-lumefantrine plus 3TC-d4T-NVP, 3TC-d4T-EFV or AZT-3TC-TDF-LPV/r and HIV-infected adults taking artemether-lumefantrine only 2. To compare the pharmacokinetic parameters (Cmax, AUC0-t, tmax and t1/2) of dihydroartemisinin, amodiaquine and the amodiaquine metabolite; desethylamodiaquine in HIV-infected adults taking artesunate-amodiaquine plus 3TC-d4T-NVP or AZT-3TC-TDF-LPV/r and HIV-infected adults taking artesunate-amodiaquine only. Note: Interactions with EFV-containing ART will not be assessed because of previous evidence of serious adverse reactions, as discussed in the background section 3. To compare the pharmacokinetic parameters (Cmax, AUC0-t, tmax and t1/2) of piperaquine, and dihydroartemisinin in HIV-infected adults taking dihydroartemisinin-piperaquine plus 3TC-d4T-NVP, 3TC-d4T-EFV or AZT-3TC-TDF-LPV/r and HIV-infected adults taking dihydroartemisinin-piperaquine only 4. Describe the tolerability and incidence of clinical and sub-clinical adverse events upon co-administration of the ACT/ART drug combinations, described in objectives #1 to #3 above.
Study design:	Phase IIIb studies. Single centre, open-label, dose-escalation, drug-drug interaction pharmacokinetic study. The study, conducted at MLW (Malawi) only, is being implemented in the following two steps: • In Phase 1 Step 1, half adult doses of the ACTs were administered in HIV positive malaria-negative individuals on steady-state ART and a control group of HIV positive individuals who are not on ART. This step served as a safety evaluation step in drug interaction studies, checking for unexpected clinical toxicities or interactions. Blood samples for data-rich pharmacokinetic assays were collected over a 28 day period alongside real time clinical, biochemical and haematological monitoring for severe adverse events. Pharmacokinetic parameters including AUC, Cmax, Tmax and t1/2 were determined and compared with existing historical data to establish the nature and extent of any drug interaction • In Phase 1 Step 2: (in study arms with no significant adverse events or high drug levels in step 1), data-rich pharmacokinetic studies of full dose ACT are currently being undertaken over a 28 day period in HIV positive malaria negative individuals on steady-state ART and a control group of HIV positive individuals who are not on ART. Close monitoring adverse events will be undertaken.

	These initial data-rich PK studies of interactions between ART and different ACT options in HIV infected malaria-negative individuals (Phase 1) are being conducted at MLW (Malawi) only. They will be followed by multicentre efficacy and safety studies of the selected ACTs with suitable PK profiles (Phase 2). This component of the study will be conducted at MLW (Malawi), TDRC (Zambia) and CISM (Mozambique). The study participants are receiving the following nationally recommended ART regimes: • 3TC (150mg) -d4T (30mg)-NVP (200mg), 1 tablet 12-hourly. Most of the study participants will be receiving this regimen. However, some study participants receiving nevirapine-based ART, may have already been switched to 3TC (150mg) -AZT (300mg) twice daily because of d4T toxicity. • 3TC (150mg) –d4T (30mg) 12-hourly plus Efavirenz (EFV; 600mg) once daily. Some of the study participants receiving EFV-based ART may have been switched to 3TC (150mg) -AZT (300mg) every 12 hours because of d4T toxicity. • 3TC (150mg) -AZT (300mg) every 12 hours plus Tenofovir (TDF; 300mg) once daily plus Lopinavir (200mg)/ritonavir (50mg) 2 tablets every 12 hours.
Clinical Trial/Study site(s):	ART Clinic at Queen Elizabeth Central Hospital (QECH, Blantyre Malawi), Ndola, (Zambia), and Manhiça (Mozambique)
Collaborating site(s):	• Malawi-Liverpool-Wellcome Trust Clinical Research Programme and Department of Medicine, College of Medicine (Malawi) • Manhiça Health Research Center (CISM), Manhiça, (Mozambique) • Tropical Diseases Research Centre, Ndola (Zambia) • Liverpool School of Tropical Medicine, Liverpool (UK) • University of Liverpool, Liverpool (UK) • Institute of Tropical Medicine (ITM), Antwerp (Belgium) • Vienna School of Clinical Research (VSCR), Vienna (Austria) • Amsterdam Medical Centre(AMC), Amsterdam (Netherlands) • Barcelona Centre for International Health Research (CRESIB)/Hospital Clinic, Barcelona (Spain)
Number of subjects:	Approximately 1,200 individuals, 200 in phase 1 and 1,000 in phase 2
Product(s):	Artemether-Lumefantrine (AL), (Coartem®, Novartis) Artesunate-Amodiaquine, (Coarsucam™, Sanofi-Aventis) DHA-piperaquine, (Euratesim®), Sigma Tau) Antiretroviral drug combinations: 3TC-d4T-NVP, Trioimune, Cipla), 3TC-AZT-EFV (combivir plus efavirenz, 3TC-AZT-NVP (combivir plus NVP) TDF-3TC-AZT-LPV/r (tenofovir, combivir plus lopinavir/ritonavir).
Manufacturer/Developer:	• Novartis • Sanofi-Aventis • Sigma Tau
Cofunders:	• Carlos III Health Institute (Spain) • MRC UK (UK) • Austrian Federal Ministry of Science (Austria)
Trial Registration number(s):	ATMR 2010030001871293 (Phase I, step 1 study) ATMR 2010030001971409 (Phase I, step 2 study)
Status:	Ongoing

Results and Outcomes:	In October 2011, the team presented preliminary results from Phase 1 Step 1 to the DSMB and at the Sixth EDCTP forum. In February 2012, the DSMB recommended progression of 9 of 11 study arms from Phase 1 Step 1 to Step 2. By 13th July 2012, it was completed enrolment of participants in 5 of the 9 Phase 1 Step2 study arms and performed a significant number of PK assays. Nevertheless, in February 2012, the DSMB requested the collection of additional data in two of the study arms in Phase 1 Step 1, before it could consider recommending progression to Step 2. In addition, in May 2012 the DSMB recommended enrolment of study participants in three (3) additional study arms that were not originally planned for in order to ascertain causes of some of the haematological abnormalities we are observing in some study arms. The enrolment of participants in these additional arms has significant cost-implications. There have been deviations in the study timelines, as follows: • Enrollment of 1st study participant was delayed from 8 October 2009 to 11 August 2010 • Completion of follow up of study participants in Phase 1 Step 1 was delayed from 31 December 2009 to 24 July 2011 • DSMB recommendation to progress from Phase 1 Step 1 to Step 2 was delayed from 30 April 2010 to 7 February 2012 • Start of Phase 1 Step 2 was delayed from 1 July 2010 to 1 March 2012. In summary, planned study activities are delayed by up to 20 months. In view of the delays described above, the timelines have changed as follows: • End of enrolment in Phase 1 Step 2 is expected on 30 October 2012 from the originally planned date of 15 February 2011. • Completion of PK assays for Phase 1 Step 2 is expected by 31 December 2012. • Commencement of Phase 2 will be delayed to March 2013 from the originally planned date of 1 October 2011. • Completion of Phase 2 is expected by December 2014 from the originally planned date of 30 June 2013.
Study / Trial 2	**Label Expansion studies**
Site Principal Investigator(s):	Dianne Terlouw (based at MLW/COM, Malawi)
Clinical Trial/Study Sponsor:	Liverpool School of Tropical Medicine, Liverpool (UK)
Trial/Study title:	Programmatic age- and weight based dosing regimens for artemether-lumefantrine and dihydroartemisinin-piperaquine.
Goal:	To design and field test age-based dosing regimens for AL and DHA-PPQ, in order to generate an evidence-base for translation of weight-based dose recommendations to programmatic dosing regimens.
Primary Objective(s):	1. To apply a newly developed modelling tool established by LSTM to determine the optimal age-based dosing regimen for AL and DHA-PIP 2. To determine the dosing accuracy, population pharmacokinetics, safety and effectiveness of the new age-based regimens compared against programmatic weight-based regimens.

Study design:	Objective 1. A new modelling tool developed by scientists at the LSTM, DNDi and TDR/WHO is used to develop practical age-based dose regimens that would result in the smallest number of patients with malaria receiving ACT doses above or below the therapeutic range. Objective 2. These modelled age-based regimens will be compared in a regulatory trial against the existing weight-based regimen for their dosing accuracy and safety and effectiveness in Malawi (N=400).
Clinical Trial/Study site(s):	Blantyre and/or Chikhwawa (Malawi)
Collaborating site(s):	• Malawi-Liverpool-Wellcome Trust Clinical Research Programme and Department of Medicine, College of Medicine (Malawi) • Liverpool School of Tropical Medicine, Liverpool (UK) • University of Liverpool, Liverpool (UK) • Vienna School of Clinical Research (VSCR), Vienna (Austria)
Study population and number of expected recruits:	Study population: Children ≥ 4 months and adults. Individuals dosed by age and weight will receive the same tablet burden (number of tablets) in 5 categories. The study will therefore focus enrolment of children and adolescents who are at the extremes of their weight or age category (i.e. the heaviest and lightest children per category, at an age around the age cut-offs when a dose increase step is conducted) as this is the group where a differential treatment effect is likely to occur. Anticipated sample size is under review as part of the development of the optimal population PK schedule. Initial estimates assumed Ar-Lu n = ~600, DHA-PPQ n = ~600. Justification: most weight-based regimens consist of 5 weight categories. We will compare drug levels in between individuals dosed by age and weight within the 5 dosing categories, as well as a 6th group of large adults (≥ 70 kg).
Product(s):	Artemether-Lumefantrine (AL), (Coartem®, Novartis) DHA-piperaquine, ((Euratesim®), Sigma Tau)
Cofunders:	• MRC UK (UK) • Austrian Federal Ministry of Science (Austria) will provide training
Status:	Ongoing
Results and Outcomes:	Not yet recruiting
PhD studies:	Title: Review and development of statistical methodologies for handling missing observations in comparative and non-comparative anti-malarial efficacy and pharmacokinetic /pharmacodynamic studies (Registered at the LSTM, UK) Candidate: Mavuto Mukaka (Malawi) Dates: 1 December 2009-30 November 2013
	Title: Interaction between HIV and malaria: implications for public health and medical decision making Candidate: Victor Chalwe (Zimbabwe) Dates: September 2011 (discontinued)
MSc studies:	MSc in Computer Science focussed on Data Management Candidate: Rueben Dickman Ndindi Dates: September 2010-November 2011
	MPH in Public Health Disease Control Candidate: Sebastian Hachizovu (Zimbabwe)
Publications:	

3.2 Malaria vaccines clinical trials

Project Acronym (Coordinator)	Phase of trial	Product(s)	Manufacturer / Developer	Study population	Status of trial
GMZ2 (Theisen)	I	GMZ2: GLURP + MSP3 hybrid	SSI, Denmark	Children N=30	Completed
GMZ2 (Theisen)	II	GMZ2: GLURP + MSP3 hybrid	SSI, Denmark	Children N=1847	Ongoing
MVVC/VAC040 (Imoukhuede)	I	ChAd63 ME-TRAP; MVA ME-TRAP	Clinical BioManufacturing Facility (CBF), Old Road, Headington, Oxford, OX3 7JT, UK IDT Biologika GmbH, Am Pharmapark, 06861 Dessau-Rosslau, Germany	Adults N=30	Completed
MVVC/VAC041 (Imoukhuede)	I	ChAd63 ME-TRAP; MVA ME-TRAP	Clinical BioManufacturing Facility (CBF), Old Road, Headington, Oxford, OX3 7JT, UK IDT Biologika GmbH, Am Pharmapark, 06861 Dessau-Rosslau, Germany	Children and adults N=52	Completed
MVVC/VAC042 (Imoukhuede)	I	ChAd63 ME-TRAP; MVA ME-TRAP	Clinical BioManufacturing Facility (CBF), Old Road, Headington, Oxford, OX3 7JT, UK IDT Biologika GmbH, Am Pharmapark, 06861 Dessau-Rosslau, Germany	Children N=72	Completed

MVVC/VAC046 (Imoukhuede)	II	ChAd63 ME-TRAP; MVA ME-TRAP	Clinical BioManufacturing Facility (CBF), Old Road, Headington, Oxford, OX3 7JT, UK IDT Biologika GmbH, Am Pharmapark, 06861 Dessau-Rosslau, Germany	Children N=120	Ongoing
MVVC/VAC047 (Imoukhuede)	II	ChAd63 ME-TRAP; MVA ME-TRAP	Clinical BioManufacturing Facility (CBF), Old Road, Headington, Oxford, OX3 7JT, UK IDT Biologika GmbH, Am Pharmapark, 06861 Dessau-Rosslau, Germany	Adults N=120	Ongoing
MVVC/VAC050 (Imoukhuede)	II	ChAd63 ME-TRAP; MVA ME-TRAP	Clinical BioManufacturing Facility (CBF), Old Road, Headington, Oxford, OX3 7JT, UK IDT Biologika GmbH, Am Pharmapark, 06861 Dessau-Rosslau, Germany	Children N=700	Ongoing
MVVC2/Trial 1 (Imoukhuede)	I	ChAd63 ME-TRAP; MVA ME-TRAP; R21 + MF59	Clinical BioManufacturing Facility (CBF), Old Road, Headington, Oxford, OX3 7JT, UK Novartis, Vaccines and Diagnostics Division Siena, Italy	Adults and children N=60	Ongoing (not yet recruiting)
MVVC2/Trial 2 (Imoukhuede)	II	ChAd63 ME-TRAP; MVA ME-TRAP; R21 + MF59	Clinical BioManufacturing Facility (CBF), Old Road, Headington, Oxford, OX3 7JT, UK Novartis, Vaccines and	Adults and children N=120	Ongoing (not yet recruiting)

			Diagnostics Division Siena, Italy		
P27ACTB (Abdulla)	I	P27A (active ingredient: PFF0165c) Adjuvant: Alhydrogel or GLA-SEP27A doses	GMP P27A drug substance manufactured by Almac (UK); GMP drug product manufactured by Nova Laboratories, Ltd (UK); GMP Alhydrogel (aluminium hydroxide) bulk material manufactured by Brenntag (Denmark) and the final unidose vials prapared by Nova Laboratories (UK); The GMP Glucopyranosil Lipid Adjuvant-Stable Emulsion (GLA-SE) and the GMP EM060 stable emulsion (SE) manufactured by Infectious Disease Research Institute (IDRI, USA)	Adults N=56	Ongoing (not yet recruiting)
PfSPZ Challenge Study (Ogutu)	I	Aseptic, purified, cryopreserved P. falciparum sporozoites (PfSPZ) for challenge (PfSPZ Challenge)	Sanaria Inc. [Investigational New Drug 14267: PfSPZ Challenge is currently filed with the US Food and Drug Administration (FDA)]	Adults N=28	Ongoing (not yet recruiting)

3.2.1 GMZ2

EDCTP Project Coordinator:	Michael Theisen (Statens Serum Institut, (SSI), Denmark)
EDCTP Project Call:	Calls for support of integrated projects on clinical trials, capacity building and networking
EDCTP Project Title:	Fostering research capacity, networking and project management through phase I-IIB clinical trials of candidate malaria vaccine GMZ2.
EDCTP Project Code:	IP.2007.31100.001
EDCTP Project End Date:	19 January 2009
EDCTP Project End Date	18 January 2014
Collaborators:	• Frank Atuguba (Navrongo Health Research Centre, Ghana) • Kalifa Bojang (Medical Research Council Laboratories, The Gambia) • Roma Chilengi (Kenya Medical Research Institute (KEMRI), Kenya) • David Conway (London School of Hygiene and Tropical Medicine (LSHTM), UK) • Dawit Ejigu (African Malaria Network Trust (AMANET), Tanzania) • Saadou Issifou (Albert Schweitzer Hospital, Gabon) • Wen Kilama (AMANET, Tanzania) • Fred Kironde (Makerere University, Uganda) • Elie Mavoungou (Albert Schweitzer Hospital, Gabon) • Paul Milligan (LSHTM, UK) • Benjamin Mordmüller (Albert Schweitzer Hospital, Gabon) • Mark Kaddu Mukassa (Makerere University, Uganda) • Ramadhani Noor (AMANET, Tanzania) • James Aggrey Oloo (AMANET, Tanzania) • Sodiomon Sirima (Centre national de recherche de Formation sur le Paludisme (CNRFP), Burkina Faso) • Alfred Tiono (CNRFP, Burkina Faso)
Site Principal Investigator(s):	• Sodiomon Sirima (Burkina Faso) • Saadou Issifou (Gabon) • Fred Kironde (Uganda) • Frank Atuguba (Ghana)
Clinical Trial/Study Sponsor:	SSI (Denmark)
Trial/Study title:	**Phase IB** A phase I, randomised, controlled, double-blind, single-centre trial to evaluate the safety and immunogenicity of 30 µg and 100 µg of the GMZ2 vaccine in Gabonese children aged 1-5 years. **Phase IIB** A phase II, randomised, controlled, double-blind, multi-centre trial to evaluate the efficacy, safety, and immunogenicity of the GMZ2 vaccine in Gambian, Gabonese, Burkinabe and Ugandan children aged 1-5 years.
Goal:	To develop an effective malaria vaccine that is safe, effective, and can be integrated into the expanded programme on immunisation in African countries.
Primary Objective(s):	**Phase IB** • To evaluate the safety and reactogenicity of three doses of 30 µg and 100µg GMZ2 adsorbed on aluminium hydroxide, in comparison with three doses of the control vaccine (rabies), in healthy Gabonese children aged 1-5

	years. **Phase IIB** • To evaluate the efficacy of three doses of GMZ2 vaccine adsorbed on aluminium hydroxide, in comparison with three doses of the control vaccine, in healthy Gambian, Gabonese, Burkinabe and Ugandan children aged 1-5 years.
Secondary Objective(s):	**Phase IB** 1. To assess the humoral immune response to the vaccine antigens GMZ2, LURP and MSP3 by measuring the IgG and IgG isotypes by ELISA and antigen specific memory B-cell by ELISPOT 2. To assess the cellular immune response by measuring the T-cell reactivity after stimulation with medium, SEB (positive control), GMZ2, GLURP, or MSP3. Cytokine profiles will be analyzed in the supernatants of short term cultures after 24 and 48 hours of stimulation using Th1/Th2 Cytometric Bead Arrays. **Phase IIB** 1. To evaluate the safety and reactogenicity of three doses of GMZ2 adsorbed on aluminium hydroxide, in comparison with three doses of the control vaccine, in healthy Gambian, Gabonese, Burkinabe and Ugandan children aged 1-5 years 2. To assess the humoral immune response to the vaccine antigens GMZ2, GLURP and MSP3 by measuring the IgG and IgG isotypes by ELISA and antigen specific memory B-cell by ELISPOT in a subset of participants 3. To assess the cellular immune response by measuring the T-cell reactivity after stimulation with medium, SEB (positive control), GMZ2, GLURP, or MSP3. IFN-γ production will be measured on single cell level by intracellular cytokine staining of T-cells in a sub-sample of participants. Cytokine profiles will be analyzed in the supernatants of short term cultures after 24 and 48 hours of stimulation using Th1/Th2 Cytometric Bead Arrays 4. To evaluate the protective efficacy of GMZ2 vaccine on anaemia and severe anaemia as defined by haemoglobin cut-offs at 10mg/dl and 5mg/dl respectively.
Clinical Trial/Study site(s):	• MRU Lambaréné (Gabon) • CNRFP (Burkina Faso) • Makarere University (Uganda) • Navrongo Medical Research Centre (NMRC, Ghana)
Collaborating site(s):	• Medical Research Council Laboratories (The Gambia) • London School of Hygiene and Tropical Medicine (LSHTM) (UK) • Staten Serum Institut (Denmark) • Albert Schweitzer Hospital (Gabon) • Makerere University (Uganda) • Centre national de recherche de Formation sur le Paludisme (CNRFP) (Burkina Faso) • NMRC (Ghana) • University of Tübingen (Germany)
Study design:	Phase IB: Double-blind, randomised, and controlled trial Phase IIB: Double-blind, randomised, controlled, Multi-centre trial
Product:	GMZ2
Manufacturer/Developer:	SSI (Denmark)

Cofunders	• University of Tübingen (Germany) • Statens Serum Institut (Denmark) • European Vaccine Initiative (EVI, Germany) • Federal Ministry of Education and Research (BMBF, Germany) • AMANET (Tanzania) • Department for International Development (DFID, UK)
Trial Registration number(s):	ATMR2010060002033537
Status:	Ongoing
Results and Outcomes:	The recruitment target was reached by September 2011. The 1847 enrolled children are being followed-up. Three vaccinations were given at day 0, 28 and 56 and the follow-up duration for the ongoing Phase IIb trial is 24 months after 1st vaccination. The results of baseline studies provided guidance for the sample size of phase IIb.
Total number of subjects (clinical trials only):	1840 participants
Total number of subjects (cohort/epidemiological/ other studies):	Baseline studies of at least 300 children per site have been completed
PhD studies:	Title/topic: Humoral Immune Responses and Immunological Memory against Plasmodium Falciparum Malaria Antigens Candidate: Mark Kaddumukasa (Uganda) Dates: November 2010- September 2013
	Title/topic: Protective role of IgG and FcγR in malaria Candidate: Tiendrebeogo Régis Wendpayangde (Burkina Faso) Dates: 1 November 2011-1 November 2014
MSc study:	Title/topic: MSc Professional IT (Databases) Candidate: Abubakar Ismaela (The Gambia) Dates: September 2010 -September 2013
Publications:	1. B. Mordmüller et al. Safety and immunogenicity of the malaria vaccine candidate GMZ2 in malaria-exposed, adult individuals from Lambaréné, Gabon. *Vaccine* 28 (2010) 6698–6703 2. Belard S, Issifou S, Hounkpatin AB, Schaumburg F, Ngoa UA, et al. (2011) A Randomised Controlled Phase Ib Trial of the Malaria Vaccine Candidate GMZ2 in African Children. *PLoS ONE* 6(7): e22525. doi:10.1371/journal.pone.0022525

3.2.2 MVVC

EDCTP Project Coordinator:	Egeruan Babatunde Imoukhuede (European Vaccine Initiative (EVI), Germany)
EDCTP Project Call:	Calls for support of integrated projects on clinical trials, capacity building and networking
EDCTP Project Title:	Integrating capacity building and networking in the design and conduct of Phase I and II clinical trials of viral vectored candidate malaria vaccines in East and West African children and infants (Vectored Malaria Vaccines)
EDCTP Project Code:	IP.2008.31100.001
EDCTP Project Start Date:	18 December 2009
EDCTP Project End Date:	17 December 2013
Collaborators:	• Muhammed Olanrewaju Afolabi (Medical Research Council (MRC) Laboratories, The Gambia) • Phillip Bejon (University of Oxford, UK) • Kalifa Bojang (MRC Laboratories, The Gambia) • Badara Cisse (University Cheikh Anta DIOP de Dakar (UCAD), Senegal) • Katie Flanagan (MRC Laboratories, The Gambia) • Adrian Hill (University of Oxford, UK) • Nathalie Imbault (European Vaccine Initiative, Germany) • Ya Jankey Jagne (MRC Laboratories, The Gambia) • Issa Ouedraogo Nebie (Centre national de recherche de Formation sur le Paludisme (CNRFP), Burkina Faso) • Alfredo Nicosia (Okairos s.r.l, Italy) • Ogwang, Caroline (Kenya Medical Research Institute (KEMRI), Kenya) • Sodiomon Sirima (CNRFP, Burkina Faso) • Britta Christine Urban (Liverpool School of Tropical Medicine, UK) • Jean Baptiste Yaro (MRC Laboratories, The Gambia)
Site Principal Investigator(s):	• Kalifa Bojang (The Gambia) • Caroline Ogwang (Kenya) • Sodiomon Sirima (Burkina Faso) • Badara Cisse (Senegal)
Clinical Trial/Study Sponsor:	University of Oxford (UK)
Trial/Study title:	Safety, Immunogenicity and Efficacy Study of Adenoviral-MVA prime-boost Vaccination for Preventing Clinical Malaria in Young African Children: a large multi-site phase IIb trial following two initial phase Ib trials.
Goal:	To integrate capacity building and networking in the design and conduct of Phase I and II clinical trials of viral vectored candidate malaria vaccines.
Primary Objective(s):	1. Demonstration of the safety and immunogenicity of a new adenovirus encoding malaria antigens in adults and young children in sub-Saharan Africa 2. Demonstration of the safety and immunogenicity of an adenovirus prime MVA boost regime encoding malaria antigens in adults and young children in sub-Saharan Africa 3. Assessment of the safety, immunogenicity and efficacy of this new prime-boost regime in protection against clinical malaria in 5-17 month old children followed for 12 months at multiple sites in East and West Africa.
Secondary Objective(s):	Vaccine safety and immunogenicity; efficacy as measured by other measures of malaria infection and disease: e.g. parasite

	density, other definitions of clinical disease, anaemia, cross-sectional parasite rates.
Clinical Trial/Study site(s):	• The phase I trial in Kenyan adults and children was conducted at the KEMRI coastal research unit at Kilifi, Kenya • The phase I study in Gambians was conducted at the Sukuta site near to Banjul in The Gambia • The phase IIb trials are conducted at KEMRI (Kenya), Gwediawaye (Senegal) and at the CNRFP Banfora site in Burkina Faso.
Collaborating site(s):	• CNRFP (Burkina Faso) • KEMRI Wellcome Trust Centre, Kilifi (Kenya) • Farafenni and Sukuta Field Stations (The Gambia) • Université Cheikh Anta Diop (UCAD, Senegal) • The European Vaccine Initiative (EVI, Germany) • University of Oxford (UOXF, UK) • Okairòs s.r.l. (Italy) • Vienna School of Clinical Research (Austria)
Study design:	Randomised, controlled, double-blind phase IIb efficacy trial
Product(s):	Adenovirus ME-TRAP and MVA ME-TRAP
Manufacturer/Developer:	Impfstoffwerke Dessau-Tornau (Germany)
Cofunders:	• Swedish International Development Cooperation Agency (SIDA, Sweden) • Medical Research Council (UK) • Department of Foreign Affairs (Ireland) • Kenya Medical Research Institute (KEMRI, Kenya) • University of Oxford (UK) • Okairos s.r.l (Italy) • Vienna School of Clinical Research (Austria) • CNRFP (Burkina Faso) • Medical Research Council Laboratories (The Gambia) • Austrian Federal Ministry of Science (Austria) • EVI (Germany) • UCAD (Senegal)
Trial Registration number(s):	The VAC040 trial: NCT01379430 The VAC041 trial: NCT01373879 The VAC042 trial: NCT01450293 The VAC046 trial: NCT01666925 The VAC047 trial: NCT01658696 The VAC050 trial: NCT01635647 Other reg. numbers: Phase Ib trial in Kenyan adults: ATMR2010020001771828 Phase Ib trial in Gambian adults: PACTR201008000221638
Trial 1	The VAC040 trial:phase Ib, dose escalation trial to assess tolerability and immunogenicity of the malaria vectored vaccine candidates AdCh63 ME-TRAP and MVA ME-TRAP in Kenyan adults
Trial 2	The VAC041 trial: phase Ib, age de-escalation trial, to assess the safety, tolerability and immunogenicity of the malaria vectored vaccine candidates AdCh63 ME-TRAP and MVA ME-TRAP in Gambian adults and children (2-6 years)
Trial 3	The VAC042 trial: phase Ib, age de-escalation trial, to assess the safety, tolerability and immunogenicity of the vaccine candidates in Gambian infants (5-12 months)
Trial 4	The VAC046 trial: phase IIb, to evaluate the efficacy of the vaccination strategy against natural P. falciparum in Kenyan adults

Trial 5	The VAC047 trial: phase IIb, to evaluate the efficacy of the vaccination strategy against natural P. falciparum in Senegalese adults
Trial 6	The VAC050 trial: phase Ib/IIb, to assess the protective efficacy against clinical malaria in infants and children, in Burkina Faso
Status:	Ongoing
Results and Outcomes:	The VAC040 trial is now completed. The VAC041 trial enrolled 36 children aged 2-6 years, 12 in the placebo group and 24 in the vaccine group receiving staggered doses of ChAd63ME-TRAP and MVA ME-TRAP at day 0 and day 56. It was conducted between 18 January and 22 December 2011. The trial is completed and a paper has been published. The VAC042 trial enrolled 48 infants in October 2011 and followed them up until January 2013. The close-out visit was condicted in February 2013 and a manuscript on the results from this study is being prepared. In the VAC046 trial, 120 healthy adult males were enrolled in March 2012 and are being followed up until Janauary 2013. The database cleaning for lock-up was done at the end of Jan 2013. In the VAC047 trial, recruitment of 120 participants for VAC047 has been completed and follow up is ongoing. The VAC050 trial, was initiated in October 2012 with the first subject first visit in December 2012 for the phase-I lead-in study (30 children). The phase IIb efficacy study, which will enrol 700 participants, started in March 2013. Both adult and pediatric studies showed a good safety profile at the doses tested. The studies have concluded that ChAd63-MVA ME-TRAP is a safe and highly immunogenic vaccine regimen in adults with prior exposure to malaria. These findings have supported further evaluation of ChAd63/MVA.ME-TRAP vaccines in the ongoing efficacy trials now being conducted in Kenya, Senegal and Burkina Faso.
Total number of subjects (clinical trials only):	In total, 1084 participipants in phase I and II trials
Total number of subjects (cohort/epidemiological/other studies):	1516 participants in epidemiological baseline studies
PhD studies:	Dr Muhammed Afolabi, PhD student from MRC, is registered at the London School of Hygiene and Tropical Medicine, for a PhD project “Evaluation of alternative informed consent procedures in clinical trials conducted in The Gambia”, which he started in September 2011 and plans to complete September 2014.
	Dr David Kangoye, PhD student from CNRFP (Burkina Faso) for his project entitled “Malaria burden in the first two years of life”, is conducting a prospective cohort study in which 140 infants were enrolled at their 4-6 weeks of age and were followed-up for at least 24 weeks. Dr Kangoye started his project in September 2011 and plans to complete in June 2014.
	Mr Mansour Ndiath, PhD student from UCAD (Senegal) started

	his PhD project in October 2010 and is scheduled to complete December 2013. His work is tilted “Evolution of malaria morbidity from 2000 to 2011: Identification and Characterization of malaria hot spots in Keur Soce health and demographic surveillance site system”.
MSc studies:	Massamba Syll, MSc student from UCAD (Senegal) started his training in October 2010. His work focuses on the “Optimization of operational research processes in Keur Soce health”. He is registered at the University Cheik Anta Diop (Dakar).
	Dr Jean Baptiste Yaro, MSC student from CNRFP (Burkina Faso) completed his training in July 2012. His work was on “Seasonal variation of malaria infection in a stable malaria transmission area in Burkina Faso” and another part of his training was on “Trial Protocol Development” at the Vienna School of Clinical Research. Dr Yaro continues how his work at CNRFP as one of the clinicians for the VAC050 trial.
	Ya Jankey Jagne (from MRC, The Gambia) started her MSc training at the London School of Hygiene and Tropical Medicine in September 2012 and will complete in September 2013
PostDoc study:	Dr Francis Ndungu, Postdoctoral fellow from KEMRI (Kenya), is working on “B cell memory and immunity to malaria”. Dr Ndungu work started in August 2011 and will be completed by December 2013.
Other sub-studies	Baseline Study in Burkina Faso: Assessing malaria morbidity during the first two years of life and age-specific sero-prevalence of adenovirus type Ad5, Ad35 and ChAd63, potential malaria vectored vaccine candidates in two settings of seasonal malaria transmission. Study sample: 750 enrolled participants Baseline Study UCAD: Malaria morbidity during the first two years of life and age-specific seroprevalence of adenovirus type Ad5, Ad35 and ChAd63, potential malaria vectors vaccines candidates in two settings of seasonal malaria transmission. Study sample: 766 enrolled participants
Publications:	1. Ogwang C, Afolabi M, Kimani D, Jagne YJ, Sheehy SH, et al. (2013) Safety and Immunogenicity of Heterologous Prime-Boost Immunisation with Plasmodium falciparum Malaria Candidate Vaccines, ChAd63 ME-TRAP and MVA ME-TRAP, in Healthy Gambian and Kenyan Adults. *PLoS ONE* 8(3): e57726. doi:10.1371/journal.pone.0057726 2. Ndungu FM, Olotu A, Mwacharo J, Nyonda M, Apfeld J, Mramba LK, Fegan GW, Bejon P, Marsh K. Memory B cells are a more reliable archive for historical antimalarial responses than plasma antibodies in no-longer exposed children. *Proc Natl Acad Sci U S A*. 2012 May 22;109(21):8247-52. Epub 2012 May 7. 3. Illingworth J, Butler NS, Roetynck S, Mwacharo J, Pierce SK, Bejon P, Crompton PD, Marsh K and Ndungu FM. Chronic Exposure to Plasmodium falciparum is associated with phenotypic evidence of B and T-cell exhaustion. *J Immunol*. 2013 Feb 1;190(3):1038-47. doi: 10.4049/jimmunol.1202438. Epub 2012 Dec 21. 4. Ibison F, Olotu A, Muema DM, Mwacharo J, Ohuma E, Kimani D, Marsh K, Bejon P and Ndungu FM. Lack of Avidity Maturation of Merozoite Antigen-Specific Antibodies with Increasing Exposure to Plasmodium

falciparum Amongst Children and Adults Exposed to Endemic Malaria in Kenya. *PLoS One*. 2012;7(12):e52939. doi:10.1371/journal.pone.0052939. Epub 2012 Dec 26.
5. Ndungu FM, Mwacharo J, Kimani D, Kai O, Moris P, Jonger E, Vekemans J, Olotu A, Bejon P. A Statistical Interaction Between Circumsporozoite Protein-Specific T cell and Antibody Responses and Risk of Clinical Malaria Episodes Following Vaccination with RTS,S/AS01E. *PLoS One*. 2012;7(12):e52870. doi:10.1371/journal.pone.0052870. Epub 2012 Dec 27.
6. Bakshi S and Imoukhuede EB. Malaria Vectored Vaccines Consortium (MVVC). *Human Vaccines* 6:6, 4-5; June 2010.
7. Imoukhuede EB. Vaccine Ventures, International Innovation. *Healthcare*, May 2012, issue 15.