PROGRAM/ RESEARCH GROUP: MU-UCSF Research Collaboration

LOCATION: Kampala, Tororo, Mbarara and several sentinel sites throughout Uganda

INSTITUTIONAL PARTNERS:

Uganda:
Makerere University (MU)
Infectious Diseases Research Collaboration (IDRC) *[an NGO formed by MU College of Health Sciences, MU School of Public Health, and Uganda Ministry of Health]*

UCSF:
School of Medicine, Department of Medicine (HIV/AIDS Division; Division of Infectious Diseases; Division of Experimental Medicine; Center for AIDS Prevention Studies)
School of Pharmacy, Department of Clinical Pharmacy

OBJECTIVES:

Basic research on malaria, HIV, and TB has been ongoing at SFGH since the 1980s. The current collaboration between Makerere University and UCSF investigators began in 1998 with the aims of conducting high-quality malaria research, building capacity through training, and strengthening infrastructure to help integrate research into policy by linking researchers and policy makers. The collaboration focused on characterizing the efficacy of new antimalarial therapies, defining new public health approaches to malaria and understanding the evolution of antimalarial drug resistance in urban and rural Ugandan settings. In 2004, MU and UCSF investigators began studying other infectious diseases including HIV and TB. To date, the scientists of the MU-UCSF Research Collaboration have led 17 clinical trials of infectious diseases involving over 7,500 participants. The scientific leadership of the collaboration currently consists of US and Ugandan Principal Investigators with expertise in HIV, malaria and TB; extensive experience in clinical and translational research; and a track record of developing and overseeing rigorously conducted clinical trials in Uganda. The MU-UCSF Research Collaboration conducts clinical trials and laboratory research in Kampala, Tororo, and Mbarara and supports UMSP surveillance programs and cohort studies throughout Uganda at government health facilities. The collaboration has also sought advice and worked with the Ugandan Ministry of Health and variety of Ugandan country partners to ensure that the research programs are harmonized with local priorities. Since its inception in 1998, the MU-UCSF Research Collaboration has produced over 200 publications, most of which had Ugandan or US trainees as first authors. In addition, the MU-UCSF Collaboration has trained 31 Ugandan researchers in degree accredited programs at UCSF, MU, UC Berkeley and the London School of Hygiene and Tropical Medicine and over 30 UCSF medical students, fellows and post-docs at UCSF.

PRINCIPAL INVESTIGATOR(S):

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PROJECTS:

Novel Strategies to Prevent Malaria and Improve HIV Outcomes in Africa (PROMOTE)

UCSF PI: Diane Havlir; UCSF Investigators: Grant Dorsey, Phil Rosenthal, Deborah Cohan, Edwin Charlebois

Major goals: 1) To evaluate the impact on the incidence of malaria in children of protease-inhibitor based antiretroviral therapy. 2) To evaluate the impact on placental malaria of protease-inhibitor based antiretroviral therapy. 3) To compare the antimalarial protective efficacy of different regimens in children. 4) To evaluate the impacts of different therapies on the selection of resistance in malaria parasites. This Program supports 3 FDA clinical trials, 1 lab-based project and 2 cores.

Program for Resistance, Immunology, Surveillance and Modeling of Malaria in Uganda (PRISM)

UCSF PI: Grant Dorsey; UCSF Investigators: Phil Rosenthal, Bryan Greenhouse, Edwin Charlebois

Major goals: 1) To identify optimal strategies for malaria surveillance in Uganda and estimate the impact of key malaria control interventions. 2) To investigate the role of immunological assays for estimating transmission intensity and predicting disease risk. 3) To identify markers of antimalarial drug and insecticide resistance and investigate the role of these markers as malaria surveillance tools. In addition to the research activities described, this program will place a strong emphasis on local training and capacity building, the transfer of technology, and building strong relationships between researchers and policy makers. This Program supports cohort and entomology studies, large scale surveys, in- and out-patient malaria surveillance programs, immunology and drug and vector resistance lab programs, mathematical modeling, and 2 cores.

Supporting the Implementation of Malaria Prevention and Control Strategies Relevant Ancillary Activities in the Republic of Uganda (PMI/UMSP)

UCSF PI: Grant Dorsey

Major goals: The purpose of this project is to support the implementation of strategies to prevent and control malaria, and relevant ancillary activities in the Republic of Uganda as part of the President's Malaria Initiative (PMI). Activities outlined in this proposal will be carried out by the Uganda Malaria Surveillance Program (UMSP) in collaboration with the Uganda National Malaria Control Program, the Centers for Disease Control and Prevention (CDC), and other partners including: Makerere University School of Public Health, University of California, San Francisco, UC Berkeley School of Public Health, London School of Tropical Medicine and Hygiene, Institute of Tropical Medicine, Antwerp, Belgium, Malaria Consortium Uganda, the Infectious Disease Institute (Uganda).

Sustainable East Africa Research on Community Health (SEARCH)

UCSF PI: Diane Havlir; UCSF Investigators: Edwin Charlebois, Gabe Chamie, Elvin Geng, Vivek Jain, Tamara Clark, Craig Cohen

Major goals: SEARCH is a multinational, multidisciplinary consortium assembled to conduct research that evaluates bold health interventions at the community level that inform policy makers and funding agencies through the inclusion of health, economic and education parameters and through innovative, efficient study designs. The intervention is widespread community HIV testing, treatment of all HIV+ persons, and offering HIV therapy for targeted periods for those at highest risk. We plan to study 32 communities of 10,000 in Uganda and Kenya. HIV testing is done at community health campaigns that diagnose and provide services for hypertension, diabetes, malaria, TB and childhood diseases.

Streamlining care in high CD4, HIV+ adults in Africa (Recapture, EARLI and POV studies)

UCSF PI: Diane Havlir; UCSF Investigators: Elvin Geng, Vivek Jain, Edwin Charlebois

Major goals: 1) to develop a new streamlined care model for HIV+ adults with high CD4 counts; 2) evaluate clinic patients enrolled into and eligible, but not yet enrolled into an ongoing program of a streamlined model of health care delivery in which medical officer visits will occur at 6 month intervals, and pharmacy/nurse only visits will occur at 2 month intervals.

Early Antiretroviral Therapy Intervention to Improve Community Health and Productivity in East Africa (SEARCH pilot studies)

UCSF PI: Diane Havlir; UCSF Investigators: Edwin Charlebois, Gabe Chamie, Elvin Geng, Vivek Jain

Major goals: ongoing research and planning for the Sustainable East Africa Research on Community Health (SEARCH) Collaboration including ethnographic mapping of communities in Uganda and Kenya and pilot community health campaigns.

Reducing Failure-to-Initiate ART: Streamlined ART Start Strategy (START)

UCSF PI: Diane Havlir; UCSF Investigators: Elvin Geng, Edwin Charlebois

Major goals: Test a Streamlined ART Start Strategy (START) in a randomized, controlled trial in 24 clinics in Uganda.

Family-Based HIV VCT in Patients at Risk for TB

UCSF PI: Edwin Charlebois; Key personnel: Diane Havlir

Major goals: To determine the uptake and barriers to HIV VCT among TB evaluation patients offered same day HIV counseling and testing in Kampala, Uganda; to compare VCT utilization between clinic based provision of services and home-based VCT services; and the effectiveness of linking infected persons into locally available medical care and social support systems.

Role of Nutrition in HIV Treatment Outcomes in Pregnant Women and Children

PI: Diane Havlir; Other key personnel: Deborah Cohan

Major goals: Among those with HIV, we will compare measures of HIV RNA, CD4 cell counts to identify nutrition-related predictors of poor virologic and immunologic response to ART in Tororo, Uganda

Antimalarial Pharmacology in HIV Coinfected Children and Pregnant Women in Uganda

UCSF PI: Fran Aweeka

Major goal: To assess the pharmacokinetics and pharmacodynamics of antimalarials in the context of HIV therapy, age, and pregnancy.

Training in Malaria Research in Uganda

UCSF PI: Phil Rosenthal; UCSF Investigators: Grant Dorsey, Diane Havlir, Fran Aweeka

Major goals: Training Ugandan investigators in 1) clinical malaria research, 2) epidemiologic methods relevant to the study of antimalarial drug resistance, and 3) methods of molecular parasitology research pertinent to the study of antimalarial drug resistance.

Research Activities in Support of Malaria Prevention and Control in Uganda (PMI/TES)

UCSF PI: Grant Dorsey

Major goal: To compare the efficacy and safety of 2 artemisinin-based combination therapies (ACT), amodiaquine-artesunate (AQ+AS), and artemether-lumefantrine (AL) for treatment of uncomplicated malaria in children in Uganda conducted at 3 of the Uganda Malaria Surveillance Project (UMSP) sentinel sites.

Resistance of Malaria Parasites to Artemisinin-Based Combination Therapies

UCSF PI: Phil Rosenthal; UCSF Investigators: Grant Dorsey

Major goals: 1) To identify genotypes associated with decreased responses to ACTs in Africa. 2) To assess molecular mechanisms and parasitological consequences of increasing resistance to ACTs. 3) To characterize the specific impacts of parasite polymorphisms on drug sensitivity and fitness.

Comparison of home-based vs. health facility-based management of malaria in Uganda

UCSF Co-investigators: Grant Dorsey, Phil Rosenthal (PI: Staedke - LSHTM)

Major goals: 1) To compare the impact of home-based management of fever/malaria (HBMF) to enhanced health facility-based care on key population-based indicators. 2) To assess the safety and tolerability of AL when given repeatedly in HBMF and health facility-based care programmes. 3) To evaluate the cost-effectiveness of delivering HBMF and enhanced health facility-based care.

Translational studies of antimalarial drug resistance

UCSF PI: Phil Rosenthal

Major goals: (1) Assessment of associations between the complexity and diversity of malaria infections and treatment outcomes. (2) Characterization of the selection of drug resistant malaria parasites. (3) Determination of molecular mechanisms of antimalarial drug resistance.

Discovery of Oxaboroles as New Antimalarial Agents

UCSF PI: Phil Rosenthal

Major goals: (1) Hit-to-lead discovery of oxaborole antimalarials. (2) Lead optimization of oxaborole antimalarials. (3) Characterization of the mechansism of action and resistance for lead oxaboroles.

Effector and regulatory T cell responses and protection from clinical malaria

UCSF PI: Maggie Feeney

Major goals: The specific aims of this study are to: 1) prospectively evaluate the impact of potent chemoprevention on the development of effector T cell responses to P. falciparum among infants; 2) assess the impact of recurrent high-level parasitemia on the development of immune suppresssor mechanisms and T cell dysfunction; and 3) determine whether Pf-specific T cell responses (and induced suppressor populations) are associated with prospective protection from malaria following cessation of chemoprevention.

Immune protection from malaria: age, exposure intensity, and the T cell response

UCSF PI: Maggie Feeney

Major goals: The specific aims of this study are to: 1) To utilize individual-level Pf exposure data to discern the relationship between the malaria-specific T cell response and susceptibility to clinical malaria. 2) To characterize the cytokine and gene expression signatures associated with acute malaria infection, and determine their relationship to biological age and to characteristics of the subsequent adaptive immune response

Patient-Oriented Research and Mentoring in *Pneumocystis*

UCSF PI: Laurence Huang

Major goals: (1) To continue my patient-oriented research in *Pneumocystis*; (2) To expand my research to include other respiratory pathogens, such as *Mycobacterium tuberculosis*; (3) To devote more time to mentor junior patient-oriented researchers interested in pulmonary infections; and (4) To build an international clinical research program in Kampala, Uganda focused on pulmonary infections.

International HIV-Associated Opportunistic Pneumonias (IHOP) Study

UCSF PI: Laurence Huang

Major goals: (1) To determine the frequency and mortality of HIV-associated opportunistic pneumonias in an international, multi-center, longitudinal cohort and to test the hypothesis that

PCP is associated with increased mortality. (2) To estimate the sensitivity and specificity of molecular tools for PCP and TB diagnosis and to test the hypotheses that 60-second oropharyngeal washing (OPW, gargle) specimens combined with polymerase chain reaction (PCR) assays are sensitive tests to diagnose PCP and TB. (3) To test the hypothesis that *P. jirovecii* dihydropteroate synthase (DHPS) gene mutations are associated with an increased morbidity and mortality and to explore potential mechanisms. (4) To characterize the predominant *P. jirovecii* Msg-C variant recognized by antibodies at the 3 study sites, to examine systemic (serum) and local (BAL) antibody responses, and to test the hypotheses that the level of antibodies to the predominant variant is correlated with PCP status.

Lung Microbiome in Cohorts of HIV-Infected Persons (Lung MicroCHIP) Study

Co-PI: Laurence Huang

Major goals: (1) To compare the lung microbiome in subjects with and without HIV infection. (2) To determine whether the degree of HIV-mediated immunosuppression is related to the lung microbiome of HIV-infected subjects without acute illness/pneumonia. (3) To determine the effect of initiation of antiretroviral therapy and opportunistic pneumonia prophylaxis on the lung microbiome of HIV-infected subjects over time. (4) To determine the effects of opportunistic pneumonia and accompanying pneumonia treatment on the lung microbiome of HIV-infected subjects over time. (5) To correlate lung microbiome composition and function with HIV-associated morbidity and mortality.

Oral Wash for Nucleic Acid Diagnosis and Prognosis of TB in HIV-infected Ugandans

UCSF PI: Lucian Davis

Major goals: To determine if nucleic acid amplification tests for *M. tuberculosis* applied to a novel research specimen, oral wash, are accurate and cost-effective for diagnosis of TB in HIV-infected patients and for prediction of the long term risk of treatment failure or relapse.

Human Exosomes for Diagnosis of Tuberculosis

UCSF Co-investigator: Lucian Davis (PI: Dobos, CSU)

Major goal: To develop a robust, inexpensive, simple point-of-care test for accurate diagnosis of tuberculosis for use in high burden, low-income countries, using measurement of exosomes.

Biomarkers for Tuberculosis

UCSF Co-investigator: Lucian Davis (PI: Broaddus)

Major goal: To identify novel biomarkers of TB treatment responses using a variety of nucleic acid markers.

A Novel Proteomic Approach to TB Biomarker Discovery using Human Exosomes

UCSF PI: Lucian Davis

Major goal: To identify novel biomarkers of TB treatment responses using established developmental proteomic assays applied to human exosomes.

MENTORED PROJECTS:

Translational Studies of Plasmodium Falciparum Infection Dynamics

UCSF PI: Bryan Greenhouse; Mentors: Grant Dorsey, Phil Rosenthal

Major Goals: 1) To optimize techniques for high-resolution genotyping of *P. falciparum*. 2) To study the effect of repeated malaria treatment on the outcomes of therapy and selection of drug resistance mutations. 3) To study the spread of drug resistance in a well characterized community in Uganda.

Impact of Chemoprevention on Humoral Antimalarial Immunity

UCSF PI: Bryan Greenhouse; Mentors: Phil Rosenthal, Grant Dorsey

Major goals: (1) To determine whether blood stage *P. falciparum* infection inhibits the development of antibody responses to *P. falciparum* antigens. (2) To determine whether blood stage *P. falciparum* infection inhibits the development of functional memory B cell responses to *P. falciparum* antigens. (3) To determine which patterns of humoral responses are associated with protection from malaria and how these associations are altered by the use of chemoprevention.

Differences in Humoral Immune Response to Plasmodium Falciparum in HIV-1-infected and HIV exposed/uninfected Ugandan Children

UCSF PI: Chris Keh; Mentors: Bryan Greenhouse, Nixon

Major goals: (1) To compare the differences in antimalarial antibody responses in HIV-1 positive and negative children living in Tororo, Uganda.(2) To describe qualitative differences in the function of B cell responses in HIV-1 positive and negative children living in Tororo, Uganda.

The impact of parasitemia on the development of cellular immune responses to malaria

PI: Pras Jagannathan; Mentors: Maggie Feeney, Grant Dorsey, Diane Havlir

Major goals: To evaluate whether parasitemia impacts the development of pre-erythrocytic immunity to malaria. Award provides funds for research supplies, travel, and capacity development at overseas site.

Molecular Epidemiology and Geospatial Analysis of TB Transmission in Uganda

UCSF PI: Gabe Chamie; Mentor: Diane Havlir

Major goals: This project will advance our understanding of how TB is spreading through a rural community with a generalized HIV epidemic in East Africa and serve as the foundation for developing novel ways to disrupt TB transmission and reduce TB mortality through early diagnosis and intensified case-finding.

The Impact of Household Ventilation on Transmission of Tuberculosis Among Household Contacts of Active Tuberculosis Patients in Kampala, Uganda (FreshAIR)

UCSF PI: Gabe Chamie; Mentor: Diane Havlir

Major goals: This proposal seeks to describe determinants of ventilation in 200 homes in Kampala with a standardized survey tool, to correlate them to measures of home ventilation in air changes per hour (ACH) using an innovative carbon dioxide (CO_2) tracer decay technique, and to conduct a case-control study comparing ACH in homes with and without demonstrated TB transmission to determine the impact of ventilation on household TB transmission.

Immunodiagnosis of active tuberculosis

UCSF PI: Adithya Cattamanchi; Mentor: Laurence Huang, Philip Hopewell

Project goals: 1) To evaluate peripheral blood interferon-gamma release assays for diagnosis of active TB in HIV-infected individuals; 2) To develop a lung-based approach to assessment of interferon-gamma responses for diagnosis of active TB; 3) To identify novel immunological biomarkers of active TB in HIV-infected individuals.

Tuberculosis Guideline Observation and Adherence in Low-income countries (TB GOAL)

UCSF PI: Adithya Cattamanchi; Mentor: Laurence Huang

Project goals: To develop a multi-faceted intervention to improve provider adherence to guidelines for evaluation of TB suspects. The pilot study tests the following components: 1) Interactive educational modules; 2) Same-day microscopy; and 3) Performance feedback.

Early Mortality in HIV Infected Patients Starting Antiretroviral Therapy in Africa

UCSF PI: Elvin Geng; Mentor: Diane Havlir

Major goal: To understand the magnitude and determinants of early mortality on ART in HIV infected patients in Africa in order to develop a targeted intervention in the future to reduce it.

HIV Disease Progression in African Children

UCSF PI: Ted Ruel; Mentor: Diane Havlir

Major goals: Data and samples from an observational cohort in Kampala Uganda will be utilized to compare, by HIV subtype, the rates of disease progression, the prevalence and evolution of CXCR4 tropism, the levels of proviral HIV DNA in naive and memory lymphocytes.

PRIMARY FUNDING:

IDRC is both a prime and subrecipient of awards from governmental and private sources:

- U.S. National Institutes of Health (NIH) and Fogarty International Center (FIC)
- U.S. PHS Centers for Disease Control (CDC)
- Bill and Melinda Gates Foundation (Gates)
- European Developing Countries clinical Trials Partnership (EDCTP)
- Doris Duke Charitable Foundation (DDCF)
- Centers for AIDS Research (CFAR)
- Uganda National Council for Science and Technology (UNCST)
- ACT Consortium

Total annual funds subcontracted from UCSF to IDRC (in 2011): $6,673,595.

PROGRAM/ RESEARCH GROUP: **GIVI – IDI Research Collaboration**

LOCATION: Kampala

INSTITUTIONAL PARTNERS:

Gladstone Institute of Virology and Immunology (GIVI), Infectious Diseases Institute (IDI) of Makerere University, Accordia Global Health Foundation, UCSF Department of Epidemiology and Biostatistics

OBJECTIVES: To develop collaborative research partnerships that would further basic and translational science capacity in East Africa.

PROJECT:

- **Mechanisms of CD4 T-cell death among HIV-infected, HAART-treated African adults displaying poor CD4 T-cell reconstitution despite effective vital suppression:** The project's aim is to gain understanding of cell death pathways operating in HIV-infected subjects that respond poorly to HAART, which could guide future development of targeted therapies to optimize immune cell recovery.

PRINCIPAL INVESTIGATOR(S): Damalie Nakanjako, Stefanie Sowinski, Warner Greene, Yukari Manabe

KEY PROGRAM STAFF: UCSF: Stefanie Sowinski, Warner Greene
Uganda: Damalie Nakanjako, Olive Mbabazi, Yukari Manabe

PRIMARY FUNDING: UCSF-GIVI CFAR International Mentored Scientist Award

AFFILIATED STUDIES:

- **The Tuberculosis-Cryptococcus-Cardiovascular Disease (TB-Crypto-CVD) Cohort:** A prospective observational study that is initiating antiretroviral therapy among HAART-naive patients, in the Kiboga District Hospital HIV treatment program, with CD4 counts<350 cells//UL. Routine screening will be performed for tuberculosis as well as crytococcal meningitis at the time of initiation of HAART and monthly thereafter for the first six months of therapy. The effects of interventions will be assessed on early morbidity and mortality over the 18 months of follow-up. *[Fogarty International Center]*

PROJECT:

- **Biomarkers That Predict the Response of AIDS-Related Kaposi's Sarcoma to Antiretroviral Therapy and the Risk of Developing Immune Reconstitution Inflammatory Syndrome:** The aim of this study is to identify biomarkers that can predict clinical responses in Kaposi's Sarcoma (KS)-AIDS patients to HAART, such as KS regression and immune reconstitution inflammatory syndrome (IRIS). Peripheral blood mononuclear cells and plasma samples from 224 clinically well-characterized Ugandans with AIDS-related KS will be analyzed by flow cytometry to identify such biomarkers.

UGANDA

PRINCIPAL INVESTIGATOR(S): Stefanie Sowinski, Jeff Martin, Warner Greene

KEY PROGRAM STAFF: UCSF: Stefanie Sowinski, Jeff Martin, Warner Greene, Marielle Cavrois
Uganda: Olive Mbabazi, Yukari Manabe

PRIMARY FUNDING: UCSF-GIVI Center for AIDS Research Pilot Award in HIV-Associated Malignancies

AFFILIATED STUDIES:

- Antiretroviral Therapy for AIDS-Related Kaposi's Sarcoma in Africa [*Jeff Martin]*

PROGRAM/ RESEARCH GROUP: IeDEA-East Africa Regional Consortium (International Epidemiologic Database to Evaluate AIDS)

LOCATION: Sites throughout Kenya, Tanzania, and Uganda

INSTITUTIONAL PARTNERS:

- USA: UCSF, Indiana University, Columbia University, New York University, NIH
- Kenya: Moi University School of Medicine, Kenya Medical Research Institute (KEMRI)
- Tanzania: National AIDS & STI Control Programme (NASCOP)
- Uganda: Mbarara University of Science and Technology (MUST), Rakai Health Sciences Program, Infectious Diseases Institute (IDI)
- Ministries of Health of Kenya, Tanzania, and Uganda
- Seven regional cross-continent IeDEA consortia (East Africa plus Central Africa, West Africa, South Africa, North America, South America, and Asia)

OBJECTIVES:

- Establish an international research consortium in East Africa to address unique and evolving research epidemiologic and clinical questions in the field of HIV/AIDS which are unanswerable by single cohorts;
- Establish protocols to harmonize routine data collected during the course of clinical care at a variety of care facilities for HIV throughout East Africa;
- Develop methods to overcome limitations in accuracy and completeness of data collected in routine care sites in resource-limited areas;
- Provide training and mentoring to emerging African scientists and data managers;
- Share data within the IeDEA worldwide consortium (7 regions throughout the world)

PRINCIPAL INVESTIGATOR(S) at UCSF: Jeffrey Martin and Craig Cohen

PROJECTS/ SPECIFIC AIMS:

This dynamic cohort follows over 120,000 HIV-infected adults and 20,000 HIV-infected children who receive their clinical care at one of 42 different health care facilities throughout Kenya, Uganda, and Tanzania. Data collected during the course of routine clinical care are captured in electronic medical record systems at each site and then harmonized centrally. These data plus other enhanced measurements made for purposes of research form the basis of the IeDEA database. A wide array of projects are ongoing, including:

- Trends over time in which patients begin ART
- Sampling-based approaches to eliminate biases conferred by losses to follow-up
- Durability of first-line ART regimens and predictors of treatment failure
- Patterns of pregnancy and reproductive outcomes
- Incidence and determinants of mortality after starting ART
- Time and motion studies in the evaluation and treatment of TB
- Impact of ART on the incidence of KS and survival after KS diagnosis.
- Cost-effectiveness strategies for optimizing HIV infection management

PRIMARY FUNDING: NIAID, NCI, NICHD

PROGRAM/ RESEARCH GROUP: Uganda AIDS Rural Treatment Outcomes (UARTO)

LOCATION: Mbarara, Uganda

INSTITUTIONAL PARTNERS:

- Mbarara University of Science and Technology (MUST)
- Infectious Diseases Institute
- Walter Reed Medical Research Institute
- Harvard University
- Massachusetts General Hospital
- Simon Fraser University
- British Columbia Center for Excellence in HIV/AIDS

OBJECTIVES:

UARTO refers to Uganda AIDS Rural Treatment Outcomes. The UARTO Cohort consists of a consecutive volunteer sample of 650 HIV-infected adults, enrolled between 2005 and 2012, who are about to initiate antiretroviral therapy at the Immune Suppression Syndrome (ISS Clinic) in Mbarara, Uganda. The ISS Clinica is a prototypical municipal HIV/AIDS clinic that has arose during the roll-out of antiretroviral therapy in sub-Saharan Africa in the past decade. Approximately 65% of the subjects are women, and the median age at cohort outset is 34 years old. Subjects are examined at 4 month intervals with questionnaires investigating a variety of domains including medication use and adherence, physical symptoms, physical and psychosocial quality of life, mental health, sexual behavior, reproductive behavior, recreational substance abuse, and food security. A novel wireless adherence device provides real-time data on medication use. Linkage to the underlying data collected at the ISS Clinic through the IeDEA Consortium adds richness to the available measurements. In addition to real-time plasma HIV RNA levels and CD4+ T cell counts, there is robust biological specimen collection including storage of serum, plasma, saliva, and peripheral blood mononuclear cells. To date, the median follow-up is over 4 years with several subjects contributing more than 6 years. Community-based tracking of lost subjects has resulted in only 10% of subjects having unknown vital status at 6 years.

The overarching objective of UARTO is to serve as an infrastructural resource to investigate a variety of aspects concerning the biological and behavioral determinants of virologic, immunologic and clinical outcomes among patients who are initiating antiretroviral therapy in sub-Saharan Africa. Through a simple application process, interested investigators have access to a wide variety of research-level questionnaire-derived measurements, biological measurements, and biological specimens. Investigators may also use the cohort to add on novel measurements on all or a selected fraction of the population.

INVESTIGATORS at UCSF: Jeffrey Martin, Peter Hunt, Elvin Geng, Judy Hahn, Sheri Weiser, Steve Deeks, Sulggi Lee, Deanna Kroetz, Milo Santos, Toby Maurer, Christina Yoon, Adithya Cattamanchi, Helen Byakwaga, Steven Asiimwe.

PRIMARY FUNDING:

- NIMH, NIAID
- UCSF-GIVI CFAR Clinical/Population Sciences Core

PROGRAM/ RESEARCH GROUP: Uganda-UCSF Research Training in HIV-Associated Malignancies

LOCATION: Kampala, Hoima, Kiboga, Kyankwanzi Districts

INSTITUTIONAL PARTNERS:

- Infectious Diseases Institute
- Uganda Cancer Institute
- Uganda Ministry of Health

OBJECTIVES:

In sub-Saharan Africa, the catastrophic intersection between the HIV epidemic and the endemic nature of Kaposi's sarcoma-associated herpesvirus (KSHV) infection has resulted in Kaposi's sarcoma (KS) becoming the most common malignancy amongst adults -- and an important threat in children -- in many parts of the region. Emerging data indicates that the single largest obstacle to prevention of KS morbidity and mortality in Africa is late stage diagnosis. We therefore hypothesize that the fastest route to the greatest public health impact on cancer in Africa is by detection of KS in its earliest stages, at a time when antiretroviral therapy (ART) alone is most effective. While early KS diagnosis in Africa is attractive, there are challenges at many levels – all of which can be remedied with training. Therefore, the overarching aim of this training grant is to build a multidisciplinary research team poised to promote and investigate early KS diagnosis in Uganda and to perform research on the epidemiology, clinical course, and treatment of KS in the ART era. The specific aims are to:

1) Train several hundred community health workers and traditional healers in Uganda in the promotion of early recognition of KS in the community and of early presentation to health care providers;
2) Instruct several hundred health care providers in Uganda in the clinical recognition of early KS and in the conduct of simple bedside skin punch biopsies for the pathologic confirmation of KS;
3) Educate four Ugandan pathologists in the field of dermatopathology and arm them with suitable reagents for the specific and sensitive histopathologic diagnosis of KS;
4) Comprehensively train five emerging Ugandan scientists in the methods of clinical research to transform them into independent principal investigators to study a variety of aspects of KS; and
5) Develop a cadre of three Ugandan clinical research coordinators in order to play a vital support role on multidisciplinary research teams that investigate KS in the ART era.

At the conclusion of this three-year training program, we will have assembled a multidisciplinary team of health care professionals and researchers which is able to: a) study the optimal approach to encourage early diagnosis of KS; b) understand which patients still develop KS in the ART era; c) document the impact of early KS diagnosis on survival; and d) conduct clinical trials to optimize the treatment of early diagnosed KS. Once established, the approach to early KS detection can be used as a model for other cancers as well.

INVESTIGATORS at UCSF: Jeffrey Martin, Paul Volberding, Phil LeBoit, Tim McCalmont, Beth Ruben, Toby Maurer, Erin Amerson, Peter Hunt, David Glidden

PRIMARY FUNDING: NCI

PROGRAM/ RESEARCH GROUP: **Prevention & Public Health Group (PPHG)**

LOCATION: Kampala and surrounding area (Mpigi District)

INSTITUTIONAL PARTNERS:

Makerere University School of Public Health (MakSPH), CDC-Uganda, Uganda Ministry of Health, Uganda Virus Research Institute (UVRI), Makerere University-Johns Hopkins University Research Collaboration (MU-JHU Care), Mulago National Hospital

OBJECTIVES:

- Training of in-country professionals, evaluation of data to inform policy, conduct of research, and capacity building.
- Technical assistance and mentoring in surveillance methodologies, core and ancillary survey design, implementation, evaluation, and use.

PROJECT:

- **Provision of Technical Assistance to Strengthen HIV Strategic Information Activities and Monitoring and Evaluation Systems for PEPFAR Implementing Partners in the Republic of Uganda (META):** This 5-year Cooperative Agreement (2009-2014) with CDC-Uganda aims to provide training and capacity building in M&E to CDC implementing partners, and to support strengthening of national M&E systems.

- This activity includes TA to harmonize national M&E and health information systems, and contribute to the development of a Center of Excellence in M&E at MakSPH.

PRINCIPAL INVESTIGATOR: Christina Lindan

KEY PROGRAM STAFF: Julia Fleuret, Rachel King (Uganda)

PRIMARY FUNDING: CDC-Uganda

PROJECTS:

- **Primary HIV Prevention in Pregnant and Lactating Ugandan Women: A Randomized Trial:** To evaluate an extended HIV retesting and enhanced counseling intervention to help HIV-negative pregnant women remain HIV-free throughout pregnancy and breastfeeding.

- Makerere University-Johns Hopkins University HIV Clinical Trials Unit *(ended in 2012)*

- Collaboration with the CDC-Uganda to establish family-based comprehensive HIV care services within government health facilities

UGANDA

PRINCIPAL INVESTIGATOR: Jaco Homsy (Uganda)

KEY PROGRAM STAFF: Donna Langston

PRIMARY FUNDING: National Institute of Child Health and Human Development (NICHD), Johns Hopkins, CDC

PROJECT:

- **Enhanced HIV Prevention in the Republic of Uganda under the President's Emergency Plan for AIDS Relief (PEPFAR):** To increase reported risk reduction practices by high risk women and their partners by integrating biomedical, behavioral and structural interventions using combination prevention packages at multiple levels. The Enhanced Prevention Project includes the development of a detailed monitoring and evaluation framework with specific indicators, data sources, and data analysis plan for implementation planning that specifies the project activities, roles and responsibilities.

PRINCIPAL INVESTIGATOR: Rachel King

PRIMARY FUNDING: CDC

PROJECT:

- **Evaluating a Web-based Electronic Medical Records (WEMR) system:** To develop and pilot test an WEMR system using unique identifiers linked with targeted phone messages to link up to 20 health facilities in Kampala and Mpigi District, Uganda. The project's aim is to improve long-term retention of HIV-infected and uninfected pregnant women and their infants in post-natal care, and to evaluate the feasibility and impact of this system to allow medical providers to access real-time data, deliver care, and reduce loss to follow-up among mothers following pregnancy

PRINCIPAL INVESTIGATOR(S): Zikulah Namukwaya, Andrew Abutu

KEY PROGRAM STAFF: Donna Langston

PRIMARY FUNDING: CDC-DGHA, Atlanta

AFFILIATED STUDIES:

- **Comparative effectiveness of pediatric HIV disclosure interventions in Uganda** *[Lisa Butler, R21 through NICHD] :* To test the effectiveness, cost and cost-effectiveness of an innovative, cognitive-behavioral intervention designed to support developmentally-appropriate disclosure to HIV-infected children by their caregiver.

- Ongoing technical assistance to the Centers for Disease Control and Prevention, Global AIDS Program (CDC-GAP) in Uganda and Ghana. *[Lisa Butler]*

PROGRAM/ RESEARCH GROUP: Global Health Group

LOCATION: Various

INSTITUTIONAL PARTNERS: Living Goods, PACE

OBJECTIVES:

- The UCSF Global Health Group is an "action tank," dedicated to translating major new paradigms in global health into large-scale action, to positively impact the lives of millions of people. Since its establishment in 2007, the Global Health Group has conducted new research, synthesized evidence, and convened high level groups of experts to inform critical policy decisions and answer practical questions. Leveraging the expertise of its small team based in San Francisco, the Global Health Group works with a wide network of partners to gain insight, forge broad consensus, catalyze action, and implement solutions in countries. The Group's three core initiatives focus on:
    - Providing practical and intellectual support for the **elimination of malaria**
    - Strengthening the **role of the private sector** in delivery of healthcare
    - **Translating evidence into policy** to support informed debate on current global health issues

PRINCIPAL INVESTIGATOR(S): Sir Richard Feachem
Dominic Montagu (PSHi)

KEY PROGRAM STAFF: Elizabeth Brashers
Anna De La Cruz (PSHi)

PROJECTS:

- The **Private Sector Healthcare Initiative (PSHi)** specializes in documenting and advancing understanding of innovative platforms to engage the private sector in strengthening delivery of health services in low- and middle-income countries. Since 2008 the Initiative has conducted a significant program of research on social franchising, in collaboration with implementers and other partners, to document and evaluate this innovative platform, including: supporting a community of practice of 55 social franchises around the world, documenting scope, scale and impact of services provided, evaluating service expansion and cost effectiveness, and supporting development and implementation of quality standards and reporting. In Uganda, PSHi liaises with a series of social franchises:
    - Living Goods (launched in 2007): provides reproductive health, maternal child health and malaria testing and treatment services through 686 outlets (mobile health workers) in 22 provinces, via an "Avon Lady" approach;
    - PACE ProFam (affiliate of Population Services International, launched in 2008): provides reproductive health, HIV and malaria screening and treatment and maternal child health services through 119 outlets in 51 provinces.

PRIMARY FUNDING: Rockefeller Foundation; Results for Development (Gates)

PROGRAM/ RESEARCH GROUP: University of California San Francisco-Gladstone Institute of Virology and Immunology Center for AIDS Research (UCSF-GIVI CFAR)

LOCATION: CFAR supports international collaborative research in numerous sites, with a focus on East Africa (Uganda, Kenya).

INSTITUTIONAL PARTNERS:

Uganda: Makerere University, Infectious Diseases Institute (IDI) at Makerere University, Infectious Diseases Research Collaboration (IDRC), Mbarara University of Science and Technology (MUST)
Kenya: Kenya Medical Resarch Institute (KEMRI)

OBJECTIVES:

- The UCSF-GIVI CFAR coordinates a robust program focused on interdisciplinary HIV research occurring at the intersections of basic, clinical, behavioral/ epidemiological, and translational scientific disciplines. Our Center's central goal is facilitating scientific progress in HIV disease by providing the broadest community of member investigators across our distributed research environment with direct services and indirect resources, such as access to emerging technologies and the availability of five (5) dynamic scientific cores.

PRINCIPAL INVESTIGATOR(S)/ CO-DIRECTORS:

Paul A. Volberding – Director, UCSF AIDS Research Institute; Director of Research, UCSF Global Health Sciences

Warner C. Greene – Director, Gladstone Institute of Virology and Immunology

KEY PROGRAM STAFF: Sara Burke, CFAR Program Manager

SCIENTIFIC CORES:

Our scientific cores operate within a larger network of clinical and scientific laboratories housed on the various UCSF campuses. These laboratories provide member investigators with access to a wide array of specialized services and significant technical expertise, including the development of unique diagnostic assays, genomic tests and similar tools.

- Clinical and Population Sciences Core:

  Provides consultation on all aspects of trial design, management, and analysis. Specimens from local Core-managed cohorts are stored with the Specimen Banking Core *[Co-Directors: Steven Deeks, Jeffrey Martin]*

- Immunology Core:

  Provides state-of-the-art immune phenotype and function assay services in support of innovative translational studies to improve the prevention or management of HIV disease and its complication. *[Director: Elizabeth Sinclair]*

- Pharmacology Core:

  Core services include development, validation, and application of innovative or specialized pharmacologic assays to support CFAR scientists. The Core is able to work with scientists to develop assays and tools to meet their project needs. *[Director: Francesca Aweeka]*

- Specimen Banking:

  Provides expertise and an infrastructure for the collection, processing and storage of biospecimens for CFAR and to many cohorts and clinical studies. *[Co-Directors: John Greenspan, Yvonne DeSouza]*

- Virology Core:

  Development and implementation of molecular diagnostic assays and analysis tools with strict adherence to rigorous operational procedures and quality assurance programs. *[Co-Directors: Teri Liegler, Joseph Wong]*

In addition, the CFAR's developmental and mentorship programs help to ensure a strong future for scientific research through its awards programs and a model mentorship program.

PROJECTS:

- See project listing for international developmental awards involving African institutions (attached spreadsheet)

PRIMARY FUNDING: National Institute of Allergy and Infectious Diseases (NIAID)

Total CFAR funding for international developmental awards involving African institutions (including subcontracts) for 2007-2012: $2,585,512**.**