HIV Vaccine Awareness Day

U.S. Military HIV Research Program (MHRP)
Walter Reed Army Institute of Research

Julie A. Ake, M.D., MSc., F.A.C.P.
LTC, MC, USA
Principal Deputy Director, MHRP

The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.
MHRP 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 find a cure.

- Oversees all HIV testing for the Army, and serves as the Tri-Service Reference Laboratory (1M+ tests/year)
- Informs policy and develops strategies to reduce HIV infections in the U.S. Military
- Supports the President’s Emergency Plan for AIDS Relief (PEPFAR)
- Developing a globally effective HIV vaccine and pursuing a functional cure
- Leveraging broad international network, basic science capabilities and clinical trial infrastructure to respond to emerging public health emergencies
MHRP: Scientific Contributions

**Prevention**
- Supported early diagnosis, comprehensive care and prevention in DoD (1986)
- Identified heterosexual transmission of HIV-1 (1986)
- Led the RV144 vaccine study (2009)

**Treatment**
- Developed candidate MVA HIV vaccine candidate now in clinical trials (2009)
- Only network to integrate care and treatment (PEPFAR) with research (2004)
- Helped conduct study in Kenya that found early ART was associated with a lower rate of new AIDS-defining illnesses and death (NEJM, 2011)

**HIV Remission**
- Characterized acute (early) infection in ground-breaking cohort of Thai and East African volunteers (NEJM, 2016)
- Part of “Collaboratory” awarded funds to develop an integrated approach to finding an HIV cure (2016)
- Found that early ART dramatically reduces HIV DNA set point (2016)
Landmark RV144 HIV Vaccine Trial

The Thai HIV Vaccine Study

- First HIV vaccine to show modest effectiveness in preventing HIV in humans.
- A preventive vaccine IS possible
- Efficacy of ~60% at year 1; demonstrated 31.2% efficacy at end of study (3.5 years)
- Major international collaboration with 16,000 Thai volunteers.
Identified clues why the vaccine protected

- “Correlates of risk”
  - International collaboration with 120+ scientists
  - V1V2 antibodies key correlate of decreased risk

Informed vaccine regimen for future testing

- Follow up Clinical Studies in Thailand, adding a boost to extend and increase the immune response
  - **RV305** - Evaluated re-boosting at Month 0, 6 with AIDSVAX, ALVAC, or combination in volunteers who participated in the RV144 study (n=162)
  - **RV306** - RV144 vaccine regimen + month 12 boost with ALVAC, AIDSVAX, or combination (n=360)

Subsequent MHRP studies will focus on subtype B infection
MVA product developed by WRAIR/NIAID scientists

- Early testing with DNA vaccines candidates for HIV prevention
- New vaccine candidate: Ad26/MVA prime-boost strategy for HIV remission
  - Collaboration with NIAID, Harvard University, Beth Israel Deaconess Medical Center and J&J/Janssen
Ad26/MVA/Protein Mosaic HIV Vaccine

**Designed for protection against all HIV subtypes**

1. **Vectors that elicit optimal immune responses**
   - Low seroprevalent Ad26
   - Ad26.HIV-Gag-Pol
   - Ad26.HIV-Env
   - (MVA.HIV-Gag-Pol-Env)

2. **Mosaic inserts for global coverage**

3. **Trimeric env protein for improved humoral immunity**

Adolescents (11-17 years) / Adults (18-65 years) in endemic countries and populations at risk in Western world
MHRP led study with combination TLR7 agonist+Ad26/MVA delayed time to viral load rebound and decreased viral load set point and viral DNA.

TLR7 Agonist+Ad26MVA Vaccine Reduced Viral Load in Monkeys after ART Discontinuation

MHRP, Nature 2016

Total n=32
Remission in 3 of 9 with Ad26/MVA+TLR7
MHRP Acute Infection Studies

**RV217**
Prospective acute infection study in high risk individuals

- Twice weekly testing in E. Africa/Thailand of 2276 uninfected persons
- Acute HIV infection (n=115)
- 50+ Fiebig I/II

*Robb ML, NEJM 2016*

**RV254**
Acute infection cohort with early ART

- Real-time screening of 200,000 samples in Thailand
- Acute HIV infection (n=450)
- 100+ Fiebig I/II

*de Souza M, Ananworanich J, AIDS 2015*

**Fiebig I/II**: RNA+, HIV IgM-

These studies are informing HIV vaccine science and provide platform for functional cure studies.
RV 405: Ad26/MVA with ATI

Volunteers from Thai Red Cross
- 18-50 years old
- Started on ART during AHI (FI-FIV)
- HIV-1 RNA <50 copies/mL
- CD4 >400 cells/mm³

Parallel social, behavioral and ethics research

Primary Endpoint (Efficacy): Virologic control at week 84 (RNA <50 copies/mL)
Primary Endpoint (Safety): ≥ grade 3 vaccine-related adverse events by week 96

Ad26 + MVA Vaccines (n=24)
Placebo Vaccines (n=12)

- Ad26 or Placebo Injection
- MVA or Placebo Injection

Optional: LP, Gut Biopsy, Lymph Node Biopsy
MHRP and PEPFAR

- 1999: WRAIR began HIV research in Africa
- 2004: PEPFAR begins; MHRP’s Kericho, Kenya sites was one of the first to provide ARTS
  - Ensures ethical framework for clinical research
  - Engages civilian and military populations in Kenya, Nigeria, Tanzania and Uganda
  - Sustainable approach develops capacity and fosters ownership
- Builds infrastructure and relationships to enable research on other emerging diseases
  - Our site in Nigeria, established through PEPFAR, is conducting HIV research and an Ebola vaccine studies
HIV in Nigeria

- Most populous African country (over 180M)
- 9% of all persons living with HIV worldwide live in Nigeria
  - Only South Africa has more
- 10% of all new infections worldwide occur in Nigeria
  - Only South Africa has more
- 14% of all AIDS-related deaths occur in Nigeria
  - More than any other country in the world*

*2013 data
TRUST study reflects the dual MHRP mission in Nigeria to promote HIV prevention, care and treatment as well as HIV research.

- Prospective cohort study of 2125 MSM volunteers at two urban centers: Abuja, in North-Central Nigeria, and Lagos, in Southwest Nigeria
- HIV Prevalence: 46.0% in Abuja, 70.3% in Lagos
- HIV Incidence in Lagos: 20.2 cases per 100 person-years (95% confidence interval 12.7-30.6)
- Chlamydia Prevalence: 14.7% in Abuja, 19.3% in Lagos
- Gonorrhea Prevalence: 20.9% in Abuja, 16.5% in Lagos
Ebola Research in Africa:
Leveraging HIV Network

Pioneering studies in Uganda

- MHRP’s HIV vaccine site conducted first Ebola vaccine clinical trial in Africa in 2009
- Currently testing NIH’s ChAd3 vaccine, Janssen/J&J Ad26/MVA platform
- Conducted the largest published long-term follow up study on Ebola survivors

African clinical trials network based upon MHRP HIV sites

- ChAd3 (GSK) Phase II Ebola vaccine trial began in 2015 in Abuja, Nigeria
- Ad26/MVA Phase II Ebola vaccine trial began in US in 2016 and enrolling in Kenya, Uganda, Nigeria, Tanzania and Mozambique in 2017 (includes HIV infected volunteers)

WRAIR has conducted 6 Ebola vaccine studies
Joint West Africa Research Group (JWARG)

Response to gaps identified in West Africa Ebola outbreak

- Army/Navy partnership
- Build upon established effort and relationships in Nigeria, Ghana, Liberia
- Military and academic partners in U.S. and West Africa

Goals

- Prevent repeat emerging infectious disease surprise in West Africa
- Advance DoD medical research mission for countermeasures to infectious diseases threats (diagnostics, vaccines, therapeutics)
- Build sustainable partnerships and platforms to address DoD research needs and host-nation public health
In 10 months, WRAIR went from vaccine concept to clinical testing

**Proven Vaccine Platform**
Successfully developed licensed vaccine for Japanese Encephalitis, another flavivirus

**Early Zika Detection**
Biosurveillance in SouthEast Asia aided in vaccine design

**In-house Capabilities**
Developed and produced ~1,700 doses for clinical testing
Ensuring Future Success

- A new level of collaboration/partnerships
- Leveraging prevention and treatment research
- Vaccines being developed for prevention and “functional” cure
- Understanding HIV as a public health threat requiring sustained intensity of effort

“While we have many prevention tools available to help curb the HIV epidemic, we need a safe, globally-effective vaccine to end it.”

COL Nelson Michael, MD, PhD  
“The Vaccine Hunter”
Many thanks to clinical trial volunteers, researchers, clinical and support staff, funders, collaborators and advocates for making progress towards an AIDS free generation possible.