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News Release

Gene mutations tied to immune comeback during therapy for HIV-1

Patient outcome study may signal need for change of thought in HIV management

BETHESDA, MD – Researchers with the Infectious Disease Clinical Research Program (IDCRP) at the Uniformed Services University of the Health Sciences (USU) here and the University of Texas Health Science Center at San Antonio have published a patient outcome study in the March 30 online edition of *Nature Medicine* that may signal a need for a change of thought in the management of HIV. The IDCRP was established in 2005 by the National Institutes of Allergy and Infectious Diseases and USU as a major new initiative to focus on clinical infectious diseases of military importance. This collaborative program encourages the exchange of scientific ideas and fosters progress in fighting new health challenges. Among the IDCRP collaborators in this program are Drs. Matthew Dolan, Brian Agan and Maj. Vince Marconi at Wilford Hall Medical Center, San Antonio.

The IDCRP is headquartered within the Department of Preventive Medicine and Biometrics (PMB) at USU. The Principal Investigator, CAPT Gerald V. Quinnan, Jr., M.D., is also the chair of PMB. According to Quinnan, “This research is another accomplishment of the IDCRP in our efforts to connect with other researchers throughout the country and bring new insights to the care and prevention of infectious diseases including HIV.” According to the press release from University of Texas Health Science Center at San Antonio:

“A new study by U.S. scientists provides compelling evidence that two genes are linchpins in defining the course of immune restoration in HIV-positive individuals undergoing virus-suppressing therapy.

Nature Medicine, one of the world’s highest-impact journals, posted the study online March 30. The findings explain why some subjects’ immune systems fail to have a sustained immune comeback, despite suppression of HIV-1 replication by highly active antiretroviral therapy (HAART), while others’ immune systems roar back.

The two genes are CCR5, an HIV-1 co-receptor or portal of entry for the virus into CD4+ T cells, and CCL3L1, an HIV-suppressing molecule that binds to CCR5.

“The new results suggest that we may be able to personalize the treatment of HIV as we might be able to predict, based on the presence of these gene variations, whether someone will have a better or worse immunological response when taking HAART,” said lead author Sunil K. Ahuja, M.D.,

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professor of medicine, microbiology, infectious diseases and biochemistry at The University of Texas Health Science Center at San Antonio and director of the Veterans Administration Center for AIDS and HIV Infection at the South Texas Veterans Health Care System in San Antonio. He holds the university's President's Council Chair for Excellence in Medical Research.

"We categorized the copy number of the CCL3L1 gene and variations in the CCR5 gene into three categories designated as high, moderate and low genetic risk groups," said Matthew Dolan, M.D., co-lead author and professor of medicine at the Uniformed Services University, Bethesda, MD. Dolan also helped oversee the cohort of subjects at Wilford Hall Medical Center, San Antonio, which contributed to this study.

"Those HIV-positive persons categorized into the low genetic risk group did the best on HAART. In contrast those categorized into the high genetic risk group initially did fine during the first two years of therapy, but then their immune reconstitution failed and their CD4 cell counts began to decline," Dr. Dolan said.

A 2005 study by Dr. Ahuja and colleagues suggested that individuals with fewer copies of the CCL3L1 gene than the average found in people from their same ethnic background have increased risk of acquiring HIV-1 infection and progressing faster to AIDS. Also, previous studies by these researchers defined the CCR5 variations that confer protection.

"As those in the high and moderate genetic risk groups might be especially vulnerable to both increased AIDS risk and a poorer immune response during HAART, it might be important to keep a closer eye on such patients and perhaps even consider starting them on therapy earlier," said Brian Agan, M.D., a co-author also from Wilford Hall Medical Center.

"When patients fare poorly on HAART, clinicians usually think about genetic mutations in the virus as a possible reason, but this study points to the importance of also alerting caregivers to the importance of a person's CCL3L1-CCR5 genetic makeup as another possible factor for faring poorly on therapy," added Hemant Kulkarni, M.D., a co-author from the Veterans Administration Center for AIDS and HIV Infection.

Mike McCune, M.D., Ph.D., Chief of the Division of Experimental Medicine at the University of California, San Francisco, hailed the study as one with potentially important practical applications. "By showing that the same genetic makeup increases susceptibility to immune depletion and impaired immune recovery, the authors provide novel tools that may allow us to predict both those who will progress faster after HIV infection as well as those who might benefit from earlier initiation of HAART," he said.

The study suggests the need for new thinking in HIV-1 management. "The current debate about when to initiate antiretroviral therapy might need to be redirected toward first assessing who should be considered for therapy, on the basis of the host genetic endowment," Dr. Ahuja said.

Capt. Gregory Martin, M.D., U.S.N., program director for the Infectious Diseases Clinical Research Program at the Uniformed Services University, said, "The finding that CCL3L1-CCR5 genetic makeup has its greatest impact on immune recovery when persons were started on therapy with CD4+ counts of less than 350 cells/mm³ highlights the importance of starting persons on therapy earlier rather than later."

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Joel Kupersmith, M.D., chief research and development officer for the Veterans Health Administration, said, "Dr. Ahuja's groundbreaking research is in line with the VA's mission of providing personalized medicine for veterans. We look forward to the translation of these findings into improved care for HIV-infected veterans and HIV patients worldwide." The Veterans Health Administration is a part of the U.S. Department of Veterans Affairs and in part funded this work.

The CD4+ restoration was more closely associated with number of copies of CCL3L1 than with CCR5 status. "This suggests that drugs that mimic or amplify the activity of CCL3L1 could be effective for HIV treatment," Dr. Dolan said.

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The University of Texas Health Science Center at San Antonio is the leading research institution in South Texas and one of the major health sciences universities in the world. With an operating budget of \$576 million, the Health Science Center is the chief catalyst for the \$15.3 billion biosciences and health care sector in San Antonio's economy. The Health Science Center has had an estimated \$35 billion impact on the region since inception and has expanded to seven campuses in San Antonio, Laredo, Harlingen and Edinburg. More than 23,000 graduates (physicians, dentists, nurses, scientists and allied health professionals) serve in their fields, including many in Texas. Health Science Center faculty are international leaders in cancer, cardiovascular disease, diabetes, aging, stroke prevention, kidney disease, orthopaedics, research imaging, transplant surgery, psychiatry and clinical neurosciences, pain management, genetics, nursing, allied health, dentistry and many other fields. For more information, visit www.uthscsa.edu.

USU, located in Bethesda, Maryland, on the grounds of the National Naval Medical Center, is a traditional U.S. academic health center with a unique emphasis on educating the next generation of health care providers and researchers in military medicine, humanitarian efforts as well as responses to disasters, emerging infectious diseases, and other public health emergencies.

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