Infection with Multiple HIV-1 Variants Leads to Poorer Clinical Outcomes

Study shows number of HIV-1 variants at the beginning of infection affects viral load setpoints

August 31, 2015 (SILVER SPRING, Md.) — HIV-1 infection with multiple founder variants points to poorer clinical outcomes than infection with a single variant, according to a paper published today in the journal Nature Medicine.

In the study researchers analyzed large sample sets from two important HIV vaccine efficacy trials—the Step HIV vaccine clinical trial (HVTN 502) and RV144, the landmark vaccine clinical trial conducted in Thailand — to evaluate whether genetic characteristics of the founder viral populations could influence markers of clinical outcomes. Specifically, they examined viral loads and CD4 T-cell counts against measures of HIV-1 diversity. The study group included researchers from the U.S. Military HIV Research Program (MHRP), Fred Hutchinson Cancer Research Center, University of Washington, Armed Forces Research Institute of Medical Sciences (AFRIMS), Thai Ministry of Public Health and Mahidol University.

In both studies, data collected up to one year post HIV-1 diagnosis showed that subjects who had multiple founder viruses had significantly higher mean viral loads.

“Our results brings into sharp focus how the earliest interactions between virus and host have a profound impact on the course of the entire disease,” said Morgane Rolland, PhD, of the Military HIV Research Program (MHRP), Walter Reed Army Institute of Research and senior author on the paper.

The researchers used two large data sets of viral sequences to test the association between HIV-1 diversity and markers of disease progression. The analysis included 63 Step study participants (infected with HIV-1 subtype B) and 100 RV144 participants (infected with CRF01_AE) who had viral load and CD4 T-cell measurements in the absence of antiretroviral therapy.

The setpoint for HIV-1 is the viral load of an infected person. It is established after the early HIV-1 infection phase and is generally stable over time. Given previously observed broad differences in viral load setpoint across subjects versus relatively stable viral loads over time, isolating characteristics that affect setpoint could be critical to understanding clinical outcomes.
“When studying the host response early after infection, we are looking at two types of infection. An homogeneous viral population will evolve in a stepwise manner, whereas the presence of two or more viral variants can immediately foster complex viral evolutionary processes,” according to Rolland.

These findings point to new opportunities to analyze the effect of preventive interventions, including developing new analysis methods that will take into account viral diversity measures.

“This study emphasizes the value of vaccine efficacy trials for gathering rich datasets—even if a trial fails to show efficacy, the data may be used to investigate important questions regarding HIV pathogenesis which informs next steps for HIV vaccine development,” according to Col. Nelson Michael, MHRP Director.

Sequencing and analysis in this study were performed under grants from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health.

References:

About RV144:
Results from RV144, an Army-led clinical trial involving more than 16,000 adult volunteers in Thailand, were published in the New England Journal of Medicine in 2009. The results showed that the prime-boost combination of ALVAC® HIV and AIDSVAX® B/E was safe and lowered the rate of HIV infection by an estimated 31.2% compared with placebo (p=0.04). These data provided the first evidence in humans that a safe and effective preventive HIV vaccine is possible. The study was funded by the National Institute for Allergy and Infectious Diseases (NIAID) at the National Institutes of Health and the US Army, and conducted by the Thai Ministry of Health. For more information, visit: http://www.hivresearch.org/rv144-trial

About Step:
The Step HIV vaccine clinical trial (HVTN 502) was an international multi-center, randomized, double-blind, placebo-controlled Phase II test-of-concept clinical trial that enrolled 3,000 HIV-negative volunteers from diverse populations at high risk of HIV infection. These included men who have sex with men, heterosexual men at risk, and female sex workers, with the overall population ranging in age from 18 to 45 years. Immunizations in the study were stopped in 2007 because the vaccine was not efficacious. Further analysis showed increased risk of HIV acquisition in vaccinated men. Merck & Co. Inc. and NIAID co-sponsored this investigational HIV vaccine trial. For more information, visit: http://www.niaid.nih.gov/news/qa/pages/step_qa.aspx
About MHRP:
The US Military HIV Research Program (MHRP) at the Walter Reed Army Institute of Research conducts research to develop an effective HIV vaccine and integrates prevention, treatment, diagnosis and monitoring as part of a global effort to protect troops and reduce the impact of HIV worldwide. MHRP has six clinical research sites in the US, Africa and Asia. The program successfully collaborates on HIV prevention care and treatment services, funded by the President’s Emergency Plan for AIDS Relief (PEPFAR), with African militaries and in the communities where it conducts research. For more information, visit www.hivresearch.org or find MHRP on Facebook, www.facebook.com/hivresearch, and Twitter at @MHRPInfo.