

Discovery

The Newsletter of
the Institute of
Human Virology

FROM LABORATORY TO CLINIC



▶ **ROBERT C. GALLO, M.D.**
Director of the Institute

Message From The Director

Centers of Excellence in Virology: A concept in need of implementation

In the late 1970s, one unhappy legacy of success in public health was overconfidence in the United States regarding serious epidemic infectious disease. This became apparent with the closure of some U.S. medical school departments of microbiology and pressure for contraction of the Centers for Disease Control and Prevention (CDC).

The discovery that viruses were involved in the origin of some human cancers and the emergence of what would become the greatest pandemic in medical history, AIDS, in the early 1980s proved once again Nature's propensity to challenge human nature.

In retrospect, we see other examples of recent unexpected infections like Legionnaire's disease and Lyme disease, respectively caused by air conditioning and, presumably, closer contact of humans to deer as a result of their shrinking natural habitat.

Today, new epidemics of Hepatitis C, emerging diseases such as SARS, recurrent Ebola outbreaks and the threat of bioterrorism all point to an on-going transfer of pathogen from animals to humans and spread of infection by human behavior.

Fifteen years ago, I noted that no person and no group was responsible for quick reaction to a new epidemic save the CDC and that the CDC may or may not have expertise in the type of microbe ultimately shown to be involved in the cause of new disease. I noted then that my group (then at the National Cancer

Institute) and the group of Montagnier/Chermann came into HIV/AIDS research not by request or any directional program but mainly by chance and advocated creation of Centers of Excellence in Virology, which collectively would provide expertise in all classes of viral pathogens. These centers need not be regional, but rather would be distinct by areas of focus and expertise.

Dr. Tony Fauci, director of NIAID, has made a major stride in that direction with his creation of Centers for Bioterrorism & Emerging Diseases. These centers are to be regional (and therefore may exclude better and newer talent elsewhere), and do include bacteria. Indeed, excluding small pox, bacterial diseases (e.g. anthrax and botulism) are the most prominent targets.

Centers of Excellence have been formed in several disciplines including cancer, Alzheimer's disease, heart disease, neurosciences and genetics. I believe virology and immunology merit the same. We cannot afford "chance" responses to new epidemics.

We already have seen firsthand the rapid devastation that comes with a fragmented approach to research, treatment and prevention. We must channel our scientific resources to combat the most destructive and deadly diseases known to mankind. Our future – as well as that of our children and generations to come — depends upon it.



The IHV's Director of Epidemiology Dr. William Blattner and Dr. Alash'le Abimiku with Dr. Larry Ayuba, Chief Medical Director for Plateau State Specialist Hospital

AIDS in Africa IHV Initiatives in Nigeria

The IHV has a longstanding presence helping to combat HIV in Nigeria, the African nation in the heart of the global AIDS epidemic.

Since 1991, in fact, when Alash'le Abimiku, an assistant professor in the Institute's Epidemiology and Prevention Division, helped set up the first research laboratory in Jos equipped to diagnose HIV/AIDS. That was five years before the official opening of the IHV and formed the very foundation of a pioneering partnership designed to equip Nigeria with the professional skills and training needed to better detect, treat and prevent the virus that causes AIDS.

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IHV Initiatives in Nigeria

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Abimiku has had a hands-on presence, spending much time in the laboratory she helped create, and her contributions have been pivotal to AIDS advances in Africa. It was Abimiku who first isolated, then scientifically analyzed and characterized the HIV strain most prevalent in Nigeria and West Africa and now recognized as the second leading cause of HIV infection worldwide.

In the decade to follow, the IHV has become an invaluable asset whose presence and expertise have proven crucial in addressing what has since become the deadliest epidemic in medical history, most dramatically and disproportionately in developing nations such as Nigeria where medical care and resources are scarce and sometimes non-existent.

"We literally had to go in and build from scratch," says Abimiku, explaining that there were few doctors trained to diagnose or treat HIV, no clinics available to provide testing or counseling, no community outreach or public education programs in place to spread the word on ways to prevent infection.

IHV is currently developing HIV prevention programs designed for specific high-risk populations under the AIDS Prevention Initiative in Nigeria (APIN) with funding from the Bill and Melinda Gates Foundation and in collaboration with the Harvard School of Public Health. This program will expand access to care to help prevent mother-to-child infection

and fill gaps in knowledge identified in research surveys.

The Centers for Disease Control and Prevention recently awarded a \$4.4 million grant to the IHV to provide technical assistance and scientific expertise to Nigeria, where one of five HIV infections in Africa occur in sub-Saharan Africa's most populous nation. The focus of this work is to build capacity to support the request of the Nigerian Government to develop four national centers of excellence for HIV care. These centers will promote prevention of mother-to-child transmission, provide high quality HIV care and allow Nigerian physicians to give antiviral therapy based on a high level of understanding of how complex, multi-drug regimens work. To this end, IHV is providing in-depth training to physicians, counselors, social workers, nurses and lab personnel who make up the multidisciplinary team required to give HIV care.

The U.S. Navy, meanwhile, under its Department of Defense HIV/AIDS Prevention Program, has retained the Institute to build laboratory infrastructure for HIV diagnosis in the Nigerian Army, identify high-risk behavior and design appropriate intervention programs to help halt infection. They've since been recruited to extend that project into the Nigerian Air Force.



Fogarty International Fellows:
Victoria Eyo, M.D.; Patricia Lar, Ph.D.;
and Johnson Onoja, Ph.D.

Five Nigerian Fogarty International Training Program fellows currently are being trained at the Institute of Human Virology and upon completion, they will return home to provide vital resources, expertise and help Africa build capacity to deal with the escalating epidemic.

"We've been intricately involved from the ground up," says Abimiku, who was born in Nigeria and now travels to Africa



Dr. Alash'le Abimiku
Institute of Human Virology

several times a year to provide professional expertise, intensive training and public outreach.

Much of the work is behind the scenes working with civilian, military and African leaders and policy decision makers. Days often are filled with meetings, training seminars, interviews with media, tours of facilities and – sometimes – visits home.

Her cultural background, Abimiku acknowledges, provides the scientific community at large an edge in earning trust in the African communities where HIV has been most uncontrollable and caused the most mass destruction.

She knows first-hand of loved ones who've succumbed to this disease.

"I'd be surprised if you could find any Nigerian who has not lost a close relative to HIV/AIDS," she says.

Despite the staggering statistics – nearly three-quarters of all HIV infections worldwide are on this single continent – most Africans refuse to openly discuss the risk of HIV infection. Sex is a taboo subject and women may be ostracized and beaten for suggesting use of a condom to prevent HIV spread.

"AIDS is synonymous with sex," says Abimiku. "Promiscuous sex. Meanwhile, in a polygamous society, what we have are a lot of innocent women and children getting infected."

Spouses often find out, after a partner is deceased, that their mate was infected or that they themselves are.

Abimiku says one of her most important tasks is helping dispel the myths associated with HIV/AIDS and heightening public awareness and sensitivity. Her work, she says, has and must go far beyond the confines of the laboratory.

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Taming a Virus; Targeting a Population

What works to halt HIV in one community won't necessarily help end the epidemic in another.

In the U.S., tremendous strides have been made through the development of anti-retroviral agents that enable HIV-infected patients to live longer and better lives. In developing nations, however, these drugs until recently weren't available or were too costly to be widely administered.

Raising public awareness and effecting change in public behavior, therefore, requires tactics and techniques tailored for individualized communities. Helping to develop and design AIDS prevention programs globally is the IHV's Epidemiology and Prevention Division.

Even prevention measures, however, must be packaged to address the needs of various audiences. HIV transmission occurs through sexual activity, drug use, childbirth and breastfeeding.

Over the years, the IHV has earned a reputation for working closely with health care professionals and recognizing the varied needs within communities as diverse as Africa and the Caribbean.

The African military, for example, has noted that HIV transmission rates are higher among traveling troops who contract the disease elsewhere and then bring it home. This can lead to increased transmission, as infected men can transmit the virus to women, who can, in turn, infect their unborn children and breastfeeding infants.

Last year, the Centers for Disease Control and Prevention awarded a \$4.4 million grant to the IHV to provide technical assistance to Nigeria with the goal of advancing programs in HIV diagnostics, HIV therapeutics and adherence, HIV prevention and voluntary testing and counseling. Additionally, the Department of Defense called upon the Institute to tailor comprehensive HIV surveillance programs first for the Nigerian Army and then the Navy.

IHV researchers Abimiku, John Vertefeulle and Pacha Villalba have been intricately involved in this program. All have traveled to Africa on multiple occasions for extended stays to train project staff and to conduct focus groups and epidemiological surveys that identify behavioral factors conducive to HIV transmission and evaluate risk.

The IHV team recently oversaw the development of a training curriculum and presentation that was modified to be culturally suitable for the Nigerian military. The curriculum is now moving into pilot testing and assessment. Vital to this process has been building capacity with Nigerian colleagues to modify, administer and take full ownership of the educational/prevention program.

"You use both focus groups and epidemiological surveys in conjunction to get a more complete picture of what is going on in the population. It's very important that prevention efforts are population specific and that the target communities take full ownership of the program," says Vertefeulle, a Research Assistant Professor in IHV's Division of Epidemiology. "Then they will start to implement it on a regular basis."

Through periodic visits, the IHV team gets a more accurate assessment of what communication tactics will and won't work within a specific population and can tailor a program that's proven to be effective in terms of what that group will listen to, understand, respond to, and retain.

Through these exercises, group participants also become more aware of the many myths and misconceptions of HIV/AIDS as well as specific things they can do to prevent infection and transmission.

Vertefeulle was impressed by participant reaction to the survey/questionnaire and the positive impact testimonials have in a group setting.

"That was really something to see," he says, recalling one woman who advocated HIV testing after sharing that she became aware her husband was HIV positive only after he had died.

"Participants were very inquisitive and had a craving for knowledge."

The IHV team plans follow-up visits to evaluate the short- and long-term success



IHV Research Assistant Pacha Villalba & IHV Research Assistant Professor Dr. John Vertefeulle

of the military AIDS prevention programs.

"There definitely is a lot of interest," Villalba notes. "It was encouraging to see the transition.

"At first, the group was quiet and we weren't getting much interaction or feedback. But as time went on, they took ownership of the program and really made it their own. It's definitely been very rewarding."

Dispelling Myths

Themes identified via focus groups in the Nigerian military and validated by quantitative survey results included:

HIV transmission via witchcraft 5.6%
HIV transmission via mosquito bites 9%
HIV transmission via kissing 17.6%
Can identify HIV by appearance 18.3%
HIV is curable 19.9%
HIV is not real 21%

Grim Statistics

As of 2003, more than 40 million persons globally live with HIV/AIDS.

- Three-quarters (30 million) live in Africa
- One seventh (6 million) live in Nigeria
- One-quarter of Africa's population is Nigerian

In Nigeria, twice as many people are infected today as in 1992. The first documented HIV case in Nigeria was in 1986.



The IHV is working to develop a pediatric AIDS vaccine.

Families First Africa Breaking the Cycle of AIDS

In Africa, more than 1 in 3 infants will become HIV-infected before their very first birthday. Those born free of the virus risk infection during breast feeding, an activity we associate with love and nurturing, not transmission of a fatal infectious disease.

The clear need is for a pediatric vaccine that protects infants against HIV transmission during breast feeding. For more information on the IHV's pediatric AIDS vaccine initiative, visit www.ihv.org. Families First Africa is a comprehensive effort designed to break the cycle of HIV infection and destruction of family units.

No Elders in Malawi

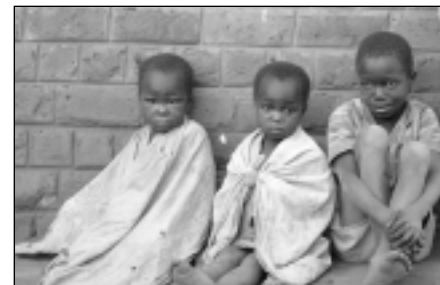
Dr. Robert Redfield, director of the Institute of Human Virology's Clinical Care and Research Division, sees HIV/AIDS patients on a daily basis. Not much surprises this physician who has been at the forefront of patient care/clinical research since the HIV virus first emerged a full two decades ago.

But even he couldn't help but be amazed at some of the stark differences in the real-life patients he encountered on a recent trip to Malawi to those he sees here in Baltimore.

"You didn't see any older persons on the wards. And there were children everywhere," recalls Dr. Redfield, adding that most patients average 20-40 years of age.

Newborns, if fortunate enough to be born HIV negative, are often infected through breastfeeding. There are some 600,000 to 800,000 orphans in the country, virtually all of them victims of the AIDS epidemic that is robbing children of both parents and grandparents and leaving young siblings alone to care for one another.

Simultaneously, there is a growing shortage of medical professionals to effectively cope with the crisis as the pandemic, meanwhile, continues to grow in unfathomable proportions.



More than one child is HIV infected every 40 seconds; more than 750,000 annually.

- Of Malawi's 10 million residents, three to four million are HIV infected.
- A high percentage of HIV/AIDS patients have other HIV-associated medical complications, such as tuberculosis and/or Kaposi's sarcoma.
- On average, there are just two physicians per every 9,000 patients.
- Of 60,000 teachers, 7,000 are lost each year.

"The epidemic in Malawi is about to explode," continues Redfield. The purpose of his visit was to offer technical assistance to physicians attempting to deal with the pandemic and to explore options with regard to collaborative partnerships studying new preventative and therapeutic strategies.

Other IHV community outreach efforts include international collaborations for epidemiological and AIDS prevention studies in Nigeria, Trinidad and Tobago.

Pediatric AIDS Pioneer Lectures at IHV

Dr. Catherine Wilfert-Katz, scientific director of the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), was a recent visiting lecturer at the IHV where she presented an update on EGPAF initiatives underway to address the pediatric AIDS pandemic in Africa, most often as a result of mother-to-child transmission.

Wilfert-Katz was a pioneer in the field of pediatric HIV/AIDS. Her group at Duke University participated in the first study of the effects of antiretroviral therapy in HIV-infected children; her concept of interruption of maternal to infant transmission of HIV by antiretroviral treatment of pregnant mothers

and their infants has reduced infant infections by more than 80 percent in the United States.

She retired from Duke in 1996 to become scientific director of the EGPAF, where she helped the Foundation launch the Call to Action Project, which supports 46 projects in 17 countries. Hundreds of health care workers have been trained and more than 250,000 women in antenatal clinics have had access to prevention of mother-to-child transmission interventions with counseling, testing, and nevirapine.

Wilfert-Katz now travels frequently to Cameroon, Zimbabwe, Uganda, Kenya, Zambia, Botswana, South Africa, Democratic

Republic of Congo, Malawi, India and other nations where the Call to Action Program provides counseling, HIV testing and interventions to reduce mother-to-child transmission of HIV.



Dr. Catherine Wilfert-Katz
Scientific Director
Elizabeth Glaser Pediatric
AIDS Foundation

Spotlight on Walter Sullivan: IHV Board of Advisors



Walter Sullivan
Morehouse School of Medicine

As Vice President of Operations and Planning at Morehouse School of Medicine in Atlanta, Georgia, Walter Sullivan is very active, identifying and obtaining funds for research and special programs, and supervising the planning, administrative, plant operations, Title III, and International Health groups.

With a Ph.D. in organic chemistry from Ohio State, Sullivan entered industry and later academia, rising to both Professor and Chair of Chemistry at North Carolina Agricultural and Technical State University. Prior to Morehouse, he was acting President and Dean of Academic Affairs for Fort Valley State College, Georgia, and Director of the Science Research Institute of Atlanta University Center. At Morehouse, Sullivan has been heavily invested in Sponsored Programs and International Health.

"I make certain researchers can expeditiously procure grants and contracts and have appropriate facilities for their work," he says, "while also helping to implement projects overseas." His satisfaction comes from "seeing others succeed," a driving force he also wields on behalf of the IHV.

Sullivan has been extensively involved in promoting the involvement and recruitment of minority youth in scientific research, spearheading annual Symposia to provide high school and college students with exposure to biomedical role models. And he's established strong connections with researchers from African and Caribbean countries struggling with HIV/AIDS.

Sullivan organized "Research Centers and Minority Institutions International AIDS Symposia" to explore the effects of HIV/AIDS on national and international minority communities and Dr. Gallo was a guest speaker for almost 10 years.

"I needed to help with the pandemic," says Sullivan, "and I have great respect for Robert Gallo."

"As a Board member, I am so impressed with the IHV, its talent, and its accomplishments," he says. "And I just know they will make even greater contributions."

Sullivan strives to assist in any way he can. "Primarily, I bring to their attention any vehicle I think could help them succeed," he states. "I make recommendations on minority involvements (in HIV/AIDS), give insights on approaching black community organizations (e.g., churches), and promote awareness and communication between the minority scientific community and the IHV, for collaborations." As for his major contribution to the IHV, Sullivan says "I'd like to think I've helped keep open the channels of communication."

Popovic Honored



Dr. Mika Popovic

Dr. Mikulas Popovic, M.D., Ph.D., basic researcher at the IHV and professor at the University of Maryland Biotechnology Institute, has been elected to the prestigious Academy of Sciences of the Czech Republic.

The Academy formulates its own

scientific policy, advises the state on major issues of its research and development policy, administers national and international research programs, and promotes cooperation with both applied research and industry to foster technology transfer and exploitation of scientific knowledge.

The first predecessor of the present-day Academy was the Royal Czech Learned Society, the oldest learned society in the entire Austrian Empire, formed in 1784.

Dr. Popovic, recognized in 1992 as one of the 100 most-cited authors for the period 1981-1990, was trained at Comenius University and the Cancer Research Institute, Slovak Academy of Sciences in Bratislava, Czechoslovakia.

He began his career in his home country, joined the National Cancer Institute in 1980 as an American Cancer Society Fellow and remained as a visiting associate, visiting scientist and senior investigator of the Laboratory of Tumor Cell Biology until 1989. He has been a visiting

scientist at Deutsches Primatenzentrum, Gottingen, Germany; a senior research scientist at Advanced BioScience Laboratories in Kensington, Md., and a visiting scientist at the Karolinska Institute, Stockholm, Sweden. He has been with the IHV since its opening in 1996.

Career highlights have included development of a system for the continuous propagation of the cytopathic human retrovirus HIV-1 in T4+ permanent cell lines. The large-scale production of the virus permitted 1) its identification as the etiologic agent of the acquired immunodeficiency syndrome (AIDS) and 2) the development of specific reagents which then permitted the development of a blood bank assay.

His work today includes biological and immunologic studies of HIV1-p17, the matrix protein (MA) of the virus; persistence of HIV-1 proteins, particularly MA, in germinal centers of lymph nodes; and immune-modulating activities of Tat *in vitro* and *in vivo* using small (mouse, rat) animal models.

New Board Members

The IHV welcomes Peter Bourne, Sheila Dixon and Aris Melissaratos to its Board of Advisors.

Bourne, M.A., M.D., former Captain and Research Psychiatrist with the U.S. Army Medical Corps, is now a visiting scholar at Green College, Oxford and Vice Chancellor Emeritus, St. George's University, Grenada, West Indies. Long active in foreign policy, he served as Special Assistant to President Jimmy Carter for Health Issues; Director of the Office of Drug Abuse Policy; Assistant Secretary General of the United Nations and Advisor on International Health and Development Issues.

Listed in *Who's Who in the World*, Bourne is a member of the board of directors for Global Hunger Project (chairman); the Center for Genetics, Nutrition and Health; Medical Education Cooperation with Cuba; Health and Development International; the National Youth Advocate Program and the Institute for Caribbean and International Studies.

Dixon, president of the Baltimore City Council, also presides over the Board of Estimates. She has sixteen years experience as an International Trade Specialist and has served three times as a City Council member before being elected President.

She currently serves as a member of the Board of Trustees for the Transplant Resource Center of Maryland, is a lifetime member of the NAACP and recently received the Circle of Excellence Award for being selected three times as Maryland's Top 100 Women by the Daily Record.

President Dixon created the Commission on HIV/AIDS, serves as an honorary chair for the American Cancer Society Relay for Life, HERO AIDSwalks 2002 and 2003 and is a member of numerous community and non-profit organizations.

Melissaratos, Maryland Secretary of Business and Economic Development, served as V.P. of science and technology for Westinghouse Electric Corporation and was president and CEO of Coleman Research Corporation and Thermo Coleman Corporation. He was founding co-chair of the Greater Baltimore Technology Council, chair of the Maryland Manufacturing Association, VP of the MD Chamber of Commerce and is a member of the National Advisory Council, Whiting School of Engineering, The Johns Hopkins University.

THE INSTITUTE OF HUMAN VIROLOGY (IHV) at the University of Maryland was established to create and develop a world-class center of excellence focusing on chronic viral diseases and virally linked cancers. The IHV is dedicated to discovery, research, treatment, and prevention of these diseases and cancers. Its unique structure seeks to connect cohesive, multidisciplinary research and clinical programs so that new treatments are streamlined from discovery to patient. The IHV serves patients locally and the scientific community globally.

Two HIV Vaccine Candidates Together Generate Positive Results Merck and Aventis to Collaborate on Human Testing

A combination of two anti-HIV-1 vaccine candidates developed by Aventis Pasteur and Merck and Co., Inc. elicited levels of a cellular immune response against HIV-1 infection in monkeys that were higher than levels observed separately. As a result, scientists from both companies plan a joint human study to begin later this year.

The pre-clinical findings in monkeys provide an early indication that the vaccine candidates used together in a complementary way, known as a prime-boost regimen, may stimulate higher-level immune responses against HIV-1 than either vaccine separately. Researchers for Aventis Pasteur and Merck say the Phase I clinical trial, to be conducted in the U.S., will provide preliminary data about whether the combination can produce similar results in humans. Phase I represents the earliest stage of

human testing for a potential vaccine.

In studies conducted in rhesus macaque monkeys, a prime-boost regimen with Merck's replication-defective adenovirus type 5 vector (Ad5) vaccine candidate given first, and Aventis Pasteur's canarypox virus vector (ALVAC) vaccine candidate given afterward, stimulated levels of cellular immune responses against HIV-1 that were higher than levels seen using the Ad5 vector alone. Specifically, the superior results were obtained when the Ad5 vector was used as the priming (first dose) vaccine and the ALVAC vector as the booster vaccine.

The findings, according to scientists from both companies, were compelling enough to merit further study.

"We are extremely encouraged by the pre-clinical data and are moving to the clinic quickly," said Michel DeWilde, Ph.D., execu-

tive vice president of research and development at Aventis Pasteur. "This is an unprecedented pairing between two companies with large, established HIV vaccine research programs. We hope that this collaboration will contribute to a solution to this devastating epidemic."

ALVAC-HIV is a canarypox vector into which HIV genes are inserted. It has been studied in more than 40 clinical trials on five continents in more than 2,000 people since 1992. The MRKAd5 HIV-1 gag vaccine candidate is based on a modified common cold virus that is used as a means of delivering an HIV gene called gag into the cells to produce a potent cellular immune response to HIV and has been in Phase I clinical trials in about half of U.S. states and the District of Columbia.



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