MHRP EXCHANGE

MHRP
U.S. MILITARY HIV RESEARCH PROGRAM

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

MHRP, WRAIR Begin New Phase 2 Trial of Ebola Vaccine Regimen

The Walter Reed Army Institute of Research (WRAIR) in December initiated a Phase 2 clinical trial to evaluate the safety and immunogenicity of a prime-boost Ebola vaccine regimen in both healthy and HIV-infected study volunteers.

This study includes two vaccine candidates, Ad26.ZEBOV and MVA-BN-Filo, which will be given sequentially as a "prime boost" regimen. Seventy-five participants will receive a prime dose with MVA-BN-Filo followed by a boost with Ad26.ZEBOV at the WRAIR Clinical Trials Center in Silver Spring, Md.

Multi-site study in Africa

In the next few months, MHRP sites in Africa will also begin evaluating this regimen, as well as a vaccination schedule beginning with Ad26.ZEBOV and then boosted with MVA-BN-Filo. Approximately 575 volunteers will participate in total in the study (RV456). It will be conducted at clinical research sites affiliated with WRAIR's Military HIV Research Program in Nigeria, Uganda, Kenya, Tanzania and Mozambique.

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Study Highlights Need for Hepatitis C Screening for U.S. Military Applicants

A study shows that two-level screening of military applicants for hepatitis C (HCV)—via antibody screening and a confirmatory nucleic acid test—could not only reduce enlistment of infected individuals and increase battlefield blood safety, but also save the DoD an estimated $3.1 million annually. The study was published in the journal *Hepatology*.

Battlefield whole blood transfusion—the use of freshly collected blood products—has been an important feature of combat casualty resuscitative care in the conflicts in Iraq and Afghanistan. The U.S. military uses whole blood when stored blood components are not available in theater, or when these components are insufficient for resuscitation.

"Screening will decrease the threat to the battlefield blood supply, may lead to earlier diagnosis and linkage to care for individuals with HCV infection, and these data show that a screening program will lead to cost savings due to treatment costs avoided," said Dr. Paul Scott, MHRP researcher and senior author on the paper.

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MHRP Scientist Discusses WHO Ebola Collaboration

"At the WHO, we were looking at vaccine development and implementation from a global policy perspective and forging a broad path forward for the expeditious licensing of an Ebola vaccine."

As an Ebola outbreak surged across West Africa in 2014, MHRP research physician, Dr. Kayvon Modjarrad, sought a way to aid response efforts on the ground. His opportunity to fight the epidemic came instead via Geneva, Switzerland, where he was called to help the World Health Organization oversee Phase I trials for an Ebola vaccine candidate.

While in Geneva, Dr. Modjarrad was charged with guiding Ebola vaccine policy by monitoring the science, building consensus among diverse stakeholders and outlining a broad scientific agenda to define critical clinical endpoints. The experience gave him a macroscopic view of vaccine development that put his hands-on research experiences into a broader context.

Dr. Modjarrad's experience with the WHO Ebola vaccine team benefits his work at MHRP. He's currently working on MHRP Ebola vaccine study RV429, a Phase II chimpanzee adenovirus type 3 Ebola vaccine study being conducted at MHRP's Nigeria site. He's also the co-protocol chair for the upcoming RV456, a Phase II Ebola vaccine candidate study that includes all MHRP clinical research sites in Africa and WRAIR.

Dr. Modjarrad is also leading efforts in other emerging viral vaccine research, and is principal investigator on a first-in-human MERS-CoV vaccine study at WRAIR.

"I've been fortunate enough to work in vaccine development at multiple phases, starting at the molecular level at the National Institutes of Health, and then the clinical stage here at MHRP" said Dr. Modjarrad. "Working with the WHO offered another perspective on vaccine development"

New Ebola Vaccine *Continued from page 1*

Researchers will assess the safety and tolerability of the vaccine schedules and characterize the immune response, which should help them better understand these different regimens. Janssen and other development partners have generated preliminary data from a small group of healthy subjects demonstrating that both regimens were safe and immunogenic.

The study will strengthen safety and immunogenicity evidence of the regimens in healthy subjects and extend the population studied in Phase 1 to include volunteers up to and including 70 years of age and volunteers with stably suppressed HIV-infection.

"It is critical that we know these vaccines are safe and immunogenic in the communities where they will be used in Africa," said Lt. Col. Julie Ake, MHRP's Principal Deputy and protocol chair for the international study.

The study includes HIV-infected volunteers because they represent some of those who might benefit from a preventive Ebola vaccine in Africa. "It's an important consideration given that both of these viruses can be present in the same communities," said Col. Nelson Michael, MHRP Director.

This is the second Ebola vaccine clinical trial conducted at WRAIR, and will be the fourth Ebola vaccine study conducted in Africa by the Institute and MHRP.

Infectious diseases such as Ebola pose a significant threat to the U.S. Military and the global community," said Col. Stephen Thomas, WRAIR's Deputy Commander of Operations. "WRAIR has extensive expertise in infectious diseases and an international research network in countries where diseases are endemic, giving us an ideal platform to conduct these types of studies.

First-in-Human Phase 1 Clinical Trial of MERS Vaccine Begins

WRAIR began vaccinations in February for a Phase 1 clinical trial to evaluate the safety and immunogenicity of a candidate vaccine for MERS-CoV (Middle East respiratory syndrome coronavirus), led by MHRP research physician Dr. Kayvon Modjarrad.

The vaccine (GLS-5300) was co-developed by Inovio Pharmaceuticals and GeneOne Life Science, Inc. Though other vaccine candidates have previously been tested for use in camels, which are the suspected source of MERS-CoV, GLS-5300 is the first MERS-CoV vaccine to be tested in humans. Seventy-five participants will receive the vaccine at WRAIR's Clinical Trials Center in Silver Spring, Md.

MERS-CoV, which causes a severe respiratory disease akin to the Severe Acute Respiratory Syndrome (SARS), was first identified in Saudi Arabia in 2012. MERS-CoV has infected more than 1,600 people and killed nearly 40% of those infected. The most common symptoms of this disease are fever, cough and shortness of breath.

Older people and those with weakened immune systems are at greater risk for severe disease and death. There are currently no approved vaccines or specific treatments for MERS.

The virus has been circulating primarily in Saudi Arabia, where the majority of cases have been reported. According to the World Health Organization, cases have now been confirmed in 26 countries, but experts believe these cases were acquired in the Middle East and then exported outside the region. A 2015 outbreak in the Republic of Korea is the largest outbreak outside of the Middle East.

"MERS is a growing global concern given its high fatality rate," said MHRP Director Col. Nelson Michael. "Given global deployments to the Middle East and South Korea coupled with close living quarters in those situations, military personnel are at increased risk for exposure to MERS."

HIV-1/2 Rapid Diagnostic Tests Compared in Nigeria

A study authored by Dr. Mark Manak, chief scientist in MHRP's Department of Laboratory Diagnostics and Monitoring, and published in the *Journal of Clinical Microbiology*, found that two HIV-1/2 rapid diagnostic tests (RDTs) performed well compared to enzyme immunoassay tests in both high and low prevalence populations in Nigeria.

Enzyme immunoassay (EIA) tests detect HIV antibodies in bodily fluids, and results from most EIA tests and confirmatory Western blot tests are usually available within two to 14 days. Using technology similar to that of an EIA, a rapid test produces results in approximately 20 minutes.

The Nigerian study was part of a larger program for development of a cohort for evaluation of an HIV vaccine. Samples collected in that study were tested by rapid test in the field and sent to the MHRP HIV Diagnostics Reference Laboratory in the U.S. for testing by the FDA cleared HIV-1/2/O EIA assay (Bio-Rad) and confirmation by the Bio-Rad Western Blot (WB).

This study then compared the performance of the combination of Determine and Stat-Pak RDTs relative to the EIA and WB. The combination of the two RDTs demonstrated excellent sensitivity (97.8%) and specificity (>99.9%), indicating a high level of confidence that positive results were correctly diagnosed. This diagnostic reliability compares to that of laboratory employing 3rd generation EIA screening.

The availability of reliable HIV-1/2 rapid tests in resource-limited settings represents an important advancement in the accurate diagnosis of HIV infection and presents opportunities for implementation of effective prevention and treatment interventions among vulnerable populations.

Systems Serology Seeks to Profile Immune Responses

Systems Serology, a multi-dimensional analysis of humoral immune response, may aid in the evaluation and design of HIV vaccines by identifying unexpected predictive mechanisms of protective immunity, according to a paper published in the journal *Cell* in November.

The technique, termed 'Systems Serology,' was developed by Galit Alter and her collaborators at the Ragon Institute of Massachusetts General Hospital (MGH), Massachusetts Institute of Technology (MIT) and Harvard University in Boston.

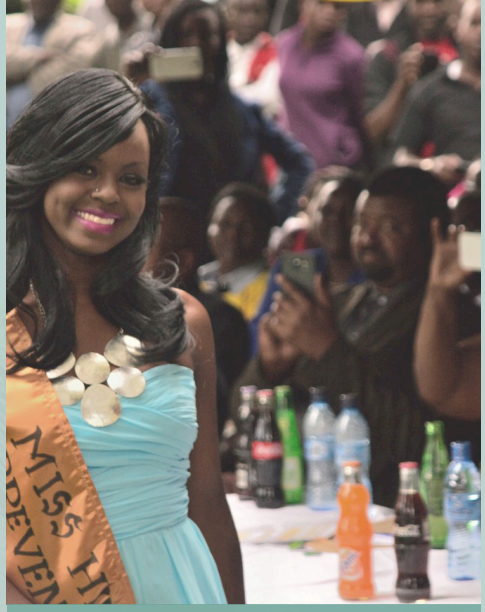
Researchers profiled the relationship between 64 biophysical measures of humoral immune response by applying a battery of modeling techniques to samples from four HIV vaccine trials, including MHRP-led RV144. Each vaccine regimen elicited a "fingerprint," a unique co-variation in immune response measurements.

"This approach dives deep into the data, and looks at integrative and network-oriented relationships between a broad range of antibodies associated with vaccine regimens and outcomes," said COL Nelson Michael, one of the study's co-authors.

This novel vaccine-profiling approach may have broad applications and could assist in vaccine development efforts against other deadly global pathogens.

World AIDS Day 2015

U.S. Ambassador to Nigeria, James Entwistle, (left) tours an exhibit of art created by Nigerian youths as part of a 2015 World AIDS Day program.



MHRP's Kericho, Kenya, site hosts a Miss HIV Prevention competition as part of its World AIDS Day 2015 activities.

Students of Command Secondary School in Enugu, Nigeria, take part in an HIV-themed debate as part of World AIDS Day 2015.

Kenyan Member of Parliament Dr. James Nyikal plays soccer with some Kisumu locals on World AIDS Day 2015.

Dr. Ananworanich Discusses Cure Prospects in World AIDS Day Presentation

In a World AIDS Day presentation at Walter Reed Army Institute of Research on December 1, 2015, Dr. Jintanat Ananworanich discussed HIV cure research strategies, and stressed the need to conduct social, behavioral and ethics research in parallel with cure research.

Dr. Ananworanich serves as the Associate Director for Therapeutics Research at MHRP. Her cure studies investigate whether administering antiretroviral therapy to patients as soon after infection as possible can reliably increase their likelihood of achieving a functional HIV cure, or HIV remission—meaning that HIV remains virtually undetectable in the blood even after the patient stops treatment. She is currently the principal investigator on the MHRP/NIAID-funded acute HIV infection study, RV254.

Dr. Merlin Robb, Dr. Jintanat Ananworanich and Col. Nelson Michael at World AIDS Day seminar.

New Grants Awarded to Two MHRP Research Teams

MHRP's Dr. Michael Eller and collaborators received a $2.5 million, five-year award for a project on "Intestinal MAIT cells in HIV-1 infection" from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dr. Eller is chief of MHRP's Flow Cytometry Core, and key collaborators include Karolinska Institute, the University of California, Davis, and a clinical site at the University of California San Francisco.

"Mucosa-associated invariant T-cells (MAIT) cells are a recently described type of white blood cell that plays a major role in host defense against disease-causing bacteria and fungi," said Dr. Eller. "Because MAIT cells were recently impact discovered, very little is known about how they impact HIV disease progresion."

Dr. Eller will leverage samples from MHRP's acute infection studies, RV217 and RV254, to better understand how and why MAIT cells are killed or damaged during acute HIV infection; and to test whether taking anti-HIV drugs during acute infection can restore MAIT cells, or improve their function, in HIV-infected people.

Dr. Gary Matyas, chief of vaccine adjuvants and formulations at MHRP, was awarded a new five-year grant from DoD's Congressionally Directed Medical Research Programs (CDMRP) for a new clinical trial in Kenya, which will test various adjuvants with a DNA vaccine candidate followed by gp145 protein boosts. Dr. Fred Sawe is collaborating in Kenya, and Dr. Shan Lu at the University of Massachusetts Medical School is collaborating on the DNA portion of the vaccine.

The clinical study, which will be conducted in Kenya, aims to identify a vaccine-adjuvant formulation that will induce potent HIV-specific immune responses that may prevent and/or control HIV. This study uses adjuvants with a proven record of inducing high titer durable antibody responses in humans, but is innovative in that these adjuvants have not been used with DNA vaccines in humans.

Researchers hope to determine which of the vaccines resulted in the highest amount of antibodies to the V1V2 region and then move that vaccine to further studies that test the effectiveness of the vaccine, both as a preventive and therapeutic vaccine.

MHRP Acute Infection Study Updates

MHRP's acute cohorts provide insight into crucial stages of early HIV infection. The acute, or first stage of HIV infection immediately follows exposure to the virus and occurs before common tests to diagnosis HIV are able to identify infection.

In order to better understand how the immune system responds during the critical moments of early infection, MHRP launched two innovative cohort studies in Thailand and East Africa, RV217 and RV254. By focusing on the earliest stages of infection, scientists hope to understand what's needed to create an effective HIV vaccine and possibly inform future investigations into a functional cure.

RV217 has many unique elements, including the acquisition of samples prior to HIV infection, the potential to acquire samples during the eclipse phase of infection prior to detectable HIV nucleic acid but after actual infection has occurred, and the collection of samples prior to peak viremia and the advent of antibody responses. As of late 2015, there were 112 incident cases of acute HIV infection in this cohort, with more than 50 cases in the very earliest stage (Fiebig I/II).

It's important to understand acute infection because in those earliest days a tremendous amount of virus is laid down in a latent reservoir. If we want to cure people, this may be our point of opportunity to intervene." — Dr. Merlin Robb, Deputy Director (Clinical) of MHRP and protocol chair of RV217

For RV254/SEARCH, more than 160,000 samples have been collected from individuals receiving voluntary testing and counseling at two clinics in Bangkok, where 325 individuals have been found to be in acute stages of HIV infection, or within the first four weeks of infection. Of those individuals, most were then enrolled in a study where they immediately received Antiretroviral therapy—either HAART or MegaHAART. More than 100 volunteers were in Fiebig I/II stage of infection.

MHRP will begin several functional cure studies with these cohorts in 2016.

MHRP and Collaborators at CROI 2016

Presenter	Title	Date	Session Time	Session Title
Mark Manak	Western Blot Index for estimating recency of HIV infection	23-Feb	2:45 PM - 4:00 PM	HIV Diagnostics
Trevor Crowell	Virologic Failure is Uncommon after Treatment is Initiated during Acute HIV Infection	23-Feb	2:45 PM - 4:00 PM	Insights from ART Use: Low Income Settings
J. Kalpana	Brain Volumetric Changes After Two Years of ART Initiated During Acute HIV Infection	23-Feb	2:45 PM - 4:00 PM	Neuroimaging: Brain Structure and Functional Response
Sandhya Vasan	Early CSF Viremia and CNS T Cell Infiltrate in a Non-Accelerated SHIV Infection Model	24-Feb	2:45 PM - 4:00 PM	CNS HIV Entry, Reservoir, Compartmentalization
Siriwat Akapirat	Specific IgG Subclasses Induced in RV305, a Late Boost Vaccination of RV144 Subjects	24-Feb	2:45 PM - 4:00 PM	Evaluating HIV Vaccines: Preclinical to Clinical
Jintanat Ananworanich	HIV DNA set point remains elevated in untreated vs. treated acutely infected Thais	24-Feb	2:45 PM - 4:00 PM	Impact of ART on Viremic Control and Tissue Reservoirs
Trevor Crowell	Stigma, Access to Care, and HIV among Men who Sell Sex in Nigeria	24-Feb	2:45 PM - 4:00 PM	MSM in Low and Middle Income Countries
Alexandra Schuetz	Peripheral Immune Activation Modulates HIV RNA Entry to CSF in Early Acute Infection	24-Feb	2:45 PM - 4:00 PM	CNS HIV Entry, Reservoir, Compartmentalization
Morgane Rolland	Limited Evidence for a Bias toward Consensus Residues upon HIV-1 Transmission	25-Feb	2:45 PM - 4:00 PM	Defining the Sequence Characteristics of Transmitted Viruses
Lydie Trautmann	Dual Role of Activated and HIV-specific CD8 T cells in CSF during Acute HIV Infection	25-Feb	2:45 PM - 4:00 PM	Host and Virus Biomarkers and Immune Response
Alexandra Schuetz	Reduced Peripheral α4β7+ CD4+ T Cells Correlate with Mucosal CD4+ T Cell Loss in AHI	25-Feb	2:45 PM - 4:00 PM	Pathogenesis of Mucosal Transmission
Joanna Hellmuth	Neurologic Signs and Symptoms Frequently Manifest in Acute HIV Infection	25-Feb	2:45 PM - 4:00 PM	Clinical Distinctions and Therapeutic Response
Joanna Hellmuth	Psychiatric Symptoms are Common in Acute HIV and Correlate with Disease Biomarkers	25-Feb	2:45 PM - 4:00 PM	Host and Virus Biomarkers and Immune Response

Career Opportunities at MHRP

MHRP is an international HIV vaccine and cure research program that successfully integrates HIV/AIDS prevention, care and treatment. We are currently looking for research physicians, research associates, clinical research associates, research laboratory director, site manager and program managers for positions in the U.S. and Africa. Visit our website for more details: hivresearch.org/careers

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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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