MHRP EXCHANGE

MHRP U.S. MILITARY HIV RESEARCH PROGRAM

Fall 2018

NEWS FROM THE U.S. MILITARY HIV RESEARCH PROGRAM AT THE WALTER REED ARMY INSTITUTE OF RESEARCH

Landmark Acute HIV Infection Cohort Study Concludes

MHRP's RV217, an ambitious early capture acute HIV infection cohort study led by Clinical Deputy Director Dr. Merlin Robb, is concluding this year after nine years of research activity.

The study began in 2009 and prospectively followed a group of high-risk volunteers in East Africa and Thailand, tracking HIV status and characterizing progression through the acute stages of HIV infection. Volunteers were enrolled before they began to show detectable HIV antibodies, and if they became infected, researchers were able to capture samples from some of the earliest stages of HIV infection – in some cases within days.

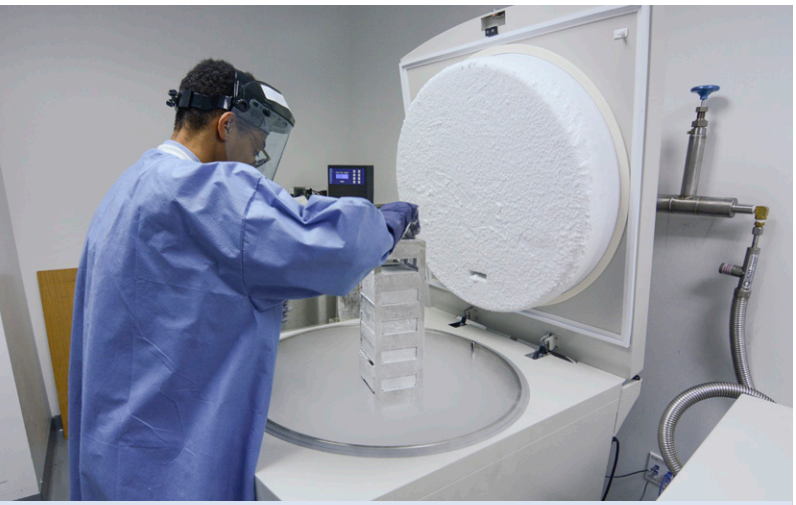
Local researchers screened 5436 volunteers over the course of the study, and 153 incident cases were observed. 235,950 blood-draw visits occurred, and the 86% rate of volunteer visit compliance was key to Rv217's success.

"We were able to capture people with HIV infection before they had symptoms and before they had antibodies, which is how a diagnosis of HIV is usually made, and while their viral loads were actually very low," said Dr. Robb. "We were able to define the symptoms and signs during the acute interval, and intensively evaluate the relationship between the virus and host immune response."

RV217 provided the first characterization of acute HIV infection, and the study's impact on HIV research will last beyond its conclusion. *The New England Journal of Medicine* publication stemming from the study has been cited more then 100 times, and 21 additional papers have been published using RV217 samples and data.

RV217 demonstrated that viral and immune events during acute infection are abrupt and decisive, meaning they play a role in later disease outcomes over many years of HIV infection, influencing clinical decisions about early testing and treatment.

Natural Killer Cell RNA Signatures Suggest Increased Activity Following HIV Vaccination



An MHRP scientist removes samples from a liquid nitrogen freezer in a lab at the Walter Reed Army Institute of Research.

Natural killer (NK) cells are able to kill virus-infected or transformed cells and represent an important component of the human immune system. In a new study led by MHRP, researchers utilized cell sorting and transcriptional profiling to identify unique RNA transcription signatures to help unveil the potential mechanisms through which NK cells respond to HIV infection and vaccination. Findings from the study were published in March in *Nature Communications*.

Researchers compared NK cells at the protein and transcript level in samples provided by healthy donors, volunteers with chronic HIV infection and healthy recipients of an HIV vaccine. They found the three distinct transcriptional fingerprints in NK cells associated with functions through which NK cells may limit HIV-infection.

"There was prior evidence that NK cells are important in combating HIV infection, but we need to learn more about their response," said Dr. Margaret Costanzo, an immunologist and first author of the paper. "Insights from this research may inform how to better engage these cells through vaccination."

WRAIR Walter Reed Army Institute of Research

Soldier Health • World Health

MHRP Efforts Beyond HIV Lead to Spinoff of Emerging Infectious Disease Branch

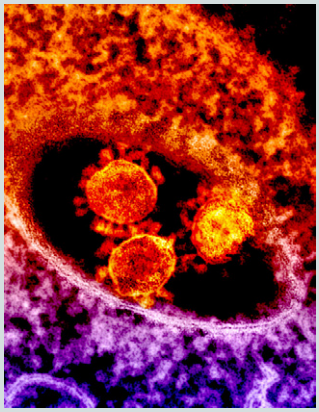
In the August issue of the *Journal of Infectious Diseases* experts from the NIH's National Institute of Allergy and Infectious Diseases (NIAID) wrote a commentary highlighting the unanticipated extended impact that HIV/AIDS research has had on other health and medical fields.

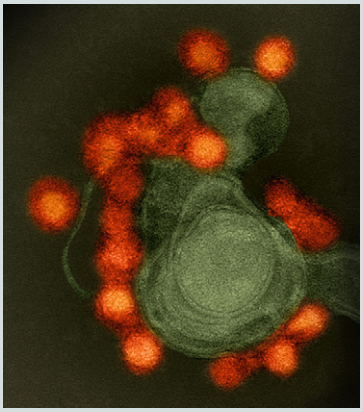
"The collateral broader scientific progress resulting from the support of HIV/AIDS research over the past 30 years is extraordinary," write the commentary's authors, Dr. Tony Fauci and his NIAID colleague Dr. Tara Schwetz. "The positive impact has ranged from innovations in basic immunology and structural biology to treatments for immune-mediated diseases and cancer and has had an enormous effect on the research and public and global health communities well beyond the field of HIV/AIDS."

MHRP's development over the past several years has mirrored this phenomenon. The program's deep bench of infectious disease experts and its international laboratory and clinical research network has allowed MHRP to pivot efforts to address military and global health threats beyond HIV.

One of the earliest examples of this agility came during the 2014-2015 Ebola outbreak in the West Africa. Because of MHRP's decade-long collaboration with partners in Africa, WRAIR and MHRP scientists were able to assist local authorities as they strove to expedite vaccine trials and consulted with the World Health Organization to help guide Ebola vaccine development policy.

Other expanded research initiatives have grown out of MHRP's primary mission. MHRP has partnered with the Nigerian Ministry of Defence for more than 10 years, implementing public health programming, administering PEPFAR and conducting research.



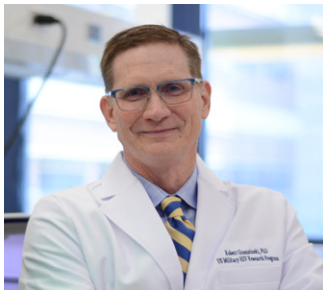


This longtime partnership served as a cornerstone of the Joint West Africa Research Group (JWARG), which was established in 2015 to improve biopreparedness in the region.

MRHP's focus on HIV vaccine development has expedited R&D of countermeasures for other viruses. WRAIR's ZPIV Zika vaccine was able to transition from concept to clinical trials in less than a year thanks in part to collaborations sprung from MHRP efforts.

MHRP's successes beyond the field of HIV have led to a spin off of a separate Emerging Infectious Disease branch within WRAIR to be directed by Dr. Kayvon Modjarrad, an alumnus of MHRP. The new branch has already launched research into MERS, Marburg, Lassa fever and tick-borne encephalitis, and will oversee ongoing JWARG efforts. The new branch will continue to work closely with MHRP as the HIV program redoubles its efforts in HIV vaccine development and functional cure research.

Meet MHRP's New Director



Dr. Robert Gramzinski has been named as the new Director of the U.S. Military HIV Research Program (MHRP) at the Walter Reed Army Institute of Research (WRAIR), stepping into a role vacated by COL Nelson Michael, recently retired from the U.S. Army.

Dr. Gramzinski has had a distinguished career serving at WRAIR and MHRP in several roles for the last 10 years, most recently as the HIV Vaccines Project Manager for the U.S. Army Medical and Materiel Development Activity, where he led a Program Management Office responsible for vaccine product development.

Dr. Gramzinski also served MHRP as Deputy Director of Research Operations, and in this capacity had operational oversight of MHRP activities in the United States, Kenya, Nigeria, Uganda, Tanzania, Mozambique, and Thailand. In that role he provided and coordinated research support and logistical activities for international MHRP operations, including good clinical laboratory practices, information technology, international project management, quality assurance, safety, regulatory compliance, U.S. Government acquisitions, human resource recruitment and development and research administration.

Prior to joining MHRP, Dr. Gramzinski spent five years as a program officer with the Vaccine Research Branch at the Division of AIDS within the National Institute of Allergy and Infectious Diseases, National Institutes of Health. Dr. Gramzinski also served 10 years in the U.S. Navy as a Medical Service Corps Officer with duty stations in the malaria program at the Naval Medical Research Center in Maryland, U.S. Naval Medical Research Unit-2 in Indonesia and the Bureau of Medical Research and Development in Washington, D.C.

Dr. Gramzinski is a graduate of Loyola University of Chicago with a Bachelor of Science in Biology and holds a doctorate in Experimental Pathology from the University of Colorado Health Sciences Center. He has over 20 years of research experience in infectious diseases, including malaria and HIV, and over 15 years experience in management of international research operations and science program development.

Study of Severe Infectious Disease Opens in Three Countries

The Joint West Africa Research Group RV466 research protocol, a study designed to identify and characterize cases of suspected severe infectious disease, reached a key milestone in August with the enrollment of its 100th volunteer.

This multi-site protocol led by MHRP opened in Nigeria late last year and has now been activated at sites in Liberia and Ghana.

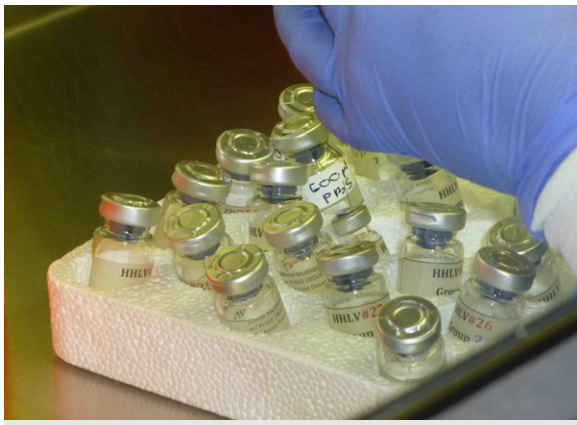
The study enrolls adult volunteers who present to clinics as severely ill with a suspected infectious source. In addition to receiving care, they provide specimens for laboratory analysis and complete a brief questionnaire that captures basic clinical, demographic and exposure data.

RV466 brings advanced diagnostic methods to bear in the West African hospital setting, including assays for the diagnosis of Lassa and other viral hemorrhagic fevers, generating data on circulating infectious disease threats in the region and informing countermeasure development.

This effort represents new collaborations between military, academic and public health labs in the subregion, developing a network of sites with infectious disease research capability.

Clinicians at 37 Military Hospital in Accra, Ghana conduct a mock RV466 visit.

Heroin Vaccine Technology Advances as Researchers are Awarded Grant for Further Testing



Vaccine vials in Dr. Gary Matyas' lab

Researchers at MHRP, centered at the Walter Reed Army Institute of Research (WRAIR), and SUNY Upstate have been awarded a grant to advance an experimental heroin vaccine through Phase I/IIa clinical trials to assess both its safety and its efficacy against a morphine challenge.

In preclinical studies, the vaccine induced antibodies that prevented heroin from crossing the blood-brain barrier in mice and rats for a period of up to three months. By binding heroin in the blood and thus reducing its passage into the brain, the vaccine aims to block the euphoria and addictive effects of heroin and other commonly misused opioids.

Dr. Gary Matyas, Chief of Adjuvants and Formulations for MHRP said, "Our goal is to develop a safe and effective vaccine that could be used as an additional therapy for those addicted to heroin. By blocking the effects of heroin in the brain, we hope to give people a window so they can overcome their addiction."

The heroin vaccine was co-developed by researchers at MHRP and the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. The new grant from the National Institutes of Health will fund pilot production of the vaccine candidate and preliminary safety testing. If successful, the candidate heroin vaccine will progress to a clinical trial evaluating the effectiveness of the technology in human volunteers. The first phase of testing is expected to begin late fall of 2020. The grant also funds pre-clinical development of a fentanyl vaccine.

The misuse of opioids, which include heroin and fentanyl, is a growing problem in the United States. Among the more than 72,000 drug overdose deaths estimated in 2017, the sharpest increase occurred among deaths related to fentanyl and synthetic opioids with nearly 30,000 overdose deaths. Most pharmacological treatments for opioid misuse involve opioid management therapy (OMT), but treatment access is an issue. In addition, adherence varies greatly and relapse rates can be high. To end the opioid overdose crisis, many different medical tools, treatments and medications, will be needed to meet the needs of individuals addicted to these drugs.

Long-term, researchers plan to combine the heroin vaccine with a viable HIV vaccine candidate to address the intertwined health issues of injection drug use and infectious disease spread through needle sharing.

WRAIR researchers leveraged their expertise in vaccine development and novel adjuvants research to develop this experimental heroin vaccine with their partners at NIDA. The vaccine includes a potent adjuvant to stimulate the immune system called the Army Liposome Formulation (ALF), which was also developed by researchers at WRAIR. The vaccine was developed jointly with intramural scientists at the Drug Design and Synthesis Section (Dr. Kenner C. Rice, Chief), Molecular Targets and Medications Discovery Branch, NIDA.

HIV Viral Load Rebounds Rapidly After Treatment Interruption, Even Very Early ART

HIV viral load rebounds rapidly despite suppressive antiretroviral therapy (ART) initiated at the earliest stage of infection before seroconversion. These findings were reported in the journal *Nature Medicine* by researchers at MHRP and SEARCH Thailand.

HIV latent reservoirs can hide from the immune system and pose a major obstacle to HIV remission. HIV remission is the ability to control HIV viral load without ART. Individuals who begin ART during the Fiebig I stage, which corresponds to the first two weeks of infection, have a remarkably low HIV burden, and many never seroconvert. Researchers therefore hypothesized that starting ART in Fiebig I may facilitate HIV remission.

The MHRP/SEARCH Thailand study followed 8 participants who initiated ART in Fiebig I and were fully suppressed on ART for at least two years. They underwent ART interruption with viral load monitoring every 3-7 days and resumed ART when viral load was confirmed above 1000 copies/ml. Most individuals had viral load detection above 20 copies/ml within two to four weeks, at a median of 26 days after interruption. This indicates that very early ART alone is not sufficient to induce remission and that additional strategies are required to control HIV.

"Reactivation of even a single latently infected cell can lead to viral load rebound in the absence of ART," said Dr. Jintanat Ananworanich, MHRP's Associate Director for Therapeutics Research and protocol chair of the study. "We posit that rapid viral load rebound despite very early ART was because of inadequate immune control and inability to achieve a small enough pool of latently infected cells, particularly in lymphoid tissues."

These findings suggest that, regardless of timing of ART, future research should aim to eliminate cells with replication competent HIV in blood and tissues by boosting immune responses. Potential strategies include combination therapies with latency reversal or immune adjuvant agents, broadly neutralizing antibodies, therapeutic vaccines and/or cell-based or gene-based therapies.

Researchers check R254 samples at the SEARCH Thailand Clinic in Bangkok.

mHealth Initiative Aims to Improve ART Adherence in Tanzania

In August the Tanzania Ministry of Health launched FASTA, a new intervention that will provide an opportunity for stable patients on ART to fast track access to their medication refills after completing a phone based self-assessment. This mHealth initiative is a collaboration with MHRP, HJFMRI and the mHealth Tanzania Partnership program, with funding from PEPFAR.

Hon. Ummy Mwalimu, Tanzania's Minister of Health, Community Development, Gender, Seniors and Children, unveils a promotional sign for FASTA at the launch of the mhealth ART adherence app in Songea, Tanzania, in August.

FASTA will work to improve ART adherence among stable patients in line with the Government of Tanzania's Differentiated Service Delivery Model, recommending that stable clients on HIV therapy move to less frequent clinic visits and ART refills.

Speaking at the FASTA launch the Minister of Health, Hon. Ummy Mwalimu, applauded this intervention. "Apart from reducing opportunity costs for the client, FASTA will decongest clinics and allow for more quality time for those clients that need to see a clinician. As a result, clients will have an improved experience when accessing ART services, thus improving adherence and retention and with that supporting the 2nd and 3rd 90 of the 90-90-90 UNAIDS goal," said Hon. Ummy.

The mobile application consists of a virtual self-check-in, where the client will complete a series of questions similar to those a clinician would pose during a physical visit. Based on their responses, the client will either obtain a refill of medication from a nearby pharmacy or pick-up point, or be referred back to the Care and Treatment Center (CTC) for physical check-up and management.

Biomarker Signatures in Acute HIV Infection Associate with Viral Dynamics and Reservoir Size

Distinct biomarker signatures arising during acute HIV infection appear to be associated with the establishment and persistence of the viral reservoir, according to findings from a new study from MHRP published in *JCI Insight*.

The viral reservoir poses a challenge in the quest to cure HIV infection since it contains cells in which HIV can lie dormant for many years, thereby avoiding elimination during antiretroviral therapy (ART). Estimating the size of the viral reservoir is critical for HIV cure strategies. Biomarkers in peripheral circulation may give insights into the establishment of the viral reservoir in parts of the body where it is difficult to measure.

In the recent study, researchers measured systemic levels of 84 soluble biomarkers belonging to a broad array of immune pathways in acute HIV infection in both ART-naive individuals as well as individuals who began ART upon early detection of HIV infection. These biomarkers were measured during acute and chronic infection and their relationship to viral reservoir establishment and persistence was assessed.

"Levels of several of these factors directly correlated with viral loads and occurrence of blood cells harboring HIV DNA during acute HIV infection, a maker of reservoir establishment," said Dr. Shelly Krebs, Chief of MHRP's B cell laboratory and co-author of the publication. "These markers offer potentially novel tools for gaining insight into relative reservoir size in acutely infected individuals and the potential of associated risks of treatment interruption."

The Krebs lab at the Walter Reed Army Institute of Research

This study stems from MHRP's acute infection cohort, RV254/SEARCH010, which is a collaboration with the Thai Red Cross AIDS Research Centre to identify acutely infected individuals and place them onto ART immediately.

HIVR4P 2018 SATELLITE SESSION

Please join us in a conversation about

ENGAGEMENT OF AFRICAN MSM IN HIV PREVENTION RESEARCH:
Effective Recruitment and Retention

Sunday, 21 October 2018

Hosted by the International AIDS Vaccine Initiative and the U.S. Military HIV Research Program

iavi International AIDS Vaccine Initiative

MHRP U.S. MILITARY HIV RESEARCH PROGRAM

World AIDS Day 2018

Dr. Robert Redfield, Director of the Centers for Disease Control and Prevention, will deliver the keynote speech at the Walter Reed Army Institute of Research (WRAIR) World AIDS Day event on November 30, in Silver Spring, Maryland.

Dr. Redfield served as the founding director of the Department of Retroviral Research within MHRP, spending 23 years at WRAIR before retiring from the U.S. Army Medical Corps. His talk, which will be live streamed, will focus on ongoing efforts in HIV research. Visit https://www.facebook.com/hivresearch/ after November 29 for the video streaming and archive link.

MHRP and Collaborators at HIVR4P 2018

Author/Presenter	Title	Date/Time	Location
MHRP/IAVI hosted satellite *	Engagement of African MSM in HIV Prevention Research: Effective Recruitment and Retention	Sunday, Oct. 21, 15:00-18:00	Marsella
Rasmi Thomas*	Vaccine-induced Gene Signature Correlates With Protection Against Acquisition in Three Independent Vaccine Efficacy Trials Including RV144	Tuesday, Oct. 23, 11:30 – 11:45	Bristol
Alexandra Schuetz* (AFRIMS)	Meet the Experts Lunch	Tuesday, Oct. 23, 12:00 – 13:00	Toulouse & Lyon
Alexandra Schuetz (AFRIMS)*	Mucosal Immunology in the Context of Acute HIV Infection and HIV Remission Studies	Tuesday, Oct. 23, 16:06 – 16:28	Bristol
Lindsay Wieczorek*	AIDSVAX (R) B/E gp120 Late Boost Increases HIV-1 Neutralizing Antibodies to the Highest Levels in RV144/RV305 Participants Boosted With ALVAC-HIV Alone	Tuesday, Oct. 23, 17:03 – 17:12	Oxford
Kristina Peachman	Prolonged Intervals Between Boosts Induces High Magnitude Transient V2-specific Functional Antibodies That Inhibit the Binding of V2 to α4β7 Integrin	Tuesday, Oct. 23, 17:30 – 19:30	Poster Hall
Syna K Gift	SERINC Expression Varies Significantly Within CD4 T Cells and Monocytes Among Healthy Adults	Tuesday, Oct. 23, 17:30 – 19:30	Poster Hall
Poonam Pegu	"Immunogenicity of HIV-1 gp120 DNA Prime and Env gp145 Protein Boost Vaccine Regimen in Combination With Novel Adjuvants"	Tuesday, Oct. 23, 17:30 – 19:30	Poster Hall
Thomas Musich (AFRIMS)	Anatomic Site of Origin Affects the Immune-cell Composition of Bone Marrow in Rhesus Macaques	Tuesday, Oct. 23, 17:30 – 19:30	Poster Hall
Siriwat Akapirat (AFRIMS)	"An Additional Late Boost of AIDSVAX B/E in RV144 Participants Induced Plasma HIV Envspecific IgG4 and IgG1 With Enhanced Durability"	Tuesday, Oct. 23, 17:30 – 19:30	Poster Hall
Tanyaporn Wansom (AFRIMS)	Characterization of Behavioral and Clinical Risk Factors for HIV Risk Among Transgender Women	Wednesday, Oct. 24, 17:30 – 19:30	Poster Hall
Alexandra Schuetz (AFRIMS)	ALVAC-HIV/AIDSVAX (R) B/E Late Boost Strategies (RV306) Increase the Proliferative Capacity of CD4+ Effector Memory T Cells	Wednesday, Oct. 24, 17:30 – 19:30	Poster Hall
Sandhya Vasan	"Altered CD4+ CCR5+ Expression and Cellular Activation in Mucosal and Lymphoid Tissues of Transgender Women"	Wednesday, Oct. 24, 17:30 – 19:30	Poster Hall
Jiae Kim	Quantitative Examination of the Capture of HIV-1 Primary Viruses by Human PBMCs in the Presence of Broadly Neutralizing Antibodies	Wednesday, Oct. 24, 17:30 – 19:30	Poster Hall
David Chang	"Differential Infection of Cultured Peripheral and CNS Cells by Distinct Transmitted/ Founder HIV-1 Infectious Molecular Clones (IMC)"	Wednesday, Oct. 24, 17:30 – 19:30	Poster Hall
Zoltan Beck	Army Liposome Formulations, ALFA and ALFQ, Are Potent Adjuvants	Wednesday, Oct. 24, 17:30 – 19:30	Poster Hall
Morgane Rolland*	"The Eclipse Phase Lasted a Week in HIV-1-infected Adults in East Africa and Thailand"	Thursday, Oct. 25, 08:30 – 10:00	Bristol
Bonnie M. Slike*	"Soluble Immune Activation Biomarkers Predict Accelerated Viral Rebound During Treatment Interruption in Fiebig I-treated Individuals"	Thursday, Oct 25, 10:45-11:00	Bristol
Sandhya Vasan*	Session co-chair	Thursday, Oct. 25, 13:00-14:30	Londres

* oral presentation

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Please submit your questions and comments via email to communications@hivresearch.org. Editors: Lisa Reilly, Jamie Livengood

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