The U.S. Military HIV Research Program (MHRP) conducts research to develop an effective preventive HIV vaccine and integrates prevention, treatment, diagnostics and monitoring as part of an international effort to protect U.S. and allied troops and reduce the impact of HIV infection worldwide.

MHRP is centered at the Division of Retrovirology at the Walter Reed Army Institute of Research (WRAIR), the largest and most diverse biomedical research laboratory in the Department of Defense (DoD) and part of the U.S. Army Medical Research and Materiel Command.

Program activities are conducted in collaboration with the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF) through a cooperative agreement.

**INTERNATIONAL NETWORK**

MHRP has developed an extensive clinical research network in the U.S., Africa and Asia, including:

- MHRP Laboratories and Headquarters  
  > MARYLAND
  Walter Reed Project (WRP)
  > KENYA
  Walter Reed Program (WRP-T)
  > TANZANIA
  Makerere University Walter Reed Project (MUWRP)
  > UGANDA
  Department of Defense HIV Program (DODHPN)
  > NIGERIA
  Armed Forces Research Institute of Medical Sciences (AFRIMS)
  > THAILAND

(See page 26 for more details)
HIV is a global crisis, and a safe and effective vaccine is imperative if we are to end this pandemic.

The MHRP-led Thai HIV vaccine trial, known as RV144, altered and propelled the field of HIV vaccine research, offering the first proof that a vaccine can protect against HIV.

With more than 33 million HIV infections worldwide and thousands of new infections occurring every day, the HIV pandemic remains a pressing global public health challenge. While advances such as antiretroviral therapy (ART) have made a significant impact on the disease, AIDS-related illnesses continue to be one of the leading causes of death globally.

The U.S. Military HIV Research Program (MHRP), centered at the Walter Reed Army Institute of Research (WRAIR), strives to protect U.S. troops from HIV infection and reduce the global impact of the pandemic. While our primary mission is to develop a globally effective HIV vaccine, MHRP integrates prevention, treatment, diagnostics and monitoring as well.

MHRP locations comprise the headquarters and main laboratories at WRAIR, located in Maryland, and five international research sites. This extensive infrastructure provides a unique and effective network for conducting research and assessing candidate vaccines in overseas endemic settings.

In the communities where we conduct research, MHRP provides HIV prevention, care and treatment through the President’s Emergency Plan for AIDS Relief (PEPFAR). Integration of research and preventive services ensures an ethical, non-coercive environment in which to conduct clinical research.

Over the past 25 years, MHRP has achieved global recognition in HIV research by employing a distinctly multi-dimensional approach to the pandemic. From strong preclinical research programs to the design and successful execution of large-scale clinical trials, MHRP’s vast experience, robust international network and collaborative environment have led to breakthrough discoveries paving the way towards an effective preventive vaccine.

MHRP collaborates with many U.S. and international agencies and research institutes including the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, which provides funding for many of our research programs. Key to MHRP’s achievements are our partnerships with host country governments, universities and community organizations, which help leverage research dollars and expertise, accelerating the progress towards a globally effective vaccine.

Launched in 2003, the President’s Emergency Plan for AIDS Relief (PEPFAR) is the largest U.S. Government international health initiative in history and is the cornerstone of the U.S President’s Global Health Initiative.

The worldwide genetic variability of HIV in both individuals and populations has a direct impact on vaccine development as well as diagnosis, monitoring and treatment. New epidemics continue to emerge in places like Eastern Europe, Asia and Afghanistan, which pose an unknown risk to U.S. Service members deployed to these regions. MHRP works to protect troops and minimize the toll of HIV on the global community by monitoring the epidemic in areas where troops are or may be deployed. HIV is a global crisis, and a safe and effective vaccine is imperative if we are to end this pandemic.
**PROTECTING TROOPS AND MINIMIZING THE GLOBAL IMPACT OF DISEASE**

**A History of Success**

Global deployment requires global expertise and resources, and that is why infectious disease research has always been an essential focus for the DoD. Since the time of Walter Reed’s discovery that led to the control of yellow fever, military researchers have made, and continue to make, significant contributions and play an important role in worldwide public health. Our military researchers focus on Soldier health and ensure that the DoD is prepared to prevent, diagnose and treat diseases, and able to identify and effectively manage emerging threats.

**Combating HIV**

In 1985, the U.S. Military recognized the emerging HIV epidemic as a new threat to U.S. and allied forces worldwide. A military directive emerged to develop effective preventive measures including education, vaccine development and implementation of novel antiviral therapies for the DoD. Shortly thereafter, the U.S. Congress mandated the formation of a U.S. Army-led HIV/AIDS research unit to protect military personnel and serve the global community. Central to this effort is the development of a globally effective vaccine and the establishment of policies and procedures such as the force-wide HIV screening program, designed to protect individual health and assure military readiness.

**Military Medicine Highlights**

1777
Immunized first army against smallpox

1836
Developed treatment for malaria

1900
Identified mosquito as yellow fever vector

1914
Developed typhoid immunization

1945
Invented influenza vaccine

1957
Isolated vaccine strain for influenza A virus

1958
Unveiled cholera oral rehydration regimen

1969
Invented vaccine for rubella

1980
Developed adenovirus vaccine

1981
Developed meningococcus and hepatitis B vaccine

1986
Invented the initial HIV disease staging system

1988
Demonstrated heterosexual contact as major route of HIV transmission

Watch a video on your phone with COL Nelson Michael, M.D., Ph.D., Director, MHRP.

Go to get.beetag.com on your smartphone to download the app. Hold your phone over the square above to scan it. Or view video at www.hivresearch.org.
Reducing “the toll of HIV/AIDS and other infectious diseases” is a stated goal in the most recent U.S. National Security Strategy. Collaborative international efforts towards this end are critical as they sustain progress and stability in many parts of the world.

Military medical researchers continue to lead the charge against infectious diseases, and play a key role in global efforts to develop vaccines against HIV as well as dengue and malaria. These collaborative efforts protect our troops; they also translate into improved global health and help promote security in unstable parts of the world, where infectious diseases have a devastating impact on individuals, communities and many nation-states.

President Kikwete emphasized the importance of developing regional, national and international strategies to combat the HIV/AIDS pandemic, adding a “very special thanks to the leadership of the U.S. Military HIV Research Program at the Walter Reed Army Institute of Research for the good leadership in HIV research and treatment efforts globally.”

**RECOGNIZED AS A LEADER BY THE INTERNATIONAL MILITARY COMMUNITY**

“HIV/AIDS has now become a personal, communal, economic and global security threat. It has the potential to undo decades of social and economic progress made in our countries. It can be so pervasive that it destroys the very fabric of what constitutes a nation,” said Tanzanian President Jakaya Mrisho Kikwete in a keynote address at the 2010 International Military HIV/AIDS Conference.

**U.S. Military researchers contributed to the development of eight U.S.-licensed vaccines—approximately one-half of nonpediatric vaccines that are currently administered to Service members.**

1992
*Developed vaccine against Japanese encephalitis*

1995
*Developed efficacious hepatitis A vaccine*

1997
Conducted first HIV-1 trial with non-B protein

2003
Initiated Phase III study of HIV vaccine candidate in Thailand (RV144)

2004
Performed pivotal research and efficacy testing on leading malaria vaccine candidate

2006
Characterized new circulating recombinant forms of HIV in East Asia

2009
Announced results of RV144, which showed that a vaccine regimen was safe and modestly effective in lowering rate of HIV infection in humans
MHRP has developed a highly-successful program to address military-specific concerns that include ensuring accurate HIV testing and clinical monitoring of HIV infected personnel for U.S. Army Active, Reserve, and National Guard units, and for individuals applying for Army service; tracking the HIV epidemic in Active-duty Forces; and assessing risk of HIV exposure to deployed U.S. and Allied Forces.

Working in tandem, MHRP’s epidemiology expertise and state-of-the-art diagnostics capabilities inform policy development and public health practice to control and prevent HIV and co-infections in U.S. and foreign militaries.
An unprecedented amount of whole blood has been used in combat casualty care during current operations in Iraq and Afghanistan. When the blood supply of FDA-compliant products is exhausted, the use of partially screened, non-FDA-compliant blood products donated by other Service member volunteers from the ‘walking blood bank’ is allowed.

To better understand the risk this blood posed to those serving in Iraq and Afghanistan, MHRP researchers analyzed available pre- and post-transfusion samples from the 761 U.S. Service members who received freshly collected whole blood or platelets. Investigators tested the samples for evidence of HIV, hepatitis B virus (HBV) and hepatitis c virus (HCV).

MHRP researchers found that no HIV or HBV infections stemmed from an emergency battlefield transfusion, indicating that current mandatory HIV screening and HBV vaccination is effective. However, one recipient was found to have HCV associated with an emergency transfusion. This data reinforces the need to continue mandatory screening for HIV and could effect policy change to require pre-deployment screening for HBV and HCV.

A force-wide hepatitis screening policy could serve as additional protective measure to mitigate future emergency transfusion-related infections. MHRP is supporting a large U.S. Army Public Health Command investigation that will comprehensively characterize the epidemiology of HCV and HBV infection among the deployed force and will inform development of screening policy.

MHRP scientists identified rapid blood tests that screen whole blood donors in theater, helping ensure a safe blood supply on the battlefield in Iraq and Afghanistan.
CHARACTERIZING THE THREAT

MHRP threat assessment activities are aimed at determining the risk of HIV and HIV-related infections to U.S. and Allied Forces deployed overseas. MHRP conducts studies in regions of the world where the global epidemic has not yet been adequately defined, with emphasis on areas of potential or actual U.S. Military personnel deployment.

In contrast to the U.S. civilian population, which has exposure to a relatively low prevalence of HIV, the U.S. Military, through travel and deployment, can potentially be exposed to high-prevalence populations and the vast range of HIV diversity in the global epidemic.

ASSESSING RISK OF HIV TO SERVICE MEMBERS IN IRAQ AND AFGHANISTAN

Afghanistan and Iraq lie in a region of the world where information on HIV prevalence, risk groups and genetic subtypes is almost nonexistent and whose border countries are experiencing the fastest-growing incidence of AIDS in the world. In an effort to better understand the threat to U.S. Service members deployed to this region, MHRP and its collaborating partners are conducting HIV seroprevalence research in Afghanistan.

Beginning in 2005, efforts focused on high-risk groups, then expanded to assess a general population sample of recruits entering the Afghan National Army (ANA) as well as the civilian blood supply. Thus far, MHRP has defined a novel HIV subtype circulating in Afghanistan and determined that Afghanistan and Iraq lie at the crossroads of at least three distinct regional epidemics. Continued research will focus on seroprevalence, and knowledge and behavior assessments of the ANA to better understand the factors fueling this region’s epidemic.

By studying the epidemic in places such as Afghanistan, Bulgaria and Panama, MHRP aims to better understand the HIV epidemic and risk to Service members in these areas. This type of subtype surveillance is also critical to informing global vaccine development.
HIV DIAGNOSTICS

MHRP has a rich history of developing and executing state-of-the-art HIV diagnostics. As the final authority for HIV infection status for U.S. Army Active, Reserve, and National Guard personnel, MHRP oversees more than one million HIV screening tests per year.

In addition, MHRP conducts all supplemental confirmatory testing for Force Service members and upwards of 100,000 HIV tests per year for the European and Central Commands; clinical monitoring of U.S. Army HIV infected personnel; and, HIV-1 resistance genotyping for therapeutic monitoring for all DoD HIV infected personnel. This mission has allowed MHRP to become the eminent reference resource for DoD physicians and the research community.

The diagnostics program also plays a critical role in MHRP’s vaccine research efforts by deploying screening and diagnostic algorithms for accurate and early detection of HIV infection in vaccine trial participants. The diagnostics laboratory provides Quality Assurance support for all of MHRP’s clinical trials and provides technical assistance to the College of American Pathologists (CAP) accredited clinical diagnostic laboratories in Kenya, Tanzania, Uganda and Thailand.

DEFINING A CARIBBEAN HIV EPIDEMIC

In 2008, in collaboration with MHRP, the Trinidad & Tobago Chief of Defence Staff developed the island nation’s first interim policy on HIV/AIDS. Having no HIV prevalence data, the island’s chief of Defence Staff invited MHRP to collaborate on the Caribbean nation’s first seroprevalence study of Defence Force personnel. Results of this study will help Trinidad & Tobago inform the development and implementation of prevention, care and treatment programs as well as development of a force-wide screening policy.

For the study, samples will be obtained from more than 5,000 Force members. MHRP’s diagnostic laboratory will play a critical role in the screening, management and storage of the samples. The specimens collected in this study will generate a repository that will serve as a national resource and will inform measures to improve the health of the Force and general public health practice. Through on-site training and collaboration, MHRP’s extensive laboratory expertise will help enhance the host-nation’s human and laboratory capacity.
Given the significant threat of HIV infection worldwide, an efficacious vaccine is urgently needed as part of a broader prevention effort to help control the pandemic.
In 2008, sub-Saharan Africa accounted for nearly three-quarters of all AIDS-related deaths. The epidemic appears to be stabilizing somewhat in this region, yet it is increasing in other parts of the world in areas such as China, Indonesia and pockets of Eastern Europe and Central Asia as well as in high-income countries like Germany, Britain and Australia.

The President’s Emergency Plan for AIDS Relief has had a tremendous impact in Africa, preventing new cases and treating people who have the disease. However, for every two new HIV patients placed on treatment, five new cases are diagnosed. It is imperative that international efforts focus on developing new tools to prevent HIV.

History has shown that a vaccine can be the most effective public health tool to control infectious diseases. A globally effective HIV vaccine, along with other proven prevention techniques, would enable us to control the HIV pandemic. Developing a vaccine is a long-term effort, and we are confident that recent advances such as RV144 have provided not only optimism but also significant scientific momentum that will help us achieve this goal.

Finding an effective HIV vaccine will prove to be one of the greatest scientific challenges of this century. HIV attacks the body’s immune system, hides itself in the body’s cells and mutates rapidly, making it a difficult target for vaccines.

It took nearly 25 years to see the first modest success of a vaccine to prevent HIV in the RV144 study in Thailand.

The history of all vaccine research is typified by a long development period, but initial success is usually followed by a much more accelerated pace of development.

**HIV VACCINE DEVELOPMENT: AN UNPRECEDENTED CHALLENGE**

**FINDING NEW TOOLS TO PREVENT HIV**

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western &amp; Central Europe</td>
<td>820,000</td>
</tr>
<tr>
<td>North America</td>
<td>1,500,000</td>
</tr>
<tr>
<td>Caribbean</td>
<td>240,000</td>
</tr>
<tr>
<td>Central &amp; South America</td>
<td>1,400,000</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>460,000</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>22,500,000</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>1,400,000</td>
</tr>
<tr>
<td>East Asia</td>
<td>770,000</td>
</tr>
<tr>
<td>South &amp; Southeast Asia</td>
<td>4,100,000</td>
</tr>
<tr>
<td>Oceania</td>
<td>57,000</td>
</tr>
</tbody>
</table>

**HIV Destroys:**

- **Individuals** Each day, nearly 5,000 people die and more than 7,000 become infected.
- **Communities** HIV strikes during the prime productive years (age 15 to 49), undoing decades of economic and development progress and leaving children orphaned and vulnerable.
- **Nations** HIV can cause economic instability and affect the security of many nation-states.

**ADULTS & CHILDREN ESTIMATED TO BE LIVING WITH HIV (2009)**

**TOTAL: 33.3 MILLION**

*Source: WHO*
The Thai Phase III HIV vaccine trial, also known as RV144, was the largest HIV vaccine study ever conducted and involved more than 16,000 volunteers in Thailand. This U.S. Army-sponsored study showed that the ALVAC® HIV and AIDSVAX® B/E prime-boost HIV vaccine regimen was safe and reduced the risk of HIV infection by 31.2% in a community-based population in Thailand.

Detailed results were presented on October 20, 2009 by the trial collaborators to researchers gathered at the AIDS Vaccine 2009 Conference in Paris, France and published online by the New England Journal of Medicine (NEJM). While the efficacy is modest, this study represents a significant scientific achievement and provides the first evidence that development of a safe and effective HIV vaccine is possible. Already, RV144 has generated several interesting hypotheses about the types of immune responses that prevent HIV infection and raises substantive questions about the best way to measure these responses. The current planning for new efficacy trials in southern Africa, changes in the non-human primate models, and new enthusiasm for protein boosting and non-neutralizing antibodies reflect the impact of the result.

The RV144 study is an outstanding example of international and interagency collaboration, which included the U.S. Army, the Thai Ministry of Public Health, NIAID, sanofi pasteur, Global Solutions for Infectious Diseases, Mahidol University, AFRIMS (Thai and U.S. components) and HJF. It was funded by NIAID and the U.S. Army Medical Research and Materiel Command and sponsored by the U.S. Army.

The RV144 vaccine regimen topped Time Magazine’s Best of Lists in 2009 and the NEJM article was cited more than 250 times in scientific literature within the first year of publication.
Ongoing RV144 Studies

Searching for Correlates

MHRP and the RV144 collaborators have been working hard to understand how the vaccine prevented HIV infection. More than 150 U.S. and international researchers at 25 institutions are conducting intensive laboratory studies of the patient specimens collected in RV144, and working together to share data and accelerate progress. In 2010, MHRP hosted two laboratory meetings, each drawing nearly 100 collaborators.

Initial laboratory studies identified many types of HIV binding antibodies. In addition, researchers found that in the design of AIDSVAX—the gp120 protein in the vaccine—the placement of a herpes simplex virus peptide at one end of the protein had unanticipated effects. It appears to have changed the structure of the protein to make it look more “natural,” and it exposed areas of the virus that ordinarily remain hidden until HIV binds to a CD4+ T cell. Researchers will be conducting studies to further explore this interesting finding, and will begin case control studies in 2011 to identify specific laboratory tests that may be able to “predict” whether future vaccine combinations may work.

Building On the Success of RV144

Trial collaborators are also planning clinical studies to extend and build on the modest success of RV144. Results suggest that the protection against HIV appeared highest at 6-12 months, based on post-hoc analysis (60%, 95% CI 22, 80). If researchers can sustain or increase this effect, that would be a great accomplishment. To that end, and to help collect more data and samples for immunogenicity studies, MHRP has two smaller studies planned. These studies, RV305 and RV306, will add a secondary boost to try to extend and increase the immune response seen in RV144.

Future large clinical studies will likely involve populations with different risk factors/HIV incidence, and will also be executed in other parts of the world where different strains of HIV circulate. While these studies will take much longer to plan and execute, they will provide important clinical data on how to develop a more effective vaccine that could be used globally.
MHRP researchers are studying a range of vaccine candidates in an effort to identify and elicit the immune responses needed to protect humans from this complex disease. The pox/gp120 vaccine combination used in RV144 is part of MHRP’s regional vaccine approach, which is specific to the HIV subtype circulating in Thailand (B/E).

MHRP is also pursuing vaccine strategies aimed at global protection, which could be tested in a broad spectrum of genetically diverse HIV epidemics.

A NEW GENERATION OF HIV VACCINE CANDIDATES

MHRP scientists developed an attenuated viral vector—Modified Vaccinia Ankara—vaccine candidate, MVA-CMDR, in collaboration with the NIAID Laboratory of Viral Diseases. MHRP currently has two collaborators who provide a DNA prime for this vaccine strategy. One product combination has advanced to Phase II clinical testing (Karolinska DNA + MHRP MVA-CMDR). A Phase I clinical trial using another DNA candidate, PENNVAX™-G, with MVA-CMDR began in late 2010 in the U.S. and will begin in East Africa in 2011.

MHRP is also working with colleagues at Harvard University on a next-generation vaccine that would provide global protection from HIV. These vaccine candidates aim to expand the breadth of immune responses by using mosaic HIV inserts in a prime-boost strategy using heterologous vectors. Early studies show that an Ad26-MVA prime boost strategy prevents simian immunodeficiency virus (SIV) infection and, in the setting of a breakthrough infection, appears to significantly reduce the amount of virus in the blood.

Empirical clinical trials, like RV144, allow scientists to gain critical information on specific immune responses needed to protect a human from HIV acquisition. MHRP will strategically select next-generation vaccine candidates for clinical studies, based on the type and quality of immune responses they invoke.

A globally effective vaccine, along with other proven prevention techniques, would enable us to control the HIV pandemic.
CAPTURING EARLY INFECTIONS

Acute HIV infection is the first stage of HIV infection that immediately follows exposure to HIV and occurs long before an individual knows they are infected. During this time, the virus begins to replicate and invade the immune system. These early events are critical to determining long-term disease course. In addition, many researchers believe that understanding this early stage will help provide clues to developing an effective preventive vaccine.

Since the HIV research field has limited data and samples from early infections, MHRP initiated an ambitious program to follow a group of high-risk volunteers in East Africa and Thailand. Through this study, called the Early Capture HIV Cohort Study (ECHO), researchers collect frequent samples from recently infected persons before they show detectable HIV antibody. Valuable information and mucosal samples from this study will allow scientists to study the virus that is transmitted and replicated, and characterize the immune responses in the first weeks and months of infection.

The study was designed to find early infection prior to diagnosis by conventional testing methods. Thus far, the study has successfully identified acute infection prior to the detection of HIV antibody in 26 of 32 observed cases. This offers an unprecedented window into the earliest events of HIV infection and may help decipher the key events that dictate long-term outcomes. The insights into the earliest interaction of the virus with the human immune system may provide useful benchmarks for vaccine development to prevent HIV infection.

In order to relate early observations to long-term outcome, volunteers who became HIV-infected will be monitored for markers of disease progression and the advent of ART. MHRP plans to collaborate with several research groups to mine the data and samples generated from this study to gain insights into host-HIV interactions.

MHRP supports another acute infections cohort study in Thailand conducted in collaboration with the Thai Red Cross.
LAYING A SOLID FOUNDATION FOR VACCINE RESEARCH

MHRP boasts a strong preclinical HIV vaccine research program with expertise in humoral and cellular immune assessment, host genetics, viral genetics, HIV molecular epidemiology, and novel antigen discovery and liposomal formulations. Here, we highlight just a few of our recent pre-clinical research activities.

Improving Vaccine Effectiveness

Adjuvants are used in vaccines to enhance or prolong the desired immune response elicited by the vaccine. MHRP scientists have more than 20 years of experience with numerous adjuvants and antigens for human vaccines, including lipids, liposomes, and peptide and protein antigens.

MHRP scientists recently identified three highly effective, non-proprietary and easily manufactured adjuvants that proved safe and more potent than a widely used adjuvant in commercial vaccines. This finding could have important implications for the production of vaccines to infrequent, neglected or poverty-related diseases including HIV, malaria and anthrax. MHRP researchers authored a paper on this topic in 2011 in the journal, Vaccine.

Understanding Host Interactions with HIV

Researchers investigate the effect of human genetic diversity on host-pathogen interaction. They look at variations within human genes that may be correlated with disease outcomes, such as disease progression and clinical response to ART and vaccination. Scientists have found that certain genes within groups of people—such as African Americans—have a direct impact on viral load and possibly disease progression. MHRP researchers co-authored a paper in 2010 in the Journal of Infectious Diseases that identified a specific group of alleles that influences viral load in African Americans, a group that is disproportionately affected by the disease.

MHRP scientists have developed novel high-throughput tools to study the genetic composition of populations in East Africa. The implementation of these tools has allowed for rapid advances in our understanding of the genetic complexity in this region. In 2010, researchers analyzed data from a 42-month cohort study in Tanzania. They found that individuals with the HLA-A*7401 allele, a genetic variant of class I HLA alleles, were less likely to get infected with HIV during the study than those who did not carry the allele. The implications of these results may help in the design of HIV vaccines for the region. The paper authored by MHRP researchers was published in 2010 in the Journal of Infectious Diseases.
Characterizing HIV to Advance Vaccine Development

Even though HIV-1 subtype C and A predominate globally, the other viral strains co-circulate around the world and may have a major impact on strategies to control the pandemic. MHRP offers unparalleled expertise in worldwide HIV genetic characterization. Through the use of molecular techniques, our researchers work to describe the genetic diversity of the HIV epidemic, particularly in geographic areas of interest for vaccine development.

MHRP scientists have led the effort to identify and characterize mutated forms of HIV, known as circulating recombinants. These recombinants form a large part of the epidemics in two countries MHRP works in—Thailand and Nigeria.

MHRP’s molecular virologists played a key role on a research team that analyzed the HIV-1 genome sequences from infected volunteers in the Step HIV vaccine trial. They co-authored a paper in 2011 in Nature Medicine that showed the vaccine regimen, although ineffective at preventing infection, influenced the genetic makeup of the viruses that infected the volunteers (breakthrough infections). After comparing the genetic strains of HIV in vaccine and placebo recipients, they found that cellular immune responses generated by the vaccine may have impacted the HIV strains that established infections. These results may provide new ways for vaccine researchers to target HIV.

To protect deployed troops, an HIV vaccine must protect against multiple subtypes found worldwide. While subtype B is predominant in North America and Western Europe, more than 80% of infections worldwide are non-B subtypes.

Developing Lab Tests to Predict Protection from HIV

MHRP researchers are helping to develop a new set of assays, or tests, using state-of-the-art technologies to assess immune responses in vaccine and placebo recipients from RV144. The goal of this research is to gain a comprehensive view of vaccine-induced immunity. If these tests can identify the antibodies and cell-mediated immune responses that help predict protection in the laboratory, this would be a tremendous step towards developing a more effective vaccine.
The advent of life-saving antiretroviral treatment (ART) has dramatically prolonged the life expectancy of people living with AIDS. Scientific evaluation of therapeutic interventions helps us optimize therapy for patients, inform treatment guidelines, enhance the quality of life and ultimately reduce AIDS mortality.

Through many partnerships, MHRP’s therapeutics research portfolio continues to grow in scope and diversity. In 2009, MHRP became an AIDS Clinical Trials Group (ACTG) Clinical Trials Unit, a program of the National Institute of Allergy and Infectious Diseases, with two Clinical Research Sites in Kericho and Eldoret, Kenya.

MHRP also plays a role in improving the science that guides services provided through the PEPFAR program. These projects, Public Health Evaluations (PHE) and basic program evaluations, are aimed at improving health outcomes and increasing program sustainability.

HELPING TO INFLUENCE GUIDELINES FOR PREVENTION OF MOTHER-TO-CHILD TRANSMISSION

The findings of a multi-site ACTG study that included MHRP’s site in Kericho, Kenya, helped influence the World Health Organization (WHO) to change its guidelines for the treatment of HIV-infected women who receive a single dose of nevirapine to prevent HIV transmission to their babies. The study, which appeared in the New England Journal of Medicine, demonstrated that a single dose of nevirapine used to prevent mother-to-child transmission (PMTCT) of HIV can hamper the drug’s effectiveness if it is also used later as part of a treatment regimen.

“We now have a definite answer to a problem that has continued to haunt us for the last 10 years,” said Dr. Fred Sawe, MHRP partner and the local principal investigator for the study in Kenya. “We can now minimize use of single-dose-only nevirapine-based interventions, increase access to more efficacious regimens, and provide better care to women who have been exposed to single-dose nevirapine without slowing down the progress of eliminating pediatric AIDS: a win-win situation of great public health importance.”

The open-label, randomized Phase III study, called Optimal Combination Therapy after Nevirapine Exposure (OCTANE), enrolled 745 women at 10 sites in seven African countries to address the question around nevirapine resistance. Nevirapine—inexpensive and accessible—is widely used in resource-limited settings for PMTCT and treating HIV.

Since 2004, MHRP partners have tested more than 700,000 pregnant women through “prevention of mother-to-child transmission” programs and provided more than 30,000 of those found HIV-positive with antiretroviral treatment.
Evaluating HIV Treatments in Africa

In addition to the OCTANE study, MHRP partnered with the ACTG on a study evaluating when best to start ART in persons with both HIV and tuberculosis (TB) who have started TB therapy. These results may help guide policy for treating HIV and TB co-infections in Africa.

Underscoring the critical need to evaluate best practices and treatments in Africa, MHRP will also be conducting ACTG studies to inform policy makers and clinicians about best treatments for patients with HIV-related conditions including cryptococcal meningitis, Kaposi’s Sarcoma, and oral candidiasis.

Immune Reconstitution Inflammation Syndrome (IRIS)

IRIS is a clinical syndrome that has been described in AIDS patients after initiation of highly active antiretroviral therapy (HAART). It is characterized by paradoxical acute worsening of an underlying opportunistic infection or AIDS-defining illness. Conducted in collaboration with NIAID, the IRIS study will provide details about the immunopathogenesis of IRIS. It is the first Infectious Disease Clinical Research Program (IDCRP)-sponsored HIV trial to open in Africa, and will be supported by advanced laboratory studies conducted at the National Institutes of Health and WRP in Kenya. The study will expand to AFRIMS in Thailand in 2011.

Clinic-based ART Diagnostic Evaluation (CLADE)

CLADE is MHRP’s first prospective PHE funded by PEPFAR. It is an observational cohort evaluation aimed at determining the superiority and cost-effectiveness of two recommended Ministry of Health ART diagnostic evaluation approaches: routine care and viral load guided care. CLADE is unique in that it addresses critical monitoring questions at the clinic level and includes actual costs of services as part of cost-effectiveness evaluations—a primary study objective.

Analyzing PMTCT Cost Outcomes

MHRP will be conducting a study to evaluate the health facility costs of the provision of HIV/AIDS care and ART to pregnant women presenting at the Kericho District Hospital through 24 months post-partum. This study will provide key utilization and cost-effectiveness data based on the novel approach in Kericho that may serve as a future model for other programs.
MHRP carries out prevention interventions based on international best practices, which have been shown to change perception and understanding of HIV transmission and modify high-risk behavior. Funded through PEPFAR, the program has been very successful—having a direct impact in communities impacted by HIV/AIDS.

A mobile circumcision clinic designed and operated by MUWRP exemplifies innovation to expand the reach of free circumcision services to more Ugandan men.

**MEDICAL MALE CIRCUMCISION—A PROVEN HIV PREVENTION TOOL**

Adult male circumcision is a highly effective HIV prevention intervention endorsed by WHO and scientists worldwide. As a result, there is an increased effort to scale up safe and cost-effective circumcision services. The Makerere University Walter Reed Project (MUWRP) has opened two free, non-research male circumcision programs in the Kayunga and Mukono districts of Uganda. In addition to renovating the surgical theatres, MUWRP trains clinicians and educates the public about medical male circumcision.

These PEPFAR-funded surgical centers will meet much of the rising demand for circumcision as an effective HIV prevention measure. “Medical male circumcision is another speed hump against HIV,” said MUWRP’s Mark Breda, “and now that services are available, the men of Kojja Sub-County have another tool to protect themselves and their families against HIV/AIDS.”

More than 3.5 million people have participated in MHRP PEPFAR prevention programs at its sites in Kenya, Nigeria, Tanzania and Uganda.

In 2010, MHRP began supporting the provision of the first free MMC services in Uganda to more than 8,000 males between the ages of 13 and 60. Pictured at right, Ugandan teens learn more about the procedure.
With PEPFAR funding, MHRP strives to create sustainability across its areas of operation in Africa by empowering local partners to implement comprehensive and quality HIV prevention, care and treatment services for the communities participating in HIV research and vaccine studies.

MHRP’s PEPFAR program has helped support more than 200 facilities in the provision of treatment to more than 100,000 HIV-infected individuals.

**REACHING HIGH-RISK YOUTH**

How do you find and connect with high-risk individuals? By going where they go under the cover of darkness.

Staff at the Kericho Youth Centre (KYC), an NGO supported by the Walter Reed Project–Kenya (WRP), developed an innovative plan to reach out to high-risk youth including commercial sex workers and their clients. KYC staff members visit the local trading centers and truck stops surrounding Kericho between the hours of 6 p.m. and 2 a.m., or “moonlight” hours. Through one-on-one meetings, they build rapport with the individuals who frequent these truck stops, providing HIV prevention training and voluntary testing and counseling.

“In a community with a high level of stigma contributing heavily to new HIV infection rates, knowledge of HIV status is an entry point to engage in prevention and reduce the stigma levels,” said Wycliffe Obwiri, Assistant Prevention Program Manager at WRP.

Because of these off-hour services, most of the young people who live in and around the trading centers have received counseling and testing. According to Obwiri, “the community is gradually opening up space for discussion of sex, sexuality and sexual health. With the services now highly accepted in the rural villages, the level of stigma is very gradually but steadily coming down.”

**THE MANGO TREE**

The Mango Tree, an NGO and partner supported by the Walter Reed Program-Tanzania through PEPFAR funding, supports orphans and vulnerable children in areas of southwestern Tanzania where HIV prevalence is in the double digits. Almost 200 volunteers, pictured at left, are the foundation of the program, which strives to provide education and training to area youth, helping them lead self-sufficient and productive lives.
MHRP supports PEPFAR-funded programs that engage both civilian and military populations in sub-Saharan Africa. As part of the DoD’s directive to support foreign militaries in mitigating HIV among their forces, the MHRP PEPFAR program has close ties with the Nigerian, Kenyan and Tanzanian militaries. These programs are executed as part of the Navy’s DoD HIV/AIDS Prevention Program (DHAPP) portfolio.

The Nigerian Ministry of Defence, with PEPFAR support, conducts open houses where they provide free HIV prevention education and testing.

A Tanzania People’s Defence Forces (TPDF) health center in Kigamboni officially opened after undergoing renovations coordinated by MHRP. One of the main goals of the TPDF program is to ensure that all men and women who serve in the Tanzanian army remain HIV-negative throughout their military career.

Members of the Kenya Department of Defense learn about risky behaviors and how to avoid becoming HIV-infected.
MHRP’s site in Tanzania, WRP-T, is working closely with the Malaria Program at WRAIR to build much-needed capacity within Tanzania to strengthen malaria diagnostic capabilities. This collaborative program leverages WRP-T’s established infrastructure, strong local relationships and experience in capacity-building with WRAIR’s expertise in malaria diagnostics and quality assurance and control. This program is part of the U.S. President’s Malaria Initiative (PMI).

Quality diagnostic capabilities are critical to malaria control efforts in Tanzania. There is an urgent need to improve diagnostic infrastructure and develop local technical capacity for malaria microscopy and rapid diagnostic tests (mRDTs) diagnosis.

Working with local partners, WRP-T is conducting site development activities to improve infrastructure and diagnostic procedures, as well as providing training to help increase the number of qualified expert and clinical microscopists. Through these activities, WRAIR is building a sustainable platform by generating new qualified trainers and establishing quality control standards for both microscopy and mRDTs.

In addition to supporting the PMI initiative in Tanzania, WRAIR’s malaria and HIV programs are conducting similar site assessments and laboratory strengthening initiatives within the TPDF and in two regions of Tanzania using new assessment tools developed by Amethyst and WRAIR. Scientists at WRAIR are also planning to conduct research with the TPDF and other local partners, such as the Tanzania National Institute for Medical Research, to estimate the malaria attack rate in specific communities for potential execution of malaria prophylaxis studies.

More than 3 billion people are at risk for malaria, including U.S. Military personnel serving in malaria-endemic regions of the world. U.S. troops lost more person-days to malaria than to bullets during every military campaign fought in malaria-endemic regions during the 20th century.

WRP-T is committed to sustained strengthening of its long-standing collaboration in HIV prevention and treatment in Tanzania, as well as supporting relevant research on malaria and other infectious disease threats.
In the communities where MHRP conducts HIV research and provides prevention, care and treatment services, we have developed human capacity to ensure that our local programs are sustainable. Through our partnership with HJF, MHRP hires local technical and administrative staff so that local programs are administered and implemented by the sons and daughters of the communities we work with and within. MHRP also operates within the public health infrastructure of each country, working closely with local government institutions.

We have CAP accredited labs in each of our research locations and we encourage and facilitate the transfer of technologies to each site. Through the MHRP PEPFAR program alone, more than 3,265 staff members have been trained in provision of ART, and nearly 4,000 staff members have been trained in provision of palliative care. MHRP research programs have supported and enabled nearly 20 researchers to obtain advanced degrees, which helps develop in-country capacity. We also provide training on Institutional Review Boards, Good Clinical Practices and Good Laboratory Practices.

Integrating PEPFAR with MHRP research sites has created a vibrant synergy and enhanced clinical capabilities, public health infrastructure and clinical research.

“Capacity Building 101,” a PEPFAR-supported training on the foundations of basic research, provided more than 100 MHRP and partner participants the knowledge and skills to successfully build and implement research using solid methodology.
MEDICAL LABORATORY TRAINING

One of the ways MHRP supports the military health systems within Nigeria is by strengthening laboratories and integrating health activities, such as HIV testing and malaria diagnostics. The U.S. Public Health Service (PHS) initiated and led a training program in Lagos, Nigeria, on malaria diagnostics and laboratory capacity-building. This unique program enhanced the Nigeria Ministry of Defense (NMOD) participants’ proficiency in malaria diagnostics, while providing hands-on education and practical experience for the PHS officers in the field.

This training program was a great example of an effective multi-lateral collaboration between PHS, MHRP and an international military partner. The rewards of the training program will continue to multiply as NMOD trainees share their knowledge and skills with their counterparts throughout the country.

WRP-Kenya hosts a marathon on HIV Vaccine Awareness Day to help promote community engagement in research activities and to thank volunteers.
The U.S. Military’s long-standing presence and strong relationships with the partners, host governments and militaries in these countries have helped enable MHRP to effectively develop robust scientific infrastructures and long-term relationships needed for sustainable research efforts. The circulating HIV variants in these focus countries cover a spectrum of HIV subtypes, enabling our network to test candidate HIV vaccines for global protection.

MHRP works closely with its partners, other agencies and DoD research programs on collaborative studies in areas such as global emerging infections; malaria diagnostics and co-infections with HIV; Ebola and Marburg vaccines; and TB/HIV co-diagnosis. These programs help leverage resources and strengthen local research capacity and infrastructures.

**WALTER REED PROJECT - KENYA**
Walter Reed Project in Kenya works under the U.S. Army Medical Research Unit–Kenya (USAMRU-K). USAMRU-K, a Special Foreign Activity of WRAIR, has been working with Kenya for more than 30 years conducting research on infectious diseases such as malaria, leishmaniasis and HIV.

**WALTER REED PROGRAM - TANZANIA**
MHRP’s Walter Reed Program–Tanzania works in collaboration with the Ministry of Health and Social Welfare. MHRP research is conducted in partnership with the Mbeya Medical Research Programme, a National Institute of Medical Research collaborating center.

**MAKERERE UNIVERSITY WALTER REED PROJECT**
MHRP established the Makerere University Walter Reed Project in Uganda in 1999 as a non-profit partnership with Makerere University. This site recently concluded an Ebola/Marburg vaccine study.

**DEPARTMENT OF DEFENSE HIV PROGRAM - NIGERIA**
The Department of Defense HIV Program–Nigeria is based at the U.S. Embassy and works closely with the Nigerian Ministry of Defence.

**ARMED FORCES RESEARCH INSTITUTE OF MEDICAL SCIENCES**
Research is conducted out of the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand, a joint U.S. Army/Royal Thai Army research effort. For 50 years, AFRIMS has been America’s premier platform for the study of infectious diseases of military importance in the Asia-Pacific region.
U.S. Military HIV Research Program

Walter Reed Army Institute of Research (WRAIR)
503 Robert Grant Avenue
Silver Spring, MD 20910
301.251.5000

Administrative Offices
6720 Rockledge Drive, 4th Floor
Bethesda, MD 20817

www.hivresearch.org