

NIH Grant Awarded to Study HIV Drug-Resistant Genetic Mutations Across Africa

IHV researchers received NIH funding to study genetic changes in two genes from the HIV-1 virus that may make it resistant to antiretroviral therapy.

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University of Maryland School of Medicine (UMSOM)'s [Institute of Human Virology](#) (IHV) researchers received funding from the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) for \$2.7 million to study genetic changes in two genes from the HIV-1 virus that may make it resistant to antiretroviral therapy. The study, named INSPIRE, will analyze genetic variation in types of HIV circulating in a handful of African countries that will help to better understand the implications of these mutations and will improve clinical management of patients.

The HIV virus weakens the immune system when untreated, so the body cannot fight infections. Once a person tests positive for the virus, a health care provider prescribes an

antiretroviral drug regimen that keeps the virus in check. However, if the patient does not tolerate the side effects, does not consistently take their medication, or if the virus no longer responds to the treatment, then the patient is switched to a second-line regimen with a different combination of drugs.



Studying HIV drug-resistant genetic mutations across Africa



Man Charurat, PhD, MHS

“Our study’s goal is to identify factors that predict when certain drugs found in the second-line regimens no longer suppress HIV infection and help guide third-line antiretroviral therapy strategies for resource-limited settings. This will be particularly important, as those people that do not respond to second-line regimens are at an increased risk for developing resistance to another drug in the third-line treatment regimen,” said one of the study principle investigators [Man Charurat, PhD, MHS](#), Professor of Medicine at UMSOM and Director of the Center for International Health, Education, and Biosecurity (Ciheb) in the UMSOM’s Institute of Human Virology. Third-line drug regimens tend to be more expensive, have not been tested as extensively in children and pregnant women, so these medications are less conducive for use in lower income countries.



Nicaise Ndembi, McS, PhD

Along with Dr. Charurat, [Nicaise Ndembi, McS, PhD](#), Adjunct Associate Professor of Medicine at UMSOM and Scientist in the UMSOM’s Institute of Human Virology, will serve as the other principle investigator on the study. Dr. Ndembi also serves as the Chief Science Advisor at the Africa Centers for Disease Control and Prevention (Africa CDC).

Based on earlier findings by Dr. Ndembi, the researchers hypothesized that genetic sequences in the HIV genes env and gag could contain compensatory mutations that could evade antiretroviral treatment.

“Our studies demonstrated the first instance of new Env mutations conferring resistance to dolutegravir naturally in human cell lines in the laboratory. Our findings likely mean that these kinds of mutations may already be occurring outside of the laboratory in patient populations,” said Dr. Ndembi. Dolutegravir is a class of drug known as an integrase inhibitor that prevents HIV from inserting itself into a person’s DNA, which it needs to do in order to make more copies of itself. “We attribute the decreased effectiveness of the drug to the ability of the Env mutants to mediate highly efficient cell-to-cell transmission, increasing the multiplicity of infection” said Dr. Ndembi.

The env gene encodes the Env protein that helps HIV bind to and infect human cells. The thought is that new mutations could potentially make the Env protein more effective at doing its job binding and infecting making the virus more infectious.

A class of drugs in the second-line regimen that HIV develops resistance to is known as the protease inhibitors. These drugs stop HIV proteases from working, which have the job of cutting other HIV proteins as a final step in their production. The researchers theorize that mutations in the gag gene may be what leads to the drug resistance. The gag gene encodes the Gag protein, which is snipped by the protein cutter protease. Exactly how the gene mutations select for drug resistance though, is unknown.

The study participants will be composed of people from the AFRICOS study, which is part of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), and the PASER study. The AFRICOS study enrolled 4,200 people, including 3,500 with HIV from sites in Kenya, Nigeria, Tanzania, and Uganda. The PASER study enrolled just over 3,000 participants with HIV/AIDS with the goal of tracking treatment resistance in patients from sites in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe.

Dr. Charurat and Dr. Ndembu will work alongside researchers from the Amsterdam Institute for Global Health and Development – Amsterdam (AIGHD), U.S. NIH's National Cancer Institute, Stanford University, U.S. Military HIV Research Program (MHRP) via the Henry M. Jackson Foundation, and University of Cambridge – United Kingdom.

"Decades of research have provided life-saving treatment to a virus once thought of as a death sentence," said E. Albert Reece, MD, PhD, MBA, Executive Vice President for Medical Affairs, UM, Baltimore, the John Z. and Akiko K. Bowers Distinguished Professor and Dean at the University of Maryland School of Medicine. "It is essential that we ensure that this virus remains treatable by staying on top of HIV's mutation rate and responding with new combinations of medications if necessary."

Almost 38 million people around the world live with HIV with about 75% of these people managing the disease with antiretroviral therapy, according to the U.S. Department of Health and Human Services.

About the Institute of Human Virology

Formed in 1996 as a partnership between the State of Maryland, the City of Baltimore, the University System of Maryland, and the University of Maryland Medical System, the IHV is an institute of the University of Maryland School of Medicine and is home to some of the most globally-recognized and world-renowned experts in all of virology. The IHV combines the disciplines of basic research, epidemiology, and clinical research in a concerted effort to speed the discovery of diagnostics and therapeutics for a wide variety of chronic and deadly viral and immune disorders, most notably HIV, the virus that causes AIDS. For more information, visit ihv.org and follow us on Twitter @IHVMaryland.

Nora Samaranayake

Institute of Human Virology

+1 443-823-0613

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