MHRP EXCHANGE

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

MHRP developing novel antibody for warfighter HIV prevention

MHRP scientists are engaging in preclinical and human clinical trials to develop a novel broadly neutralizing antibody (bNAb), 10E8.4/iMab, as a tool for preventing HIV infection.

10E8.4/iMab is a bispecific antibody that limits HIV replication developed by the Aaron Diamond AIDS Research Center. The Ibalizumab (iMab) arm of the antibody targets the CD4 receptor; whereas the 10E8.4 arm targets a region of the HIV envelope. This combination blocks HIV-1 replication through two

independent mechanisms and is believed to position 10E8.4/iMAb at the site of HIV entry, aiding in the binding and neutralization of incoming viral particles.

MHRP has a particular interest in the application of bNAbs as a prevention tool to limit infection risks in deployed military settings, including those requiring blood transfusions. This strategy demands bNAbs with great breadth and potency, with less emphasis on extended durability.

In a preclinical nonhuman primate (NHP) pilot study, a group of rhesus macaques received an infusion of 10E8.4/iMab prior to a challenge with simian-human immunodeficiency virus (SHIV), and the onset of viremia in these animals was compared to a control group that did not receive the bNAb. No viremia was detected in any of the treated animals over 13 weeks, while viral replication in the control group was robust throughout the study duration.

The study was led by Dr. Matthew Parsons, Head of the Non-Human Primate Laboratory within the Department of Retrovirology at the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand, and Dr. Diane Bolton, Chief of MHRP's Animal Models and Viral Persistence Laboratory. Next steps will be to explore the window of opportunity to administer 10E8.4/iMab before and after SHIV exposure, as well as its efficacy against cell-associated virus.

Phase 1 clinical trial

MHRP and colleagues at the National Institute for Medical Research-Mbeya Medical Research Center (NIMR-MMRC) have also recently initiated the RV584 Phase 1 clinical trial of the 10E8.4/iMab bispecific antibody alone and in combination the Vaccine Research Center-developed mAb, VRC07-523LS. Researchers will evaluate how effective they are at reducing the amount of HIV in people living with HIV.

"This study will inform countermeasures that can potentially be used to mitigate HIV risk to the battlefield blood supply in pre- and post-exposure prophylaxis settings," said MHRP Director Col. Julie Ake.

This study will not only help researchers understand how these drugs might be useful for preventing or treating HIV, but will also evaluate fixed dosing and the safety of intramuscular injections of mAbs, which could greatly expand the feasibility of using them to prevent and treat HIV.

The RV584 Phase 1 clinical trial using 10E8.4/iMab and VRC07-523LS will enroll a total of 20 participants from Mbeya HIV care and treatment centers, with local research leadership provided by Tanzania's National Institute for Medical Research - Mbeya Medical Research Center. Dr. Marco Missanga, pictured right, is the principal investigator of the study.

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AFRICOS marks 10th anniversary with research symposium in Tanzania

MHRP's African Cohort Study (AFRICOS) celebrated its 10th anniversary in November in Dar es Salaam, Tanzania, with a research symposium to review key findings from the study, share ongoing analyses, and discuss future plans.

AFRICOS is a long-term cohort study conducted at multiple sites in four African countries to evaluate HIV prevention, care, and treatment services offered through local facilities and funded by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Study findings impact HIV policy and PEPFAR programming, including evidence-based antiretroviral therapy (ART) recommendations. Currently, the study is being conducted at clinics in Nigeria, Uganda, Kenya, and Tanzania.

The symposium brought together HIV researchers and collaborators from MHRP, PEPFAR, WRAIR, USAID, CDC, HJFMRI, and NIMR, who shared their insights on next steps for the planned 15-year study. During welcoming remarks to symposium attendees, MHRP Director Col. Julie Ake said MHRP initiated this large, long-term cohort study to help HIV researchers capture the broader understanding of the overall health of HIV patients, inform treatment decisions, and share best practices. To date, the study has enrolled more than 3,700 participants for the study.

The event was also attended by the Chief Science Officer of PEPFAR, Dr. Mike Reid, who presented PEPFAR's Science Priorities. Reid noted that approximately 20 percent of people living with HIV are not on treatment.

"Despite remarkable progress towards 95-95-95, gaps remain along the care cascade. In many settings, these gaps align with tracers of health inequity, such as lower income quintiles, rural vs. urban, etc. As researchers we need to identify health inequities and address them specifically for populations disproportionately affected by HIV," added Reid.

Closing the gap on last mile HIV service delivery in Kenya

As countries progress towards meeting UNAIDS 95-95-95 targets for HIV diagnosis, treatment and viral suppression, PEPFAR service implementers are approaching the "last mile" of identifying missing cases and new infections in the most hard-to-reach populations.

MHRP's PEPFAR implementing partners in Kenya's South Rift Valley (SRV) led the country in identifying individuals living with HIV and getting them on treatment, according to 2023 4th quarter performance data.

The program provides HIV testing services in Kericho, Bomet, Nandi and Narok counties. In 2023, MHRP's partners tested 286,551 individuals in the region and identified 5,634 cases of HIV, exceeding PEPFAR performance goals.

"It's so critical that we find and test those who do not yet know their status and put those who test positive on treatment," said Kim Bohince, MHRP's Director of Global Health. "Finding these remaining individuals is challenging and requires a creative and tailored case identification approach."

There are difficulties saturating the South Rift Valley region with testing services because of its expansive rural landscape. The program has worked to improve performance by closely tracking testing data and providing site-level mentorship for those facing challenges. The program focused on case identification to target testing services based on several criteria, including risk behaviors and patient symptoms.

Community outreach was critical to increasing access to testing services. "We reviewed geographical and subpopulation coverage gaps to identify opportunities that helped us reach the unreached by mapping out potential hotspots," said Dr. John Owuoth, the HJFMRI Kenya PEPFAR Country Director. For example, in Narok the case finding team targeted higher learning institutions, the gold mines, and charcoal burning and sand harvesting areas for increased engagement. A social network strategy was implemented to speak to hard-to-reach key populations and young people.

Testing and outreach staff played a key role in the program's success, including Dr. Isaac Tsikhutsu, Acting SRV PEPFAR Program Director; Fillet Lugalia, the SRV Program Manager for Case Finding; and Jane Muli, SRV PMTCT Program Manager and County Liaison.

"Achieving these targets was a significant milestone for the program that demonstrates the effectiveness of innovative strategies," said Owuoth. "The program will continue to scale up the strategies to narrow the gap on treatment coverage."

DELIVER initiative launches to expand HIV cure research capacity internationally

MHRP and partners across four continents recently launched a new collaborative HIV cure research initiative called DELIVER, or Developing Leadership and Innovation in Viral Eradication Research.

DELIVER will focus on developing laboratory and clinical site infrastructure to build capacity to conduct long-term HIV remission studies in countries most impacted by HIV.

MHRP partners in Kenya, Mozambique, Nigeria, Tanzania, Uganda, Thailand, the Philippines, and Brazil will participate in activities to foster collaboration between international and local experts to encourage knowledge transfer and sharing of best practices. This initiative is funded by the Division of AIDS of the National Institute of Allergy and Infectious Diseases, one of the National Institutes of Health.

"MHRP has gained extensive experience from our East Africa and Thailand cohort studies in conducting acute HIV research and clinical research alongside an international network of partners," said Dr. Lydie Trautmann, MHRP's Director of Translational Research. "DELIVER provides an opportunity to adapt lessons learned from those experiences to engage new partners and communities in HIV remission research."

The DELIVER kickoff event will be an HIV remission workshop held in Uganda this spring. Laboratory and staff development will build a network of sites capable of conducting a comprehensive panel of HIV cure-relevant assays. Clinical site assessments will inform strategies to facilitate future enrollment into research trials, and efforts will also focus on community engagement. In addition to training, cure-experienced community advisory boards (CABs) will coach CABs new to HIV remission research.

Ultimately, MHRP plans to work with DELIVER sites to conduct a Phase 1 multi-site trial to evaluate a combination of broadly neutralizing antibodies administered at ART initiation and a therapeutic vaccine to induce long-term remission among participants living with HIV.

"We are excited to expand HIV cure efforts across multiple continents in a single trial," said Dr. Sandhya Vasan, Director of the HJF Global ID component of MHRP. "It is crucial to engage diverse communities and people living with HIV to contribute to remission research, especially in regions that face a high HIV burden."

East Africa Research Updates

- **RapidVax trial:** Screening has begun for the RV591 "RapidVax" study, which combines candidate HIV vaccines with a novel dose escalation strategy with the goal of improving immune responses. This study is a collaboration between MHRP, Duke Human Vaccine Institute, DAIDS, and the Makerere University Walter Reed Project (MUWRP) in Uganda.
- **New consortium award:** Congratulations to our partners, MUWRP in Uganda, the Kenya Medical Research Institute (KEMRI)/Walter Reed Project (WRP), and the National Institute for Medical Research-Mbeya Medical Research Center (NIMR-MMRC) in Tanzania, for their success as part of the BRILLIANT (BRinging Innovation to cLinical and Laboratory research to end HIV In Africa through New vaccine Technology) consortium, which has been awarded up to $45.6 million from USAID to advance African-led HIV vaccine science and innovation. Dr. Betty Mwesigwa, MUWRP's Deputy Execute Director, is a Co-PI on the grant, which is led by the South African Medical Research Council.
- **Research partners meeting:** MHRP joined the annual NIMC-MMRC research partner meeting in October in Arusha, Tanzania. Participants discussed ongoing studies and plans for future projects, operational updates, developments in laboratory capacity, leadership vision for potential expansion of research activities, short presentations of selected cooperative research endeavors, ongoing challenges as well as opportunities.

WRAIR Pilot Bioproduction Facility on track to begin mRNA vaccine manufacturing this year

MHRP is collaborating with WRAIR's Pilot Bioproduction Facility (PBF), a cGMP-compliant pharmaceutical manufacturing facility on WRAIR's Silver Spring campus, to establish an mRNA manufacturing program leveraging institutional knowledge and partnerships to develop a novel mRNA vaccine for HIV prevention.

mRNA vaccines are a powerful and versatile technology because of their high potency, established safety profile, and ease of manufacture. The PBF has manufactured a variety of vaccines for previous trials conducted by WRAIR but manufacture and encapsulation of mRNA for use in clinical trials requires specialized production techniques.

Analytical testing of manufactured mRNA drug product is complex, and MHRP/PBF teams are working collaboratively to develop highly specialized assays. The product quality team is working to establish an array of assays to test for product concentration, identity and purity.

The PBF is expected to begin manufacturing an investigational mRNA HIV vaccine late this year. MHRP is planning a Phase 1 clinical trial, expected to begin in 2025, to examine dose escalation and safety of the PBF's first mRNA candidate HIV vaccine.

MHRP global health team supports Philippines anti-stigma HIV advocacy campaign

As part of a military-to-military partnership, MHRP supported the launch of an Armed Forces of the Philippines (AFP) HIV advocacy campaign called “EveryBuddy Laban sa HIV” (Everybody vs. HIV).

This initiative calls upon every AFP buddy to break down the barriers of stigma and discrimination and correct HIV misconceptions. A launch event at the Victoriano Luna Medical Center drew 100 participants, and the campaign was also promoted at the inaugural Metro Manila AIDS Walk in December.

Since 2021, MHRP, with the Armed Forces Research Institute for Medical Sciences (AFRIMS), under the Department of Defense HIV/AIDS Prevention Program, has supported a PEPFAR-funded HIV program in the Philippines.

The primary aim is to help the AFP reach sustainable HIV epidemic control by strengthening the military capacity to establish policies and systems to provide quality HIV prevention, testing, treatment, and laboratory services anchored in the Victoriano Luna Medical Center. These activities directly contribute to building a sustainable AFP-wide HIV program.

MHRP discovery labs investigate determinants of HIV vaccine durability

MHRP scientists are analyzing samples from a late-boost HIV vaccine study, RV306, to look for characteristics that differentiate durable from non-durable immune responses following vaccination.

The Army-sponsored RV144 trial demonstrated that a “prime- boost” HIV vaccine lowered the rate of HIV infection by 59.9 percent compared to placebo one year after vaccination, which dropped to 31.2 after three years. In a follow-up study, RV306, participantsreceived the RV144 regimen plus a late boost at either month 12, 15 or 18.

Data and samples from RV306 enable MHRP researchers to investigate and compare durable and non-durable immune responses to HIV vaccination. MHRP’s Laboratories of Integrative Multiomics, led by Dr. Rasmi Thomas, and B cell Biology, led by Dr. Shelly Krebs, are working to understand the unique profiles of HIV-specific B cells and interactions with peripheral immune cells to reveal factors associated with the durability of antibody responses.

HIV-specific B cell sorting and single-cell sequencing methods of samples from RV306 will examine factors like gene and protein expression to compile a signature of responses that induce antibody longevity. The ultimate goal will be to use this data to inform vaccine strategies to extend the timeframe of protection mediated by antibodies.

NIAID DAIDS Director visits WRAIR for WAD

MHRP hosted Dr. Carl Dieffenbach, director of the Division of AIDS (DAIDS) at NIAID, for a fireside chat to commemorate World AIDS Day, where discussion turned to ongoing collaborations and promising avenues for research.

MHRP’s longtime collaboration with DAIDS began as an endeavor to develop a safe, effective, durable HIV vaccine, but has expanded to include other modalities of HIV prevention and treatment. “From that early vaccine work came all other kinds of collaborations related to acute infection and how we can continue to build better immunogens,” said Deiffenbach.

When asked about promising developments in HIV research, Deiffenbach spoke of a “revolution in antibody design,” citing broadly neutralizing antibodies as a potential link between prevention and cure strategies.

“Monoclonal antibodies are one of the most important discoveries in vaccinology because it gives us potential targets for making immunogens,” he said. “A question that really interests me is, can we take people living with HIV and vaccinate them with some of these new immunogens that are triggering a broad neutralizing antibody portfolio” to support long-term remission of HIV.

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