

DECEMBER 09, 2004

## Gene Variants May Help Fend Off HIV Infection



**Image Title:** HHMI investigator Bruce D. Walker reviews patient data with nurses at a clinic in South Africa. - Courtesy of Bruce D. Walker

A team of researchers based partly in South Africa has identified a key set of immune system molecules that helps determine how effectively a person resists infection with human immunodeficiency virus (HIV). Their work shows that mothers with a specific type of genetic makeup may be less likely to pass HIV to their offspring.

The finding has important implications for the development of vaccines to combat the AIDS epidemic, according to Bruce D. Walker, a Howard Hughes Medical Institute researcher. Walker is one of the leaders of the project, and a professor of medicine at Harvard Medical School and director of the Partners AIDS Research Center at Massachusetts General Hospital.

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The research also offers an intriguing glimpse into the simultaneous evolution of a pathogen and its human host. "This is the closest we have come to being able to watch as the evolution of the human population is affected by a pathogen," Walker said.

The other leaders of the project were Philip Goulder, assistant professor of medicine at Partners AIDS Research Center, and Hoosen (Jerry) Coovadia, professor of HIV/AIDS research at the Nelson R. Mandela School of Medicine at the University of KwaZulu-Natal. A paper describing their work was published in the December 9, 2004, issue of *Nature*.

AIDS researchers long have wondered why people have varying responses to HIV infection. "Some people rapidly progress to illness within a year or two, while others after 20 years of follow-up are still doing fine," said Walker. "The range of outcomes is widespread."

To examine the question, Walker and his colleagues focused on the class I human leukocyte antigen (HLA) molecules that occur in most of the cells in the body. When a cell is infected with a virus, the HLA molecules grab pieces of the proteins made by the virus and display the protein fragments on their surface. Other immune system cells recognize the foreign proteins presented by the HLA molecules and kill the infected cell, thereby stemming the infection.

The research team found that an individual's response to HIV infection depends heavily on the varieties—or alleles—of the genes encoding HLA molecules that the person has. But not all categories of HLA genes are equally important. The class I HLA alleles are divided into three categories—HLA-A, HLA-B, and HLA-C. Specific HLA-B alleles generate much stronger immune responses than do other HLA alleles. For example, in a study of 706 infected individuals in South Africa who had not yet begun treatment, the type of HLA-B alleles a person has affected the amount of virus in the blood; the number of CD4 cells a person has (a common measure of immune system health); and immune reaction to proteins made by HIV. By contrast, different alleles of HLA-A and HLA-C genes had no effect on the immune response.

"The B alleles are doing most of the work," said Walker. Vaccine developers therefore should give close attention to responses generated by the HLA-B alleles, "since those seem to be the critical ones that influence viral load."

The involvement of the HLA-B alleles was particularly interesting to the researchers, since HLA-B alleles are much more diverse than either HLA-A or HLA-C alleles in human populations. Immunologists often have speculated that the greater diversity of HLA-B alleles indicates that they have

been important during human history in fending off attacks from other pathogens. For instance, evolutionary forces may have promoted the diversification of HLA-B alleles so that human populations would present a multifaceted defense against infection.

In their *Nature* paper, Walker and his colleagues point out that the evolutionary influence of the HIV epidemic on HLA-B alleles already can be seen in the offspring of mothers infected with HIV. Mothers with protective alleles pass on HIV infection to their children less often than do mothers with alleles that do less to stop the progression of the disease. As a result, the frequency of the protective alleles would be expected to grow in the population.

The researchers conducted much of their work at the new Doris Duke Medical Research Institute in Durban, which is the largest city of KwaZulu-Natal Province in South Africa. The province is at the epicenter of the HIV epidemic in sub-Saharan Africa. In KwaZulu-Natal Province, a third of pregnant women are infected with HIV, and in Durban, prevalence among pregnant women exceeds 50 percent.

Doing AIDS research in South Africa “is one of the things we're most excited about,” said Walker. Based on previous research experiences in the country, Walker and several colleagues associated with Harvard Medical School and Massachusetts General Hospital knew that South Africa had very talented scientists. But they were also aware that those researchers did not usually have the financial support to develop professionally.

“We decided to set our sights high,” Walker said. “We decided to build the world's best biomedical research institute and put it right in the middle of the world's worst HIV epidemic, because we knew that that would facilitate the science needed to understand why the epidemic is so bad there, as well as vaccine development.”

Funding from the Doris Duke Charitable Foundation through Massachusetts General Hospital enabled construction of the institute at the University of KwaZulu-Natal's Nelson R. Mandela School of Medicine. “The institute opened its doors in July 2003, and in December 2004 we have a *Nature* paper by a first-author, who is South African and who was not doing research when we arrived because of a lack of opportunities,” said Walker.

Photini Kiepiela, the first author of the article and a researcher at institute, agreed that the establishment of the institute was critical in generating the new results. “The purpose of doing this work here is to nurture local South African scientists. [And] if not for this institute, it would not have been possible to do this work here.”