

MHRP EXCHANGE



Fall 2016

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

Research Team to Collaborate on Immunotherapy for Cure

MHRP is part of a collaborative research team, or “Collaboratory,” that was awarded funds to develop an integrated approach to finding an HIV cure. This research project brings together some of the leading researchers in the cure field and will help further our understanding of the role of immunity in HIV persistence.

The National Institutes of Health (NIH) funded this program as part of the Martin Delaney Collaboratories for HIV Cure Research initiative. Beth Israel Deaconess Medical Center (BIDMC) was the primary recipient, and MHRP is one of three teams participating in this collaboration, called “Immunotherapy for HIV Cure” (I4C). The Collaboratory will be jointly led by Dr. Dan Barouch at the BIDMC, Dr. John Mellors at the University of Pittsburgh and Col. Nelson Michael at MHRP.

The researchers plan to intensively study the immune responses generated by therapeutic vaccines, broadly neutralizing

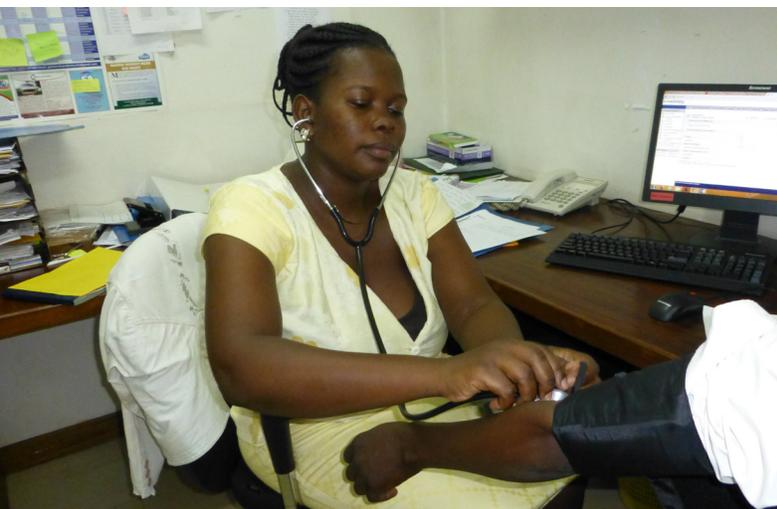
antibodies, and latency reversing agents in both acutely infected individuals and also in preclinical studies.

Col. Nelson Michael, MHRP director and co-principal investigator of the study, notes that, “MHRP brings broad expertise in clinical research for HIV vaccines, acute infection studies and cure studies to this collaboration.”

At the center of MHRP’s efforts is a Thai acute infection cohort study, RV254, which is a collaboration with the Thai Red Cross AIDS Research Center.

“Through RV254, we have been able to identify more than 400 people found to be acutely infected, and nearly all of them opted to start ART within days of discovering their status,” said Dr. Jintanat Ananworanich, who is the co-principal investigator for MHRP on the clinical portion of the collaborative project.

Early HIV Immune Dynamics Can Impact Serology, Reservoir Size



The initiation of antiretroviral therapy (ART) during acute HIV infection (AHI) may impact the development of antibodies to HIV, affecting the ability of diagnostic tests to detect HIV infection, according to a study published in *Clinical Infectious Diseases* in June.

Scientists tested the sensitivity of several diagnostic technologies using samples drawn from participants in MHRP and the Thai Red Cross’ RV254 acute infection study, in which individuals in AHI are identified and immediately begin ART, some within days of HIV exposure.

“After early ART initiation, antibodies to HIV may fail to develop, and the HIV diagnostic tests may be falsely negative,” said Dr. Jintanat Ananworanich, the paper’s senior author. “While it’s uncommon to perform HIV testing on individuals receiving treatment, there maybe instances such as re-location or doubt about testing results where re-testing may be necessary and could lead to erroneous results given these findings.”

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MHRP Supports WRAIR Efforts to Develop Zika Vaccine

2015

NOVEMBER
First case of
Zika in USA



2016

FEBRUARY
WRAIR starts
production of Zika
Vaccine, ZPIV



JUNE
ZPIV provides
100% protection
in mice



nature
Vaccine protection against Zika virus from Brazil

JULY
License technology
to Sanofi Pasteur to
scale-up production



SANOPI PASTEUR

AUGUST
ZPIV provides
100% protection in
rhesus monkeys



nature
Protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys

OCTOBER
Human Phase I
clinical studies
begin with ZPIV



Working with government, industry and academic collaborators, the Walter Reed Army Institute of Research has developed a Zika Purified Inactivated Virus (ZPIV) vaccine candidate. Researchers were able to move from initial conceptualizing of a Zika vaccine to publishing preclinical findings in two high impact publications within an unprecedented 180 days.

MHRP director Col. Nelson Michael is currently acting as WRAIR's Zika program co-lead. In June 2016, WRAIR and collaborators at Beth Israel Deaconess Medical Center (BIDMC) completed a promising preclinical study of the ZPIV vaccine, the findings of which were published in the journal *Nature* and demonstrated that single shots of the vaccine protected mice against subsequent Zika challenge.

Findings from another preclinical study in rhesus monkeys showed that vaccinated rhesus monkeys had complete protection against both Brazilian and Puerto Rican strains of Zika virus. Findings from this study were published in the journal *Science* in August 2016.

WRAIR's rapid response to the Zika threat is thanks in part to an existing relationship with Dr. Dan Barouch, formed through years of collaboration in HIV vaccine research and development activities. Dr. Barouch and his team at BIDMC conducted the preclinical testing of WRAIR's ZPIV vaccine.

"The playbook was there. The players were there. Teams were formed. We just turned to a new enemy," said Col. Michael of MHRP's HIV vaccine development work and the pivot to turn that expertise towards Zika efforts.

Researchers plan to start human testing of the ZPIV vaccine in October 2016. The Army has signed a Cooperative Research and Development Agreement with Sanofi Pasteur, transferring the ZPIV technology to Sanofi to explore advanced and larger scale manufacturing and production. In September, Biomedical Advanced Research and Development Authority (BARDA) announced they will fund \$43.2 million to Sanofi Pasteur to support the advanced development of ZPIV.

Early HIV Immune Dynamics Can Impact Serology, Reservoir Size

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A study stemming from MHRP's RV217 acute infection cohort demonstrated that when ART is initiated during early AHI, it can significantly reduce total HIV DNA levels in the body, which may have implications for the goal of achieving long-term HIV remission. Findings from this study were published online in the journal *EBioMedicine* in July.

"HIV reservoir size is pertinent to the goal of HIV remission – that is, undetectable viral load without treatment – because the size of the reservoir may predict time to viral load rebound after ART cessation," explains Dr. Merlin Robb, senior author on the paper. "It is hypothesized that people with a smaller reservoir size will have a greater chance of achieving HIV remission."

About MHRP's Acute Infection Cohorts

In order to better understand how the immune system responds during the critical moments of early acute infection, MHRP launched two innovative cohort studies in Thailand and East Africa, RV217 and RV254, which include individuals whose HIV is diagnosed within days to weeks of infection.

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.

JWARG Initiates Sepsis, Acute Febrile Illness Studies



Researchers and staff at sites in West Africa have undergone several lab trainings to prepare for clinical studies.

In July 2016, a new observational study of patients with sepsis began at Komfo Anoyke Teaching Hospital (KATH) in Kumasi, Ghana. Their first patient was enrolled from the Ghana site, who was also the first patient enrolled under the Joint West Africa Research Group (JWARG) initiative.

JWARG was initiated in late 2015 and is a collaboration between MHRP/WRAIR, Walter Reed Program-Nigeria, Naval Medical Research Center, Naval Medical Research Unit 3-Ghana Detachment, the Austere Environment Consortium for Enhanced Sepsis Outcomes (ACESO) and other military, government and academic institutions. The initiative leverages existing research platforms and relationships in West Africa to improve biopreparedness in the region.

A new surveillance study will begin in late 2016, led by MHRP, exploring severe acute febrile illness prevalence and incidence at medical centers in Nigeria, Ghana and Liberia. Through this study, JWARG will build scientific capabilities, provide an important surveillance mechanism and also broaden understanding of the epidemiology, immunology and genetics of severe acute infectious diseases.



On June 23, JWARG was officially commissioned by the Deputy Chief of Missions, Maria Brewer, in Lagos, Nigeria. Remarks were made by Commander of the Nigerian Army Medical Corps, Major-General Atilewa Amusu. This event was hosted by the Walter Reed Program-Nigeria.

Kenya PEPFAR Sites Complete Rapid Results Initiative

MHRP's participation in a four-month, massive HIV testing initiative in Kenya resulted in the identification of more than 5,000 positive cases and enrolled 4,545 people into care.

MHRP's PEPFAR-funded sites in Kenya, in collaboration with the nation's Ministry of Health, recently completed this 100-day national HIV testing and treatment Rapid Results Initiative (RRI). Staff at the Kisumu West, South Rift Valley and Kenya Defense Forces sites participated in the initiative.

The RRI also included a record review to identify those who were on care and should have been on treatment. This resulted in over 7,000 people initiating antiretroviral therapy (ART), a combination of new positives and those currently on care who qualified for ART.

The RRI, which ran from April through the end of July, aimed to improve countrywide HIV testing and treatment targets aimed to fast track Kenya's progress towards the global U.N. 90-90-90 targets. 90-90-90 is an ambitious target launched by UNAIDS in 2013 to accelerate global HIV prevention, care and treatment. By 2020, UNAIDS aims to have 90% of all people living with HIV knowing their HIV status, 90% of all people with diagnosed HIV infection receiving sustained ART and, 90% of all people receiving ART therapy having viral suppression.





A delegation from Thailand visited WRAIR in August for meetings with WRAIR and MHRP leadership. Pictured from left to right are Dr. Somkiat Siriruttanapruk, Senior Expert in Preventive Medicine; Dr. Supachai Rerks-Ngarm, Consultant, HIV Vaccine Trial Office; Dr. Amnuay Gajeena, Director General of Thailand's Department of Disease Control (DDC); Dr. Nakorn Prem Sri, Director of HIV Vaccine Trial Office; and Dr. Preecha Prempre, Director of the Bureau of Occupational and Environmental Diseases.

Infusions Begin in Therapeutic Antibody Trial

Infusions have begun in a Phase 1 clinical trial (RV397) to evaluate a novel therapeutic strategy that uses broadly neutralizing human monoclonal antibodies (mAb) administered during a period of treatment interruption in volunteers who initiated antiretroviral therapy (ART) during acute HIV infection (AHI).

The study will recruit 24 adults in Bangkok, Thailand, who were diagnosed during AHI, generally within 21 days of contracting HIV. Participants began ART immediately upon diagnosis and have been virally suppressed for more than two years. They will be randomly assigned to receive either a placebo or VRC-HIVMAB060-00-AB (VRC01), a broadly neutralizing human mAb that targets the HIV-1 virus, specifically the CD4 binding site. VRC01 was developed by the Vaccine Research Center of NIAID/NIH, and it is administered via intravenous infusion.

MHRP researchers have been screening potential participants since August, and in September four volunteers received their first infusions, with five more scheduled to receive infusions in the coming weeks. Researchers expect to reach the enrollment goal of 24 participants by mid-November.

Broadly neutralizing mAbs have the potential to treat HIV by blocking the virus from infecting new cells and helping to destroy cells that are already infected. The main objectives of RV397 will be to determine the safety of VRC01 in this cohort (RV254) and to examine whether broadly neutralizing mAbs have an impact on viral suppression in the absence of ART.

RV398 is a trial of VRC01 set to take place at MHRP sites in Uganda, Kenya, Tanzania and Thailand as part of our RV217 cohort. Volunteers in this trial, who are identified within days of infection, will be placed on ART and can opt to receive VRC01 as well. Researchers hope to determine whether the addition of VRC01 has an impact on plasma viremia when combined with ART in this early phase of infection. RV398 is currently open for enrollment.

Previously published findings from these acute infection studies have shown that during the earliest stages of AHI, the viral load set point is established, which determines how fast HIV progresses. To achieve HIV remission, this may be a critical opportunity to intervene.



Dr. Jintanat Ananworanich leads the RV254 study in Thailand.

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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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