

U.S. MILITARY HIV RESEARCH PROGRAM

STRATEGIC PLAN 2020



WRAIR

Walter Reed Army
Institute of Research





The U.S. Military HIV Research Program (MHRP) is centered at the Walter Reed Army Institute of Research, U.S. Army Medical Research and Development Command and is supported through a cooperative agreement with the Henry M. Jackson Foundation for the Advancement of Military Medicine. The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, or HJF.

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EXECUTIVE SUMMARY

The U.S. Military HIV Research Program (MHRP) has been recognized as a leader in HIV diagnostics, epidemiology and vaccine research for over three decades and, more recently, has built an international reputation for pioneering discoveries in acute infection and remission. Enabled by an experienced team with expertise across the research continuum, high-quality international clinical sites and the capacity to collaborate effectively with diverse partners, MHRP's achievements continue to uphold an enduring commitment to tackling the threat that HIV poses to the U.S. Warfighter, national security and global health. These capabilities remain highly relevant today, and in the context of this Strategic Plan, will be focused in the context of several notable operational imperatives.

MHRP has identified opportunities to: respond to the results of HVTN 702 and other high profile studies; integrate a stronger focus on pathogens impacting military populations; and navigate the complexities of an environment where priorities and resources are shifting under the pressure of the COVID-19 pandemic. MHRP's 2020 Strategic Plan prioritizes advancing a pipeline of HIV vaccines; sustaining leadership in novel acute infection and HIV remission research; analyzing preclinical, clinical and cohort studies; preserving access to high-quality international clinical sites; and, pursuing research focused on HIV-related infections.

Ultimately, the 2020 Strategic Plan will build on and sustain MHRP leadership in HIV prevention and remission research, optimize force health protection and readiness, contribute to global health security, and strengthen military infectious disease research capabilities.



HIV/AIDS remains one of the most significant global public health challenges and continues to threaten force readiness and military effectiveness.

With more than 37.9 million people living with HIV and 1.7 million new infections in 2018, HIV remains among the greatest threats to global public health¹. Today, the burden of HIV is concentrated in Sub-Saharan Africa where 61% of all new HIV infections occur²; however, the epidemic is not isolated to the developing world: as of 2018, there were 68,000 new HIV infections and 2.2 million people living with HIV in western and central Europe and North America³. Despite advances in HIV prevention, care and treatment, which have modestly reduced the total number of new infections and deaths each year, AIDS and AIDS-related illnesses are still among the leading causes of death globally⁴ and accounted for \$48.9 billion in global health care spending in 2015.⁵

Unsurprisingly, U.S. Warfighters continue to be exposed to—and acquire—HIV at home and abroad, resulting in approximately 350 new cases of HIV per year. The majority of new infections among the U.S. Warfighter are subtype B HIV⁶, which is the most prevalent subtype (or strain) in Europe, Americas and Oceania⁷. HIV-infected U.S. Warfighters can face deployment limitations which compromise unit integrity and the ability to compete in the multi-domain operational environment. With an estimated lifetime treatment cost of \$450,000 per person, the additional cost to the Department of Defense (DoD) to provide therapy for HIV-infected U.S. Warfighters is approximately \$150M annually.

Beyond the staggering health and economic impacts, HIV/AIDS is a pernicious infectious disease that decreases quality of life, destabilizes communities and disrupts health systems. Addressing the threat of HIV to military and global populations is of critical concern to health diplomacy and international security, and a challenge that requires sustained commitment to research and developing effective scientific, clinical, political and social solutions.

MHRP has been a leader in the fight against HIV since 1986.

For over 30 years, MHRP has been recognized as a leader in HIV diagnostics, epidemiology and vaccine research and, more recently, for pioneering discoveries in acute infection and remission. Enabled by an experienced team with expertise across the research continuum, high-quality international clinical sites and the capacity to collaborate effectively with diverse partners, MHRP's recent achievements include:

- Leading the field in acute infection research through two innovative cohort studies in Thailand and East Africa (since 2009)
- Providing lifesaving antiretroviral therapy to over 370,000 individuals through the implementation of the President's Emergency Plan For AIDS Relief (PEPFAR) (2014 to present)
- Contributing to the governance of the HVTN 702 efficacy study in South Africa (2016)

¹ <https://www.unaids.org/en/resources/fact-sheet>

² https://www.unaids.org/en/resources/presscentre/featurestories/2020/june/20200608_new-hiv-infections-differ-by-sex-and-by-region

³ <https://www.unaids.org/en/resources/fact-sheet>

⁴ <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>

⁵ [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(18\)30698-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30698-6/fulltext)

⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC536263/>

⁷ https://journals.lww.com/co-hivandaids/fulltext/2019/05000/hiv_subtype_diversity_worldwide.3.aspx

- Informing DoD policy on use of PrEP as a prevention tool in high risk communities that MHRP characterized (2018)
- Publishing key findings that inform HIV remission strategies including early antiretroviral therapy initiation and broadly neutralizing HIV-specific monoclonal antibodies (2019)
- Securing a patent for WRAIR's ALFQ vaccine adjuvant (2019)

MHRP's enduring commitment to HIV research, prevention treatment and care has helped to combat the threat that HIV poses to the U.S. Warfighter, national security and global health.

As MHRP looks to the future, it is setting a strategy that builds on the Program's track record of excellence and responds to pivotal dynamics shaping MHRP's operating environment.

MHRP's 2014 Strategy supported a research and development agenda that leverages the Program's notable strengths in vaccine research, clinical development, diagnosis, threat assessment and care and capitalizes on emerging strengths in preclinical non-human primate research and studies of the very early stages of HIV infection. These capabilities remain highly relevant today but must be reviewed in the context of several notable operational imperatives.

The recent termination of HVTN 702 due to efficacy futility is orienting the field toward gathering and analyzing data to understand this result. MHRP's future HIV vaccine research efforts will be guided by these outcomes, the results of HVTN 705 and other high profile studies (AMP, PrEPVacc) and opportunities to build and develop prevention products with diverse immunological responses.⁸ MHRP must also respond to changing research interests within the Military, where a growing domestic orientation is placing greater emphasis on pathogens circulating in military populations (i.e. subtype B risk populations, sexually transmitted infections). Further, as COVID-19 draws on financial and personnel resources within the infectious disease research community, MHRP must consider the complexities of the external environment when contemplating new products, partnership and funding opportunities.

The 2020 strategy reinforces MHRP's leadership in HIV prevention and remission by leveraging internal capabilities and sustaining broad collaborations.

To inform the 2020 Strategic Plan, MHRP led a consultative process designed to gather perspectives from key internal and external stakeholders on enduring strengths and opportunities that will contribute to a high impact research program in the future. Leveraging these insights and looking ahead, MHRP's 2020 Strategic Plan prioritizes advancing a pipeline of HIV vaccines; sustaining leadership in novel acute infection and HIV remission research; analyzing preclinical, clinical and cohort studies; preserving access to high-quality international clinical sites; pursuing research focused on HIV-related infections. Ultimately, the 2020 Strategic Plan will build on and sustain MHRP leadership in HIV prevention and remission research, optimize force health and military readiness, and coordinate and cultivate military HIV research capabilities.

⁸ Current HIV vaccine research efforts are represented by three major conceptual areas: eliciting non-neutralizing responses; inducing bNAbs; and eliciting T-cell initiated control or clearance of infection.

OUR STRATEGY

Given the continuing threat of HIV to force readiness, military effectiveness and global health, the 2020 Strategic Plan emphasizes MHRP's critical role in developing an HIV vaccine and other promising HIV-related products.

MISSION

MHRP will protect the U.S. Military from HIV and improve global health by conducting research to develop an HIV vaccine, reduce new infections and advance strategies to induce long-term HIV remission.

OBJECTIVES

Over the next five years, MHRP will focus its efforts on five critical **Objectives**.

1. Advance **MHRP's pipeline of HIV vaccines** and support the development of promising vaccine candidates.
2. Reinforce MHRP's **leadership in novel acute infection and HIV remission research**.
3. Deepen involvement in **analyzing the results of preclinical, clinical and cohort studies** and translate findings to advance HIV product development.
4. Enable **long-term access to populations and high-quality international clinical sites** to further product development.
5. Advance **research to help detect, prevent and treat HIV-related infections** where there is an opportunity to deliver military, scientific and/or clinical value.

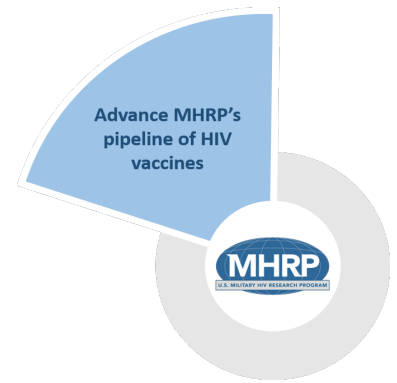
STRUCTURE

Each **Objective** will be advanced by a set of **Key Initiatives** and **Priority Activities** (specific projects on which MHRP will focus near-term effort). Progress towards these Objectives and Key Initiatives will be measured by tangible **Outputs** that contribute to the **Impact** of MHRP on U.S. Military Force Health and Readiness and the field of global HIV research.



OBJECTIVES

1. Advance MHRP's pipeline of HIV vaccines and support the development of promising vaccine candidates.



MHRP has a long track record of leadership in HIV vaccine development and an important opportunity to continue to advance diverse approaches and prevention products (e.g. new antigens, Army adjuvants and monoclonal antibodies for passive immunization). It is challenging to evolve an HIV prevention portfolio amidst the uncertainty around ongoing HIV prevention study outcomes (i.e. HVTN 705/706, PrEPVacc, AMP) and before the underlying causes of the HVTN 702 study outcome are demonstrated. Nevertheless, MHRP is committed to applying an objective, evidence-based approach to prioritizing vaccine products within the pipeline (see Box, below). Based on this framework, we will pursue opportunities to leverage our expertise and network to:

- Optimize adjuvants to elicit a stronger immune response for HIV protein subunit vaccines with potential applications to other vaccine platforms;
- Leverage the scientific understanding of RV144 and HVTN 702 to inform future work on optimizing prime-boost regimens and advancing non-neutralizing antibody approaches;⁹
- Reinforce the priorities of the Army Futures Command (AFC) which include a focus on the development of products to improve the performance and readiness of our forces.

The specific research initiatives and collaborations core to achieving this objective will establish and strengthen a diverse portfolio of prevention products at MHRP and further the field's progress in developing an HIV vaccine.

Decision-making principles for product development opportunities (internal and external)

MHRP will prioritize products that:

- Reinforce MHRP's mission
- Align with priorities of military funders and interests of key external funders
- Protect in subtype B epidemics with additional global breadth
- Ensure there are candidates across the development continuum
- Target different components of the immune landscape
- Leverage the expertise and infrastructure at MHRP (e.g. sites, NHP capabilities)
- Foster progress in meeting the Performance Attributes

⁹ These efforts will be integrated with the work proposed in Objective 3.

KEY INITIATIVES

- 1.1 Evaluate products for protection against subtype B viruses in parallel NHP studies and early phase human clinical trials
- 1.2 Raise the bar for non-neutralizing antibody vaccine approaches to require demonstration of potent, durable and multiple functional antibody responses against a diversity of viruses for the advancement of novel products (regimens including DNA priming, mRNA immunogens)
- 1.3 Optimize delivery of potent Army adjuvant ALFQ (e.g., combination with alum, potential for protein dose-sparing, improve potency and durability of trimeric protein antigens designed to elicit bNAbs).
- 1.4 Pursue partnerships to incorporate novel Army-owned adjuvants into early clinical trials of antigens designed to induce neutralizing antibodies. Capitalize on specialized specimen collection capabilities (e.g., bone marrow, lymph node) to characterize the progression of antibody response development
- 1.5 Develop collaborations to evaluate novel mAb prevention products and leverage HIV subtype diversity at international sites to expand contributions to mAb prevention trials

PRIORITY ACTIVITIES

- Optimize clinical development of the ALF family of adjuvants including dose, schedule, and formulation
- Evaluate alternate priming strategies and novel vaccine constructs such as mRNA-based approaches in preclinical and clinical studies
- Assess the potential for adjuvants to enhance responses elicited by trimers designed to induce bNAbs

2. Reinforce MHRP’s leadership in novel acute infection and HIV remission research.

A pioneer in developing and studying early acute infection cohorts, MHRP has been a significant contributor to advancing the field’s understanding of acute infection, viral reservoirs and immunological mechanisms of remission.

Leveraging this expertise and assets, MHRP will continue to propel the field by:

- Leveraging findings from treatment interruption studies to identify new biomarkers and targets for a functional cure;
- Building on past successes (e.g. RV254)—especially acute infection cohorts and early infection NHP models—by investing in emerging technologies to characterize patterns of early infection and testing combination interventions to control viral remission.

Advancing the key initiatives associated with this objective will expand the field’s knowledge of immune responses in acute infection, expose mechanisms for treatment and cure, inform rational design of vaccines and other interventions, and strengthen and sustain MHRP’s leadership in acute infection research.



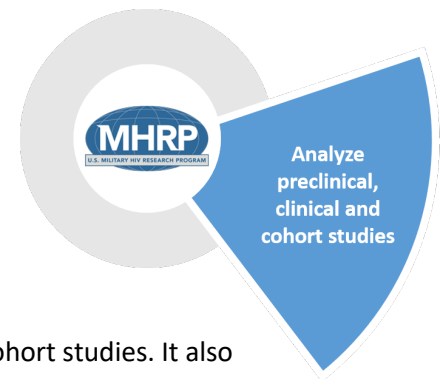
KEY INITIATIVES

- 2.1 Evaluate the impact of PrEP on HIV incidence and early HIV diagnosis
- 2.2 Study host immunology and host/virus genetics during acute infection
- 2.3 Identify new biomarkers and targets for a functional cure (e.g., engagement of CD8 T cells, NK cells, and other populations to eradicate the reservoir) using cutting-edge technologies
- 2.4 Conduct studies using NHP models to study the pathogenesis of early infection across anatomic compartments and to assess the impact of early therapeutic interventions
- 2.5 Test combination interventions (e.g., mAbs and/or therapeutic vaccination in the context of early ART) in the clinical setting with the aim of achieving ART-free remission
- 2.6 Sustain strength in the evaluation of study participants with very early acute HIV with secondary consideration for later acute and early chronic HIV infection populations

PRIORITY ACTIVITIES

- Conduct clinical trials combining novel cure interventions such as therapeutic vaccines, bNAbs, and TLR agonists
- Continue to perform NHP studies to inform the development of therapeutic interventions
- Continue interrogation of the latent reservoir across anatomic compartments in humans and in animal models

3. Deepen involvement in analyzing the results of preclinical, clinical and cohort studies and translate findings to advance HIV product development.



MHRP is known for its ability to conduct high-quality preclinical, clinical and cohort studies. It also has a long track record of excellence in characterizing study results to enable innovative translational research, improve and inform HIV vaccine development, and expand understanding of HIV infection and immune responses. Recognizing these strengths and the untapped potential within our high-quality sample and data repositories, MHRP is well-positioned to:

- Leverage our access to RV144 samples to contribute to the field’s efforts to understand the results of HVTN 702;
- Support novel science- and epidemiology-based investigations (e.g. in other military-relevant disease areas) and comparison studies across multiple sample and datasets by further examining our high-quality samples and population cohorts;
- Using large-scale applications of advanced technology such as bioinformatics and big data (e.g. multi-omics) to better dissect immune responses during vaccination, disease and remission.

The key initiatives associated within this objective will enable MHRP to optimize and advance the use of our existing research assets to generate valuable knowledge for the field and inform future HIV product development.

KEY INITIATIVES

- 3.1 Evaluate differences in responses elicited by the HVTN 702 and RV144 regimens and assess immune responses and potential correlates from clinical specimens to inform product development and identify criteria for product down-selection
- 3.2 Leverage MHRP’s robust specimen and data repository of vaccine and acute infection studies to elucidate correlates of vaccine response durability and characterize the latent reservoir (e.g., phenotypic and transcriptomic signatures)
- 3.3 Perform epidemiological research in military populations (e.g., surveillance of HIV subtypes in U.S. Warfighters, ongoing STI studies to characterize high incidence cohorts)
- 3.4 Conduct advanced computational analyses to identify HIV remission targets and dissect immune response with a focus on early infection

PRIORITY ACTIVITIES

- Conduct hypothesis-driven research on study specimens to evaluate differences across vaccine efficacy trials
- Utilize global cohort specimens to understand HIV incidence, phylogeny, and co-infections

4. Enable long-term access to populations and high-quality international clinical sites to further product development

MHRP has exceptional international trial capacity that extends the Program’s reach to global populations most affected by HIV, provides access to unique cohorts, advances HIV vaccine and remission research, and trains highly capable in-country personnel. While MHRP’s trial sites are an important and valued resource, maintaining these high-quality sites through the ebbs and flows of trial activity has been financially and operationally challenging. To ensure that product development efforts at MHRP and the broader field are enabled by sustained quality and ongoing access at these trial sites, MHRP will:

- Design and implement innovative solutions to increase and diversify site utilization by research teams within and external to WRAIR (e.g. clinical trial networks);
- Continue to engaging key populations through the international implementation of U.S. President’s Emergency Plan for AIDS Relief (PEPFAR)—a program that provides prevention, care and treatment services to civilian and Military populations— to gather data that will inform future intervention studies.

Maintaining these international sites through the following initiatives will ensure MHRP and others in the field have access to population cohorts for incidence studies and promising HIV intervention trials, while also providing a mechanism for MHRP to contribute to research on other infectious diseases (e.g. Shigella, Ebola).

KEY INITIATIVES

- 4.1 Support the utilization of clinical sites by other branches and centers within the WRAIR
- 4.2 Increase site utilization through clinical trial network participation, including in the newly formed COVID Prevention Network (CoVPN)
- 4.3 Establish external partnerships for clinical studies that diversify site activity and enable MHRP to gain access to valuable clinical samples for follow-on research
- 4.4 Maintain HIV incidence data across potential efficacy sites within the WRAIR international network
- 4.5 Leverage PEPFAR-based research (i.e., AFRICOS) to gather information on local HIV incidence hot spots (utilizing recency testing) and coinfections/comorbidities to guide recruiting efforts and inform the design of future interventional studies (e.g., acute/early infection studies providing early treatment and other interventions to newly-infected individuals)
- 4.6 Remain connected to global programs to ensure MHRP can adapt to changes in the HIV landscape

PRIORITY ACTIVITIES

- Engage with external partners, networks and sponsors to diversify and expand the scope of studies performed at overseas sites
- Support smooth integration of MHRP sites into WRAIR OCONUS network



5. Advance research to help detect, prevent and treat HIV-related infections where there is an opportunity to deliver military, scientific and/or clinical value.



Consistent with a focus on force readiness and aligned with rising rates of STIs in the U.S. military, there is renewed interest in understanding, preventing and treating STIs and other HIV-related infections. Given this opportunity, MHRP will contribute to research in this area by:

- Leveraging existing capabilities (e.g., adjuvants, epidemiology, diagnostics, research infrastructure such as NHP models and clinical sites) to study HIV-related infectious diseases of military relevance where MHRP can deliver scientific and/or clinical value;
- Seeking new partnership opportunities with research organizations in the field of HIV-related infectious diseases such as clinical trial networks, sister agencies, NGOs and industry to advance technologies and interventions familiar to MHRP.

Pursuing the key initiatives of this objective will unlock additional funding opportunities, generate new collaborations and drive research that advances knowledge and clinical care of HIV-related infections.

KEY INITIATIVES

- 5.1 Use MHRP's clinical research, specimen processing and product development expertise to study HIV-related infections when compelling opportunities and funding sources arise
- 5.2 Support site participation in clinical trial networks working in HIV-related infectious diseases (e.g., tuberculosis, STIs)
- 5.3 Partner with sister agencies, NGO's and industry to develop/advance state-of-the-art diagnostic technologies for STIs and potential preventive and therapeutic interventions
- 5.4 Perform epidemiological studies (e.g., characterizing social and sexual networks) and develop knowledge products, policies and educational tools aimed at reducing the risk of HIV and other STIs in the U.S. military

PRIORITY ACTIVITIES

- Evaluate vaccine prevention of gonorrheal infections
- Assess impact of behavioral interventions on STI rates in military populations
- Expand portfolio to diversify funding for research in HIV-related infections

KEY ENABLERS

The successful implementation of the Strategic Plan is predicated on three central enablers:

PEOPLE & PARTNERSHIPS

- Recruit talent to fill gaps in research expertise/military representation within MHRP and cultivate young researchers to be future leaders at MHRP
- Maintain network to fill gaps in internal expertise and provide products for evaluation across the product development continuum
- Establish dedicated administrative support (e.g. procurement, grant, project management support) to reduce lab administrative burden

SCIENTIFIC PLANNING & INFRASTRUCTURE

- Map the clinical development portfolio to ensure there are sufficient candidates at each stage of the development pipeline
- Redesign future clinical studies reflecting results of HVTN 702. Define potential outcomes among HVTN 705 and AMP studies, anticipate impacts on MHRP and plan for major scenarios in the short- and long-term
- Enhance infrastructure and capabilities to support internal data sharing, advanced computational analyses and development of a sophisticated relational database

COMMUNICATION & COLLABORATION

- Build awareness within the AFC and the HIV vaccine/therapeutics field around MHRP's major activities and the role of MHRP in PEPFAR
- Establish business mechanisms/agreements for MHRP to collaborate more easily with other branches of WRAIR, as well as other U.S. military research institutes, clinical facilities, and countermeasure developers
- Increase efficiency across MHRP by enhancing opportunities to present research activities and plan collaboration

IMPACT AND OUTPUTS

Building on the success of MHRP to date and capturing new opportunities in the HIV landscape, the 2020 Strategic Plan will reinforce MHRP's leadership in HIV prevention and remission research and engage a committed research team to advance AFC interests. The Objectives and Activities outlined in this plan will yield numerous, tangible **Outputs** (See Appendix A) that can be used as a measure of progress towards achieving the following three major **Impacts**:



Sustain leadership in HIV prevention and remission research

Advance hypothesis-driven studies that contribute to the development of products that diagnose, prevent and treat HIV infection

OUTPUTS

- Number of clinical trials
- Number of non-clinical animal studies
- Number of epidemiological studies
- Number of HIV preventative and therapeutic candidates identified
- Number of peer-reviewed publications
- Funding from AFC sources
- Number of knowledge products created
- Funding from non-AFC sources



Optimize force health and military readiness

Develop technologies and knowledge products that minimize the risk of HIV and HIV-related infections within the U.S. military

OUTPUTS

- Number of epidemiological studies
- Number of HIV preventative and therapeutic candidates identified
- Number of knowledge products created



Coordinate and cultivate military HIV research capabilities

Leverage excellence across basic, preclinical and clinical science to accelerate product-focused research and innovation

OUTPUTS

- Number of non-clinical animal studies
- Number of HIV preventative and therapeutic candidates identified
- Number of clinical trials

APPENDIX A

The table below includes the types and descriptions of Outputs that the 2020 Strategic Plan will achieve for MHRP.

Output Type	Description
Number of clinical trials	Tracks HIV vaccine and acute infection/remission studies
Number of non-clinical animal studies	Encompasses HIV therapeutic and prevention interventions
Number of HIV preventative and therapeutic candidates identified	Encompasses countermeasures targeting both HIV and HIV-related infections, as well as biomarkers/targets of functional cure
Number of epidemiological studies	Encompasses studies of both military and non-military populations
Number of knowledge products created	Development of knowledge products, policies, and toolkits that reduce HIV and HIV-related infections in the U.S. military
Number of peer-reviewed publications	Tracking publications from MHRP investigators and from junior/young investigators as first/senior author; disaggregated by vaccine, functional cure and other infection topics
Funding from military sources	Amount and diversity (number of different sources) of military financial support; reflects value to funders
Funding from non-military sources	Amount and diversity (number of different sources) of non-military financial support; reflects value to funders

MHRP's 2020 Strategic Plan will engage an exceptional research team to reinforce leadership in HIV prevention and remission research, enhance global health security, and promote the performance and health protection of the U.S. Warfighter.



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