VACCINE TRIALS

2015

A. Completed studies:

RV 156: A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of a Multiclade HIV-1 DNA Plasmid Vaccine, VRC-HIVDNA009-00-VP, in Uninfected Adult Volunteers in Uganda.

Site Principal Investigator: Fred Wabwire-Mangeni, MBChB, PhD

Collaborations: Vaccine study conducted by US military Research Program and Makerere University Walter Reed Project. Vaccines provides by Vaccine Research Centre VRC/NIAID/NIH Bethesda Maryland.

Background and rationale: the global impact of the HIV epidemic is staggering. In developing countries and segments of the US population, anti-HIV therapies are frequently beyond financial reach. Accordingly effective, low cost tools for HIV prevention such as vaccine are urgently needed to bring the HIV epidemic under control. The VRC, DAIDS/NIAID/NIH are committed to devt of a safe, effective vaccines to prevent HIV infections and AIDS worldwide**.**

Study design: A Phase 1, randomized, controlled, double-blinded clinical trial

Study population, duration, and sample size: 30 Healthy adult volunteers (18 to 40 years), followed for 13 months.

Study objectives:

Primary; to evaluate the safety and tolerability of VRC-HIVDNA009-00-VP IN A Ugandan population when administered intramuscularly using a needle-free injection system at a dose of 4.0 mg

Secondary; to evaluate the immunogenicity of VRC-HIVDNA009-00-VP in a Ugandan population when administered at a dose of 4.0 mg using a needle-free injection system. The HIV-1 Gag-Pol-Nef and Env-specific cellular and humoral immune responses were assessed.

Start date:
Enrollment status: 31 participants.
Study status: Completed
Results:

RV 172: A Phase I/II Clinical Trial to Evaluate the Safety and Immunogenicity of a Multiclade HIV-1 DNA Plasmid Vaccine, VRC-HIVDNA016-00-VP, Boosted by a Multiclade HIV-1 Recombinant ADENOVIRUS-5 Vector Vaccine, VRC-HIVADV014-00-VP, in HIV Uninfected Adult Volunteers in East Africa" This site enrolled 144 volunteers.

Site Principal Investigator: Hannah Kibuuka MBChB, MMED, MPH

Collaborations: Vaccine study conducted by US military Research Program, Makerere University Walter Reed Project, US Army military research Unit-Kenya. Mbeya Medical research program,

armed forces research institute of medical services (AFFRIMS). Sponsored by Division of AIDS (DAIDS), NIH, and DHHS.

Background and rationale: in the developing world the HIV/AIDS epidemic continues to accelerate**.** The global impact of the HIV epidemic is staggering. . In developing countries and segments of the US population, anti-HIV therapies frequently beyond financial reach. Accordingly effective, low cost tools for HIV prevention such as vaccine are urgently needed to bring the HIV epidemic under control.

Study design: a multicenter, randomized, placebo controlled, double blind trial conducted at three sites in East Africa.

Study population, duration, and sample size: 324 Healthy (186 receiving vaccine and 138 placebo), HIV-1 uninfected adult volunteers (18 to 50 years), at 3 study sites in East Africa. Study lasted 14 to 16 months per participant.

Primary objectives

Part A

- Evaluate the safety and tolerability of VRC HIV-1 recombinant adenovirus-5 vector (rAd5) vaccine at either 10^{10} particle units (PU) or 10^{11} PU in HIV-1 uninfected adults.
- Evaluate the safety and tolerability of three VRC HIV-1 DNA-six-plasmid vaccine doses at 4.0 mg/dose in HIV-1 uninfected adults.
- Evaluate the safety and tolerability of three VRC HIV-1 DNA-six-plasmid vaccine doses at 4.0 mg/dose boosted with VRC HIV-1 rAd5 vaccine at either 10^{10} PU or 10^{11} PU in HIV-1 uninfected adults.

Part B

- Evaluate the safety and tolerability of three VRC HIV-1 DNA-six-plasmid vaccine doses at 4.0 mg/dose boosted with VRC HIV-1 rAd5 vaccine at 10^{10} PU in HIV-1 uninfected adults.
- Evaluate the immunogenicity of three VRC HIV-1 DNA-six-plasmid vaccine doses at 4.0 mg/dose boosted with VRC HIV-1 rAd5 vaccine at 10^{10} PU in HIV-1 uninfected adults.

Enrolment status: 144 participants.
Study status: Completed

RV 156A: "A Phase I Clinical Trial to Evaluate the Safety and Immunogenicity of a Multiclade HIV-1 Recombinant Adenovirus-5 Vector Vaccine, VRC-HIVADV014-00-VP Administered Alone or Administered as a Boost To A Multiclade HIV-1 DNA Plasmid Vaccine, VRC-HIVDNA009-00-VP, in Uninfected Adult Volunteers in Uganda. Study follow up completed but manuscript development is ongoing.

Site Principal Investigator: Fred Wabwire-Mangeni, MBChB, PhD

Collaborations: US Military HIV research program and Makerere University-Walter Reed Project Makerere University Kampala, Uganda

Background and rationale: As noted in the original RV 156 protocol, the DNA plasmid vaccine delivered here is part of a prime-boost strategy using attenuated and genetically modified Adenovirus type 5 as a boost

Study design: This is a single site, Phase I, open label study with accrual restricted to current volunteers in RV 156. All volunteers (placebo and DNA vaccine recipients alike) who meet entry criteria will receive open label VRC HIV rAd5 vaccine at 10^{10} PU by needle injection(a prime boost) into the deltoid muscle.

Study population, duration, and sample size: 29 Healthy (18 to 40 years old), HIV-1-uninfected adult volunteers currently enrolled in RV 156. Study participant is 13 months per participant

Primary objectives were;

- Evaluate the safety and tolerability of VRC HIV-1 recombinant adenovirus-5 vector (rAd5) vaccine alone at 10^{10} particle units (PU) in HIV-1 uninfected adults in Uganda, i.e. among placebo DNA vaccine recipients from RV 156.
- Evaluate the safety and tolerability of VRC HIV-1 recombinant adenovirus-5 vector (rAd5) vaccine as a boost to three doses of VRC HIV-1 DNA four-plasmid vaccine at 4.0 mg/dose in HIV-1 uninfected adults in Uganda, i.e. among DNA vaccine recipients from RV 156.

Enrolled 18 enrolled of the 21 available participants.
Study status: Completed

RV 247: A Phase IB study to evaluate the safety and Immunogenicity of an Ebola DNA Plasmid Vaccine, VRC-EBODNA023-00VP, and a Marburg DNA Plasmid Vaccine VRC-MarDNA 025-00-VP in Health adults in Kampala Uganda. The site enrolled 108 participants who have completed follow-up. Manuscript in final stages.

Site Principal Investigator: Hannah Kibuuka MBChB, MMED, MPH

Collaborations: The US Military HIV Research Program (MHRP), Makerere University Walter Reed Project (MUWRP) Makerere University, Kampala, Uganda

Background and rationale: Ebola AND Marburg haemorrhagic fevers are relatively rare but are associated with a high mortality rate. The fatality rate during previous outbreaks has ranged from 50% to 90%, with death occurring 6 to 16 days after the onset of symptoms. At present, there is no effective treatment for both filo viruses yet both viruses pose a risk to national and global security. The overall goal of the VRC filo virus vaccine development plan is to develop a vaccine regimen that would be effective in prevention of both Ebola and Marburg infections.

Study design: Part I is a randomized, double-blind, placebo-controlled, study to evaluate safety, tolerability, and immunogenicity of 2 recombinant deoxyribonucleic acid (DNA) vaccines. Part II of this study is placebo-controlled and will evaluate concomitant administration of the Ebola and Marburg vaccines that are evaluated separately in Part I.

Study population, duration, and sample size: enrolled 108

Primary objectives:

1. To evaluate the safety and tolerability of VRC-EBODNA023-00-VP at a dosage of 4 mg administered intramuscularly on a 3 injection schedule using a needle-free injection system in healthy adults 18 years to 50 years old.

2. To evaluate the safety and tolerability of VRC-MARDNA025-00-VP at a dosage of 4 mg administered intramuscularly on a 3 injection schedule using a needle-free injection system in healthy adults 18 years to50 years old; and

3. To evaluate the safety and tolerability of VRC-EBODNA023-00-VP and VRCMARDNA025-00-VP at a dosage of 4 mg each administered intramuscularly on a 3 injection schedule using a needle-free injection system in healthy adults 18 years to 50 years old.

Start date: 11 Aug 2009
Enrolment status; A total of 108 participants were enrolled into the study.
Study status: Completed, manuscript drafting and publication
Results: Results demonstrate that both vaccines are safe and immunogenic

B. On-going studies:

RV 262: A phase I study to evaluate the safety and immunogenicity of PENNVAX- G DNA (ENV & GAG) administered by intramuscular Biojector 2000 or Cellectra intramuscular electroporation device followed by MVA-CMDR (HIV-1 CM 235 ENV/CM240 GAG/POL) boost in healthy, HIV uninfected adults. The site enrolled 40 participants for this multisite study. All participants have completed all scheduled study visits.

Site Principal Investigator: Hannah Kibuuka MBChB, MMED, MPH

Collaborations: U.S. Military HIV Research Program, Rockville, MD, U.S.A, U.S. Army Medical Research Unit-Kenya and Kenya Medical Research Institute, Nairobi, Kericho, Kenya, Makerere University-Walter Reed Project, Makerere University Kampala, Mbeya Medical Research Program (Mbeya Referral Hospital, Mbeya Regional Medical Office)

Background and rationale:

Study design: Part A: Open-label, safety and tolerability study to be conducted at one clinical site (Rockville Vaccine Assessment Clinic (RVAC) in Rockville, MD, USA) in 12 healthy, HIV-uninfected adult participants. **Part B:** Randomized, placebo-controlled, double blind study to start after the product has been assessed as safe and tolerable in Part A.

Part B will be conducted at three sites: Kericho, Kenya; Kampala, Uganda; and Mbeya, Tanzania. A total of twenty participants each will be enrolled in Kenya and Tanzania.
Participants will be randomized 4:1 to active study drug vs. placebo (normal saline).

Study population, and sample size: study population will consist of 80 healthy, HIV uninfected adult participants between the ages of 18 to 49 years of age at the time of study enrolment. The total study population is 92.

Study duration: 15 months of study visits with screening included (active study phase). Participants will be contacted in 9 month periods for a total of 18 months following the 15 month active study phase.

General Research Objective:
The primary objective is to evaluate the safety and tolerability of PENNVAX™-G DNA (env & gag) administered by IM Biojector® 2000 or IM CELLECTRA® electroporation followed by IM MVA-CMDR (HIV-1 CM235 env/ CM240 gag/pol) boost in healthy HIV-uninfected adult participants.

Start date: 04 May 2012
Enrolment status: 42 participants
Study status: Passive follow up of study participants, until June 2015

SALIF/Protocol TMC278IFD3002: A Phase 3b Randomized Open Label Clinical Trial to Demonstrate Non inferiority in Virologic Response Rate to HIV in RNA Suppression<400 copies/ml of TDF/FTC/RPV Versus TDF/FTC/EFV in First Line Antiretroviral NNRTI-based Suppressed Patients.

Site Principal Investigator: Francis Kiweewa, MD
Collaborations: Clinical research Africa limited (CRO)-Study monitoring in Africa, MUWRP, Janssen-Cilag International, Belgium (Sponsor).

Background and rationale: Rilpivirine (RPV or TMC278) is potent non-nucleoside reverse transcriptase inhibitor with invitro activity against wild type HIV-subtype 1 and NNRTI-resistant mutants. Rilpivirine is also able to combine the convenience of once daily dosing with potential antiviral effects and a good tolerability/safety profile. RPV is approved in the European Medicines Agency for treatment of HIV-1 infection in combination with other ARV medicines in ARV treatment naïve adults with a VL <100,000 copies/ml. and by the US FDA and not yet approved by the Government of Uganda.

Study design: 48 week, multicenter, multinational, open label, randomized phase 3b study

Study population, duration, and sample size: approximately 426 HIV-1 infected subjects, currently with HIV-1 RNA suppression < 50 copies/ml on their first line ARVregimen (NNRTI-based), will be randomised

Primary objective is to compare Non inferiority in Virologic Response Rate to HIV in RNA Suppression<400 copies/ml of TDF/FTC/RPV Versus TDF/FTC/EFV in First Line Antiretroviral NNRTI-based Suppressed Patients.

Study status: participant enrolment closed. 25 participants have been enrolled at our site and are still being followed through until the last participant reaches week 48.

C. UPCOMING/PLANNED STUDIES:

RV 398: Safety and Virologic Effect of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), With Broad HIV-1 Neutralizing Activity, Administered Intravenously to Adults During Early Acute HIV Infection. To enrol at least 6 acute infections arising from RV 217

Site Principal Investigator: Francis Kiweewa, MBChB, MMED, MPH
Collaborations: U.S. Military HIV Research Program, Silver Spring, MD Makerere University-Walter Reed Project, Makerere University, Kampala, Uganda in Collaboration with Vaccine Research Center, NIAID, NIH

Background and rationale: The incidence of new infections in 2012 is reported by the Joint United Nations Programme on HIV/AIDS (UNAIDS) as 2.3 million new cases. Long-term use of antiretroviral therapy (ART) in HIV-positive persons may be challenged by the need for high-level adherence, development of drug resistance, toxicities, and cost. There is, therefore, a growing interest and need for the development of curative approaches for HIV that include treatment strategies that confer durable virologic control while limiting the requirement for continual ART.
Study design: This is a Phase I double-blinded, placebo controlled study of the safety and impact of broadly neutralizing monoclonal antibody (mAb) therapy with VRC01 on viral dynamics in acute HIV infection, alone or in combination with antiretroviral therapy (ART).

Study population, duration, and sample size: Twenty-four subjects will be enrolled during early acute HIV infection. Study duration is 25 weeks. Adults aged 18-50 years enrolled at the time of early acute HIV infection in Pattaya, Thailand; Kericho, Kenya; Mbeya, Tanzania; and Kampala, Uganda

Primary Objectives

1. Safety of VRC01 in acutely HIV-infected individuals
2. Impact of VRC01 on plasma viremia in each mAb arm compared to the ART plus placebo control at day 7 (+/- 1 day)

RV 422: A Phase 1b, Open-label, Clinical trial to evaluate the Safety, Tolerability and Immunogenicity of the Ebola Chimpanzee Adenovirus Vector Vaccine (VRC-EBO ADC069-00-VP, CAD3-EBO), in Healthy adults in Kampala, Uganda

Site Principal Investigator: Hannah Kibuuka, M.D

Collaborations: U.S. Military HIV Research Program, Silver Spring, MD & Makerere University-Walter Reed Project, Makerere University, Kampala, Uganda in collaboration with Vaccine Research Centre, NIAID, NIH

Background and rationale: Ebola hemorrhagic fever is relatively rare but is associated with a high mortality rate. The fatality rate during previous outbreaks has ranged from 50% to 90%, with death occurring 6 to 16 days after the onset of symptoms. At present, there is no effective treatment for both filoviruses yet both viruses pose a risk to national and global security. The overall goal of the VRC filovirus vaccine development plan is to develop a vaccine regimen that would be effective in prevention of both Ebola infections.

Study design (Study population, duration, and sample size): This is an open-label study evaluating safety and immunogenicity. Ninety healthy adults in the Kampala area ages 18-65 will be randomized. Study duration is 48 weeks. It will comprise of two groups: Group 1: Sixty Ebola vaccine naïve subjects will be randomized to receive a single injection & Group 2: Up to 30 eligible subjects who previously participated in the RV 247 vaccine clinical trial and received VRC-EBODNA023-00-VP (Ebola DNA WT) will be randomized to receive a single injection.

Primary Objectives:

- To evaluate the safety and tolerability of VRC-EBOADC076-00-VP when administered IM at doses of 1×10^{10} particle units (PU) and 1×10^{11} particle units (PU) to healthy adults 18-65;
- To evaluate the safety and tolerability of VRC-EBOADC069-00-VP when administered IM at doses of 2×10^{10} particle units (PU) and 2×10^{11} particle units (PU) to healthy adults 18-65;

RV 403: Randomized, Double Blind Phase I Trial to Evaluate the Safety and Immunogenicity of Sanofi Pasteur Live Recombinant ALVAC-HIV (vCP1521) and Global Solutions for Infectious Diseases (GSID) gp120 B/E (AIDSVAX® B/E) formulated in L(MPLA) and alum in a Prime-Boost Regimen in HIV-uninfected Adults in Thailand, Uganda and Mozambique.

Site Principal Investigator: Hannah Kibuuka, MBChB, MMed, MPH
Collaborations: Office of the Surgeon General, Department of the Army.
Collaboration with the US Army and DAIDS/NIAID/NIH

Background and rationale: Despite promising but still fragile successes in prevention and care and treatment, the development of a safe and efficacious preventive HIV vaccine as part of a comprehensive prevention program remains among the highest global health priorities and the best long-term tool for the control of the HIV-1.

Study design: A total of 210 healthy HIV-uninfected volunteers at low risk for HIV infection, between 18 and 40 years of age, weighing over 45 kilograms, available for follow-up in the next 24 months and willing to provide mucosal secretions and blood samples during this period.

Study population, duration, and sample size: Estimated duration of the trial: 10 years (2-3 years screening and clinical activities: 3-10 years laboratory assays and data analysis)

Primary Objectives:

Assess the safety, reactogenicity, and tolerability of the vaccination regimens.

Title: Adaptive Randomized Trial of Early Management Interventions for Sepsis in Uganda (ARTEMIS-Uganda)

Site Principal Investigator: Shevin Jacob, MD and Banura Patrick, MD

Collaborations: This is a collaborative research involving the Makerere University Walter Reed Project, Makerere University Infectious Diseases Institute, the University of Washington. Makerere University Department of Microbiology, Makerere University Infectious Diseases Institute, Uganda Ministry of Health Uganda People's Defense Force,& IMAI-IMCI Alliance.

Background and rationale: Currently, limited data from resource-constrained (austere) settings exist to drive evidence-based interventions for severe infections (including severe sepsis), and improved management strategies that reduce morbidity and mortality in such settings are desperately needed.

Study design: Phase III Randomized Clinical Trial to determine the optimal strategy for early adult sepsis resuscitation to be conducted in a number of government national and regional referral hospitals. Once enrolled, patients will be followed until discharge or death.

Study population, duration, and sample size: The target population will include all patients entering the hospital through a department from where a clinician can admit a patient to an adult medical ward. The study is estimated to span over a period of 4 years. The clinical trial plans to enrol 2550 participants over the course of 2.5 years, with an additional 220 participants to cater for lost to follow ups.

Objectives: The overall objective of the study will be to determine an optimal sepsis management strategy relevant to resource-constrained settings like Uganda.

Protocol HIV-V-A004: A Phase 1/2a Trial to Evaluate the Safety/Tolerability and Immunogenicity of Homologous Ad26 Mosaic Vector Regimens or Ad26 Mosaic and MVA Mosaic Heterologous Vector Regimens, with High-Dose, Low-Dose or no Clade C gp140 Protein plus Adjuvant for HIV Prevention

Site Principal Investigator: Hannah Kibuuka MBChB, M.MED, MPH

Collaborations: Crucell Holland B.V.Archimedesweg 42333 CN Leiden the Netherlands and the Makerere University Walter Reed Project, Kampala, Uganda

Background and rationale: Makerere University Walter Reed Project (MUWRP) is doing this study for Crucell Holland B.V, the Sponsor. The main purpose of this study is to see if the study vaccines are safe (if they cause any side effects and how well they are tolerated). This study will compare three types of experimental vaccines (study vaccines) against the Human Immunodeficiency Virus Type 1 (HIV-1).

Study design: A phase 1/2a multi-center double blind placebo controlled clinical trial**.** About 400 participants worldwide will be randomised to receive either vaccine(s) or placebo (a substance that has no therapeutic effect, used as a control in testing new drugs).Here in Uganda, the study will be done here at the Makerere University Walter Reed Project in Kampala and at International AIDS Vaccine Initiative IAVI) at the Uganda Virus Research Institute (UVRI), Entebbe.

Study population, duration, and sample size: study will enrol healthy adults 18-50 years old, who are HIV negative from Kampala and its surroundings. About 400 participants will take part in this worldwide study. Study participation is two years, a small portion of participants will be selected and be asked to take part for another two years – only to observe their medical condition. Everyone participating in this study will get a total of 6 injections spread over 4 visits.

HIV Cohort studies:

A. Completed studies:

RV 173: Cohort Development for a Possible Phase III HIV Vaccine Trial among the Population Aged 15 - 49 years of Kayunga District, Uganda. Study started in November 2007.

Site Principal Investigator: Hannah Kibuuka, MBChB, MMed, MPH

Collaborations: Makerere University-Walter Reed Project, Makerere University Kampala, Uganda, U.S. Military HIV Research Program, Rockville, MD, U.S.A. National Institutes of Health Vaccine Research Center Bethesda, MD, USA

Background and rationale: Three decades ago, HIV-1 was first characterized and since initial discovery, we now better understand viral transmission and factors involved in subsequent disease progression but additional preventative and therapeutic strategies are needed if a cure is to be realized.

Study design: This freezer study is based on existing samples from Kayunga district Uganda, a part of sub-Saharan Africa, which corresponds to the most heavily affected geographic region and reflects global viral diversity.

Study population, duration, and sample size: This study will use plasma samples for about 70 HIV-infected participants and about 40 HIV Uninfected participants

Research objectives:
This study includes the following primary objectives:

- Estimate the incidence and prevalence of HIV-1 among the general population, and among selected sub-populations believed to be at higher risk for HIV infection in Kayunga District, Uganda
- Characterize the risk factors associated with HIV infection in Kayunga District, Uganda.
- Compare recruitment efficiency, and follow-up rates between three distinct cohort recruitment strategies.

Start date: 01 December 2005
Enrolment: 2,025
Study status: Closed

RV 283: Extended Follow Up for participants in VRC HIV-1 Recombinant Adenovirus-5 Vector Vaccine Studies in Uganda.

Site Principal Investigator: Hannah Kibuuka, M.B.Ch.B., M.MED., M.P.H.

Collaborations: U.S. Military HIV Research Program, Rockville, MD, U.S.A.& Makerere University-Walter Reed Project, Makerere University Kampala, Uganda

Background and rationale: Information from other studies, which may be relevant to the Phase I/II HIV vaccine trial conducted in East Africa by the MHRP, is the basis for a request to extend follow-up for a period of two years to volunteers who participated in the following studies: Protocol RV 156A/WRAIR & Protocol RV 172/WRAIR 1218. The purpose of this protocol is to obtain further follow-up in volunteers who have participated in HIV vaccine trials conducted with the VRC candidate vaccines with a view to establishing the immunogenicity of the vaccine over an extended period and to assess long term safety including HIV status.

Study design: This is an extended follow-up of volunteers who participated in either the RV 156A study or the RV 172 study. This is a 12 month prospective cohort of all study participants in the MUWRP protocol RV 172 and RV 156a that received placebo or an Adeno-viral vector HIV vaccine (solely or as booster) enrolled in Kampala and Wakiso districts.

Study population, duration, and sample size: The site will enroll all available participants out of those who participated in RV 172 and 156A**.**
Participants will be followed up 4 monthly to determine long-term immune responses and HIV infections for approximately one year per participant.

Primary objectives;

- To obtain longer-term safety data with respect to HIV infection acquisition among vaccine and placebo recipients;;
- Obtain long-term self-reported HIV risk behaviour data.
- Provide on-going HIV risk reduction counselling for participants and
- Provide any new and relevant information to participants regarding risk associated with participation in HIV vaccine trials.

Start date: 08 June 2010
Enrolment status: 120 participants.
Study status: closed
Results: There are 9 HIV-infected participants- 3 prevalent cases (one observed during protocol RV 172 active follow up while two were observed at un-blinding) and 2 infections observed in RV 283 at baseline and 4 new infections during study follow up

RV 288: A Virological Assessment of Patients on Antiretroviral Therapy in the US Military HIV Research Program/ President's Emergency Plan for AIDS Relief (PEPFAR) – Supported Programs in Africa. Started in January 2011 and enrolled 325 participants over the course of four months.

Site Principal Investigator: Hannah Kibuuka MBChB, MMed, MPH

Collaborations: US Military HIV Research Program

Background and rationale:

Study design: This is a multi-country, retrospective and cross-sectional survey design of adult patients on antiretroviral therapy (ART) enrolled in one of six Walter Reed Army Institute of Research/Division of Retro virology/US Military HIV Research Program (MHRP)-supported PEPFAR programs in Africa

Study population, duration, and sample size: Randomly selected adult patients (males and females ≥18 years old) enrolled in a MHRP/PEPFAR-supported antiretroviral treatment program in Kenya, Nigeria, Tanzania, or Uganda. Participants must be on first-line ART for at least 6 months and must have attended at least one follow-up ART clinic visit in the last 6 months.
All study related procedures including informed consent will be completed during a single visit.

Objectives:

The overall goal of this multi-site evaluation is to optimize the effectiveness of MHRP-supported ART programs by identifying program characteristics that result in the best program outcomes and have the greatest impact on reducing treatment failure as defined by viral suppression.

The primary objective for this study is to estimate the proportion of program participants on ART for at least 6 months who have achieved viral load suppression (defined as < 400 HIV RNA copies/ml).

Start date: 20 Dec 2010
Enrolment status: 327 participants
Study status: Closed
Results: Partial study analysis provides the following viral load and CD4+ results for the two RV 288a sites (Kayunga and Kangulumira):

Viral Load Ranges (Copies per ml)	Kayunga Hospital	Kangulumira HC IV
Undetectable (<47)	87.2%	81.1%
47-1000	7.7%	5.6%
1001-5000	0.9%	1.1%
5001-10,000	0.4%	0%
>10,000	3.8%	12.2%

B. On-going studies:

RV 217: "HIV-1 Prevalence, Incidence, Retention, Host Genetic and Viral Diversity in High Risk Cohorts in East Africa

Site Principal Investigator: Hannah Kibuuka MBChB, MMed, MPH

Collaborations:

U.S. Military HIV Research Program, Rockville, MD, U.S.A, U.S. Army Medical Research Unit-Kenya and Kenya Medical Research Institute, Nairobi, Kericho, Kenya, Makerere University-Walter Reed Project, Makerere University Kampala, Mbeya Medical Research Program (Mbeya Referral Hospital, Mbeya Regional Medical Office),National Institute of Medical Research, Department of Infectious Diseases and Tropical Medicine, University of Munich and U.S. Military HIV Research Program), Mbeya, Tanzania &Department of Retro virology, USAMC-AFRIMS, Bangkok, Thailand and Royal Thai Army AFRIMS, Bangkok, Thailand

Background and rationale: HIV disease progression rates vary substantially and correlate with early viremic set-point. Individuals who exert poor control over viral replication in this early phase of infection are destined to progress rapidly to immune deficiency and death and conversely those who are able to substantially control viral replication enjoy relatively prolonged survival.
It is critical to understand the early events associated with T-cell depletion and the mechanisms responsible for the variable control of viral replication.
It is hoped that understanding what events distinguish the elite controllers from those with a typical course of HIV infection or from those who progress rapidly will afford insights leading to novel prevention and treatment strategies.

Study design: This is a multi-Center, non-randomized prospective, 24-month clinical observational study to be conducted in two parts, a pilot study to assess feasibility (Part A) and the full study (Part B).
The study will be conducted at 4 USMHRP sites in Uganda, Kenya, Tanzania and Thailand.

Study population, duration, and sample size: The study population is 'Most-At-Risk-Persons' (MARP) HIV-uninfected men and women, aged 18-50 years old. It is a prospective, 24-month clinical observation study.

General Research Objective
The purpose of the study is to characterize recruitment, retention, human HIV prevalence, HIV incidence and biological characteristics of acute HIV infection in high-risk volunteers in Africa and Southeast Asia.

Start date: 08 Oct 2009
Enrolment status: 505 (Ugandan site only)

RV 329: African Cohort Study.

Site Principal Investigator: Hannah Kibuuka MBChB, MMed, MPH

Collaborations: U.S. Military HIV Research Program, Rockville, MD, U.S.A, U.S. Army Medical Research Unit-Kenya and Kenya Medical Research Institute, Nairobi, Kericho, Kenya, Makerere University-Walter Reed Project, Makerere University Kampala, Mbeya Medical Research Program (Mbeya Referral Hospital, Mbeya Regional Medical Office). Department of Defence Walter Reed Program Nigeria, Abuja, Nigeria

Background and rationale:

Study design: Protocol RV 329, *African Cohort Study* (AFRICOS), is an open-ended prospective cohort study; enrolling 3000 HIV infected adults and 600 HIV uninfected adults at MHRP PEPFAR-associated clinical sites in Kenya, Tanzania, Uganda and Nigeria.
The study follows participants every six months and will collect social, demographic, clinical and laboratory data as well as annual blood and sputum samples for storage in the AFRICOS Repository.

Primary objective: To longitudinally assess the impact of clinical practices, biological factors and socio-behavioral issues on HIV infection and disease progression in an African context.

Start date: 25 Oct 2012
Enrolment status: (Ugandan site only- 225, 190 HIV+& 35 HIV-)
Study status: Open and enrolling

RV 396 "Medical record abstraction study evaluating HIV and aging in a cohort of HIV infected adults in rural Uganda". Started 24 Feb 2014

Site Principal Investigator: Francis Kiweewa, DD

Collaborations: Makerere University Walter Reed Project (MUWRP) and Department of Medicine, Tripler Army Medical Centre, US Military HIV Research Program

Background and rationale: This study will provide useful descriptive information on the state of HIV disease in adults aged 50 or over in an African setting. Current literature in this area is based mostly on self-reported survey data or lacking entirely. This data will be an important hypothesis-generating activity forming the foundation for future prospective research.

Study design: This is a retrospective medical record review that will evaluate effects of HIV in an aging African cohort, comparing HIV disease characteristics and treatment outcomes in older (50 years) and younger HIV infected adult (aged 25-40 years) in a ratio of 2:1. Sample size up to 400 patients

Primary objectives:

1. HIV disease severity, including CD4 count, Viral load, and WHO stage, current, at time of ART initiation, and at time of diagnosis.
2. HIV management in terms of ART status and drug regimens as well as clinical, immunologic and virologic treatment outcomes.

Start date: 25 Feb 2014
Enrolment status; 450 charts were abstracted**.**
Preliminary Results: Records from the 50+ age group of HIV infected patients revealed lower CD4+ count, higher peak WHO stage compared to the 25- 40 years group. Members of the older group were also taking more medications and had more medical co morbidities including a higher prevalence of kidney and liver disease

Laboratory based studies:

A. On-going studies:

RV 164: Determination of Laboratory Reference Data using Anonymous Healthy Ugandan Blood Bank Donors. Study started in May 2005.

Site Principal Investigator: Hannah Kibuuka, MD

Collaborations: Makerere University Walter Reed Project (MUWRP) Kampala, Nakasero Blood Bank Kampala, Uganda, Henry M. Jackson Foundation Rockville, Walter Reed Army Institute of Research Rockville**.**

Background and rationale: Establishing a clinical research program for HIV prevention requires knowledge of normal values for routine clinical laboratory parameters, validation of HIV diagnostics and prevalence data for exposure to various pathogens which may impact upon the feasibility of clinical studies. Accordingly, the Makerere University Walter Reed Project (MUWRP) proposes the following study in collaboration with the Nakasero Blood Bank with several goals in mind.

Study design: The study population will be blood donors at the National blood donation Center in Kampala and regional donation centres who have met the Ugandan National blood donor program definition of healthy and have signed an RV 164 blood donation affidavit. Samples from healthy Ugandan blood donors will be collected from residual volume remaining in the collection tubing in anticoagulation and serum clot tubes.

Study population, duration, and sample size: Approximately 2000 donors will contribute at the Nakasero site. Male and female healthy donors in the 18-30 year old age group and 31-45 year old age group for which normal values are required

The objectives of this protocol were to determine laboratory reference data using healthy Ugandan blood donors. The four specific objectives were to:

i. Determine normal reference ranges for Clinical Chemistries, Hematology and lymphocyte subsets in blood bank donors;
ii. Validate rapid HIV testing;
iii. Determine HIV subtype using Multi-region Hybridization Assay; and
iv. Determine prevalence of antibody to potential HIV vaccine vectors.
v. Determine the prevalence of antibodies to infectious organisms circulating in Uganda in order to inform future vaccine, treatment and public health initiatives.

Samples from healthy Ugandan donors were collected from residual volume remaining in the collection tubing in anticoagulation and serum clot tubes.

Start date: 31 May 2005
Enrolment status: 960 samples were collected for objective (i) and 5252 samples were collected for the rest of the objectives

Study status: Currently in data analysis for prevalence of antibodies to infectious organisms circulating in Uganda in order to inform future vaccine, treatment and public health initiatives. Data analysis for the 5th objective of the study

RV 219: HIV subtype among HIV-infected children in Kampala, Uganda.

Abbreviated Title: Virus and Host Factors in HIV-1 infection and Disease Progression in Rakai Project, Uganda

Site Principal Investigator: Leigh Anne Eller, M.S.

Collaborations: Makerere University Walter Reed Project, NIH & the Center for AIDS research

Study design: A Cross sectional cohort study, to determine the prevalence of HIV subtypes A, D, C, multiple and recombinant virus infection in HIV infected Ugandan children.

Study population, duration, and sample size:

Research Objectives:

1. Determine the prevalence of HIV subtypes A, D, C, multiple and recombinant virus infection in HIV infected Ugandan children.
2. Validate MHA (Multi-region Hybridization Assay) using extracts from dried blood spot extracts, comparing to results from plasma specimens.

Start date: February 2007
Enrolment status: 300 specimens or participants.

Study status: Investigators continue method development for isolation/ amplication of DNA from DBS, determination and validation of MHA for HIV-subtyping.

RV 228: Evaluation of Virus and Host Factors of importance to HIV-1 infection and Disease Progression in Rakai Project, Uganda: An Integrated Community HIV Epidemiological Research (CHER) and Molecular Epidemiological Research (MER) Project.

Abbreviated Title: Virus and Host Factors in HIV-1 infection and Disease Progression in Rakai Project, Uganda

Principal Investigator: Michael A. Eller, PhD

Collaborations: United States Military HIV Research Program (MHRP) &Makerere University-Walter Reed Project

Background and rationale: In the absence of a protective vaccine, the HIV-1 pandemic continues essentially unabated. HIV-1 infection rates are highest in sub-Saharan Africa, where multiple genetic subtypes of the virus co-circulate and human populations exhibit a high degree of genetic polymorphism[2]. Three of the six most globally prevalent strains are subtype A, C and D, which co-circulate in East Africa. In these populations, the three subtypes are often intermixed, leading to dual infections and many recombinant strains. This study will continue and expand the HIV-1 genotyping activity that was initiated in WRAIR study #1025 (RV129); to include evaluation of serial samples from each HIV-1 infected individual and additional, in-depth characterization of viral strains.

Study design: The samples to be studied are derived
from the closed cohort study RV129, WRAIR#1025, and includes up to 800 individuals
with known dates of HIV-1 sero-conversion and up to 200 HIV-1 seronegative
individuals. Project.15 years.

Objective: The purpose of this study is the evaluation of virus and host factors of importance to HIV-1 infection and disease progression in a large, prospectively followed cohort in Uganda.

Start date: August 2008
Enrolment status: 611specimens utilized.
Study status: Study in specimen or data analysis.

RV 309: Antimicrobial Resistance Surveillance in Uganda.

Site Principal Investigator: Fred Wabwire-Mangen, MD, PhD

Collaborations: Makerere University-Walter Reed Project, Makerere University School of Public Health, Ministry of Health Uganda.

Background and rationale: Resistant bacteria cause debilitating infections and continue to demonstrate a large capacity to hyper mutate, duplicate and share survival information that enables them to survive within harsh environments including high concentrations of antimicrobial agents.

Study design: Protocol RV 309 above, sponsored by the Global Emerging Infections Surveillance (GEIS), is a lab-based surveillance of anonymous human, biological samples that require bacteriological culture and sensitivity at any of participating laboratories. This work seeks to support surveillance of antimicrobial resistance through support of a network of laboratories, improving standard of care diagnostic procedures involved in bacteriological sample collection, analysis, referral, and reporting of results for improved patient care.

Study population, duration, and sample size: All biological samples that may require bacteriological culture and sensitivity and/or DNA drug resistance determination from any of the study laboratories.

Primary Objectives:
The overall objective is to strengthen the capacity of a network of laboratories to conduct antimicrobial resistance surveillance for clinically important bacteria in Uganda, contributing to global efforts for resistance containment strategies.

Start date: 06 May 2010
Enrolment Status: number of specimen utilized 1157
Study status: on going.

B. Upcoming/planned studies:

RV 271: Clinical Laboratory Quality Management: Establishing Reference Ranges through Specimen Collection.

Site Principal Investigator: Hannah Kibuuka MD.

Collaborations: United States Military HIV Research Program (MHRP) &Makerere University-Walter Reed Project

Background and rationale: Establishing laboratory reference intervals is an important element in interpreting diagnostic assays. This protocol is designed to provide a mechanism to determine local reference ranges using blood and urine specimens collected from consented volunteers.

Study population, duration, and sample size: The approved Project summary will contain a sufficient number of volunteers needed to obtain statistical significance for determining normal reference across stratified population.

Objective:
Protocol RV 271 proposes to collect blood and urine collected from healthy adult men and women through routine phlebotomy and/or finger sticks and spontaneously voided urine- (stratified by HIV status); with the following objectives:

To establish reference intervals for clinical laboratory assays for application in clinical trials.

To provide a mechanism to assess quality laboratory management practices through performance verification of clinical and research laboratory instruments, and validation of clinical and research laboratory assays.

Study status: Study not yet started

Surveillance studies:

A. ON-GOING STUDIES:

RV 231: Surveillance of Influenza Viruses in Uganda Human Study Component.

Site Principal Investigator: Fred Wabwire-Mangen, MD, PhD

Collaborations: Makerere University Walter reed project, MU-COVAB, MUSPH, Nature Uganda in collaboration with UVRI, MoH, US army medical research unit-Kenya, HJF

Background and rationale: Influenza is a serious respiratory illness which can be debilitating and cause complications that lead to hospitalisation and death, especially in the elderly. Every year, the global burden of influenza epidemics is believed to be 3.5 million cases of severe illness and 300,000 - 500,000 deaths. The epidemics tend to be abrupt and very common in highly crowded conditions such as schools, markets, and refuge or Internally Displaced Persons (IDP) camps. The epidemic may last one month with 20 to 50% of the crowded population affected.

Study design: This is surveillance study using a series of cross-sectional studies.

Study population, duration, and sample size: Individuals with flu-like illnesses, and residents in the catchments areas of the study health units and live bird handlers in selected markets in central, western, Eastern, Northern, and Lake Victoria Basin.
The study population at health units will include male and female adults aged 18 and older and children aged 6 months – 17 years; with respiratory infections attending outpatient and/ or in-patient clinics at the selected health facilities in the study areas.

General Objective:

To conduct surveillance of influenza and influenza-like illnesses in Uganda, to detect circulating influenza strains in human populations, map the human populations at risk and build capacity for influenza surveillance

Enrolment Status: 6814 active subject samples,

Study status: Study started in January 2008**.**
Preliminary results to date: To date, 6,894 samples have been collected, 6,814 samples have been screened by PCR and 509 were positive for Influenza A viruses

RV 231: Surveillance of Influenza Viruses in Uganda Non-Human Study Component.

Site Principal Investigator: Denis K. Byarugaba, PhD.

Collaborations: Makerere University Walter reed project, MU-COVAB, MUSPH, Nature Uganda in collaboration with UVRI, MoH, US army medical research unit-Kenya, HJF.

Background and rationale: as above.

Study design: **This is surveillance study using a series of cross-sectional studies.**

Study population, duration, and sample size: Target species**: Avian (Aquatic and associated birds and domestic) and swine species.** These sites will include lakes, rivers, channels, swamps, marshes, rice fields and other wetland types**.**

Research Objectives:
The general objective of this proposed study component is to conduct surveillance for influenza and influenza-like viruses in non-humans in Uganda, to investigate the ecology of influenza viruses in non-human populations, undertake risk modelling for the animal populations and build capacity for HPAI surveillance.

Start date: Study started in April 2008
Study status: 14317 samples collected, currently collecting samples from four sites.
Preliminary results to date: All the virological samples tested on PCR were negative for Flu A viruses. Serological analysis of the samples showed an overall prevalence of 0.5% and all were from swine/pigs hence providing evidence of carriage of the influenza virus

Basic program evaluation studies:

A. Closed protocols

RV 277: A Program Evaluation of Voluntary Medical Male Circumcision in Kayunga District, Uganda,"

Collaboration: This program evaluation is a collaboration between local Uganda WRP-PEPFAR program staff and program coordinators from the US Military HIV Research Program, Henry Jackson Foundation.

Primary objectives

1. Describe the acceptance and uptake of voluntary medical male circumcision in a non-research setting among rural Ugandan men.

2) Describe baseline attitudes, knowledge and beliefs (KAB) surrounding circumcision. Describe change in community KAB after pilot phase and 2-years after program roll-out.

3) Monitor and evaluate clinically-related outcomes among men who undergo circumcision.

4) To evaluate the cost-effectiveness of the medical male circumcision program in preventing HIV infections.

Program evaluation rationale: Clinical trials conducted in South African, Rakai, Uganda and Kisumu, Kenya demonstrated a 60% protective effect of circumcision in preventing HIV infection in men. Male circumcision is being promoted for HIV prevention in high-prevalence heterosexual populations, but it is not without risks. The rate of moderate and severe adverse events related to surgery was almost 4% in prior clinical trials, and unprotected intercourse before complete wound healing can increase a man's risk of acquiring HIV from an infected partner. Therefore, it is paramount to monitor and evaluate the safety and cost-effectiveness of male circumcision programs as they are widely implemented in non-research settings.

Uganda will begin a pilot program of voluntary medical male circumcision in early 2009 in Kayunga Town, Uganda. This program evaluation will retrospectively monitor and evaluate the data collected during the pilot program and prospectively evaluate the program roll-out. The purpose of the monitoring and evaluation is to assess whether or not the program meets its intended objectives of

conducting safe and cost effective medical male circumcisions in a non-research, rural Uganda Ministry of Health (MoH) district hospital.

Population: Men age 15 years and above living in Kayunga District.

Evaluation design: This is a basic program evaluation of the pilot and roll-out stages of the program. Two categories of data will be monitored and evaluated. First, service utilization data will be routinely collected by PEPFAR program staff. Second, to evaluate clinically-related outcomes, WRP-PEPFAR program staff will conduct retrospective chart reviews in order to collect surgical and post-surgical follow-up data.

Sample size estimate: 300 men will be circumcised during the pilot phase in Kayunga Town. Roll-out of the program will involve ongoing service provision at Kayunga District 8 remaining Sub-Counties and Mukono District 5 Sub-Counties.

B. ON-GOING STUDIES:

RV 346: A Cost and Outcomes Analysis of Two Service Delivery Models of Safe Male Circumcision in Rural Uganda

Site Principal Investigator: Fred Magala MD

Collaborations: Makerere University Walter Reed Program, Boston University, Henry M. Jackson Foundation (HJF)

Background and rationale: The purpose of this study is to evaluate clinical outcomes and costs of providing the service for clients utilizing one of two surgical delivery models—facility-based or through a mobile surgical clinic- currently being implemented part of the MUWRP-PEPFAR SMC program in Kayunga and Mukono Districts, Uganda.

Study design: All data developed for this study will come from information already collected as part of routine program implementation and from general financial information available through the program and the sites providing the services. The study is a retrospective and prospective cohort study of clients receiving SMC services in the study sites based on de-identified data extracted from electronic and written program records.

Study population, duration, and sample size: The study population will include all adult clients who have received SMC services in one of the MUWRP-PEPFAR-supported MoH facilities listed above or through the MUWRP surgical clinic the proposed sample size is 896 patients receiving SMC services in the fixed facilities and 896 in the mobile unit

The primary objectives of the study are to:

i. Estimate and compare the average costs from the provider's perspective of two service delivery models (mobile surgical clinic vs. fixed facility) for providing male circumcision to men in Kayunga and Mukono Districts, Uganda;

ii. Estimate and compare the proportion of adverse clinical outcomes achieved for each service delivery model (a successful outcome is defined as no adverse event);

iii. Estimate and compare the average cost per successful outcome (defined as average cost divided by the proportion of patients with no adverse event).

Start date: Started 13 Jan 2012.

Study status: Collection and analyses for AE data for each service delivery model; and completion of analyses for costs data

RV 371: An evaluation of the Xpert MTB/RIF in diagnosis of Tuberculosis in a rural setting in Uganda.

Site Principal Investigator: Fred Magala, MD

Collaborations: A study conducted by MUWRP-PEPFAR program, Makerere University School of Public Health, MoH, Sponsored by the Henry M. Jackson Foundation.

Background and rationale: Tuberculosis ranks high as a major public health problem in Uganda and the country has an emerging multi drug resistant TB (MDRTB) problem; and a high HIV prevalence (6.4% among the general population and over 50% among TB patients) fuelling the TB epidemic yet there remains a lack of effective diagnostic tools, largely in developing countries. The Xpert MTB/Rif assay is a rapid test which identifies both the presence of M. tuberculosis and resistance to rifampicin in a single test.

Study design: This study is a 12-month retrospective basic program evaluation of utilization of the GeneXpert in a rural health setting. Data analysis is estimated to take an additional 12 months.

Study population, duration, and sample size: MUWRP PEPFAR program administrative data pertaining to GeneXpert and pre-existing clinical and laboratory data pertinent to GeneXpert. All available charts over 24 month period, cumulative total of 3000 charts

Primary Objectives:

i. To evaluate the feasibility and sustainability of utilization of the GeneXpert at a regional hub in a rural African health setting
ii. To determine the prevalence of diagnosed TB in OPDs of participating health centers.
iii. To determine the prevalence of diagnosed RIF-resistant and MDR TB in OPDs of participating health centers.
iv. To describe the rates of false clinical and microscopic TB-diagnoses.

Study status: Chart review and data abstraction still on going
Enrolment Status: 708 charts out of a cumulative of 3000 have been abstracted.

C. PLANNED STUDIES:

RV 415: "Evaluation of Changing Guidelines, Systems, and Practices on Prevention, Care, and Treatment Activities in the Buvuma, Kayunga, and Mukono Districts in Uganda"

RV 432: Improving Retention in HIV Care and Treatment Services through the Development of a Network of ART Clinics within the Fishing Communities on Koome Island, Uganda