

## INTERVIEW

# On Zoonotic Viruses and Yale-New Haven Hospital's AIDS Care Program

## An Interview with Warren Andiman, MD

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### **Can you tell us about your background and how you started your career in zoonotic viruses and HIV?**

I came to Yale in 1973 as a postdoctoral fellow in pediatric infectious diseases. After my fellowship, I joined the faculty. I've been here ever since. My initial research training took place in the laboratory of Dr. Dorothy Horstmann, who was a world-renowned poliovirus expert, but who, in the early 1970s, had shifted her attention to post-licensure antibody responses to the rubella vaccine. She had recruited a large school-age population in a few cities in Connecticut and when I came along, I helped to collect blood samples from the children five years or more following immunization with this new vaccine. Dr. Horstmann's goal was to examine the durability of the immune response to the vaccine virus and to learn whether those antibody responses were consistent with protection from wild rubella infection. I was taught how to measure these antibodies. It was the first test of my prowess at handling laboratory equipment and doing simple statistical analyses.

Later I moved to the laboratory of Dr. George Miller, who is a dedicated student of the Epstein-Barr Virus (EBV). He was interested in EBV not only as the cause

of infectious mononucleosis, but also in its role as an oncogenic pathogen. There are a number of cancers in the world for which EB virus is the responsible agent, including African Burkitt lymphoma and nasopharyngeal carcinoma, which is prevalent in parts of Southern China. While in Dr. Miller's lab, I became interested in the clinical manifestations of EB Virus infection in children. Normally, we think of the virus as a pathogen of adolescents and young adults. But EBV infections do occur in childhood. The infection is usually subclinical in children, but among its other more apparent clinical manifestations, some involve the blood and bone marrow, the nervous system and the lungs. As a pediatrician, I wanted to find connections between the biology of viruses and atypical forms of disease. During that early phase of my career, I was also director of the viral diagnostic laboratory for Yale-New Haven Hospital.

The entire focus of my work changed when the AIDS epidemic hit New Haven.

### **You then founded the AIDS Care Program at Yale-New Haven Hospital (YNHH) and witnessed the eradication of mother-to-child transmission of HIV in New Haven. What were**

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†Abbreviations: EBV, Epstein-Barr Virus; cART, combination antiretroviral therapy.

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***your experiences and what were some of the main obstacles?***

The AIDS epidemic came very fast and we were all taken by surprise when it arrived. This was in the early 1980s. In the beginning, those infected with the AIDS virus, were almost exclusively young men who had had sex with men. They were admitted to the hospital and filled the emergency rooms. Many were transferred to the Intensive Care Unit because they were very ill; most of them ultimately died because there were no treatments available, not for HIV infection and not for many of the supervening opportunistic infections. After a few years, the epidemic went on to include the IV drug-using population. In New Haven, as in most cities in the U.S., those most often affected were indigent people of color, a group that was frequently divorced from regular care. The epidemic in this particular population grew even more rapidly than those in the initial phase of the epidemic. The hospitals were beset with increasing numbers of admissions and visits to the emergency rooms. Most of the patients were uninsured, so the financial burden on the hospitals was enormous. None of those seeking care were denied, but many of them could not be discharged safely because they were either homeless or were regarded as “pariahs” in their own homes and communities. The hospital social workers were committed to the task of finding shelter, food, and transportation for these patients at the time of discharge.

Then the epidemic spread to women. The women were either IV drug users themselves or were the sex partners of IV drug users. Most of them were also indigent people of color. Once the epidemic spread to women, it quite naturally spread to newborns and children. When the infected women became pregnant, a proportion of their babies also became infected. We began to see the first group of pediatric patients in the early 1980s, and the population continued to grow in the ensuing years to the point where we were admitting about 24 to 30 HIV-infected babies every year. Again, there were no drugs available. Many of these children could not go home because their mothers were drug users or deemed to be physically incapable of caring for their children. By law, they were not permitted to be guardians for their own children. Consequently, many of these children went into family foster care with their grandmothers, aunts, or cousins. Several years passed before we could find state-sponsored and licensed foster families. At the onset of the pediatric epidemic, existing foster families refused to take these children into their homes. They were afraid for the health of their own biological children and for the other foster children living with them. It took a number of years of training and education, both for ourselves and for these families, to understand that there were very few risks in-



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involved in taking care of children of who had AIDS.

During the time when the great majority of our patients were adults, it became obvious to me that the hospital needed to establish a longitudinal care program for people with HIV/ AIDS. This form of care had always been created for other chronic disease, such as diabetes, arthritis, heart diseases, COPD, etc. It became imperative to follow these patients prospectively. Doing so, would allow us to forestall unnecessary admissions and burdens on the emergency department. Our patients would have a group of caregivers, doctors, nurses, and social workers, with whom they could form trusting relationships and who would be there for them as various crises occurred. There were a number of physicians from adult internal medicine who began to volunteer to see some of the adult patients. A clinic was established by a nurse practitioner for a half day per week in one of the existing outpatient facilities. Nevertheless, no physician in the department of internal medicine, was willing to take on the impending “burden” of responsibility for devising and overseeing all the hospital-based and longitudinal care of desperately ill AIDS patients. To create a true program, it became necessary to recruit physicians who would regularly attend our clinics. Pulmonologists were needed because many of these patients developed serious lung diseases and infections; neurologists were needed to help care for those who developed serious infections of the brain and various forms of neurodegenerative disease. Hematologists and immunologists were critical participants, as well. We were able to convince a number of these specialists to join us, to attend the clinics, and to teach one another and

members of the entire hospital staff.

The principle guide at the beginning of my journey as medical director of the Yale-New Haven Hospital AIDS program, Leetha Graf Filderman, had trained as a pediatric nurse practitioner.

As a practitioner with the Visiting Nurses Association, Leetha cared for many of the adult HIV-infected patients in their homes during times when they did not need to be hospitalized. She saw the need, as much as I did, to have a solid, dedicated program to provide ongoing care. We joined forces and began to bring this notion to the hospital's administration. We had to convince them this was the best thing for the patients and for the community of greater New Haven. Most of our patients came from the indigent Black and Hispanic neighborhoods that surrounded the hospital. The hospital administrators understood that it was their responsibility to provide this service, an idea that was no longer unique. New York, Newark, San Francisco, Miami, Chicago, Los Angeles, and other big cities were watching the epidemic as it spread widely. In all these cities, the large municipal hospitals became the centers of care because they were not only located within the parts of the city where the patients lived, but because they were also historically created to serve the entire population of those cities.

After many months of deliberation, YNHH agreed to create an AIDS program and provided us with dedicated inpatient and outpatient space and financial support for full-time and part-time positions. I have always emphasized that the program's social workers played as critical a role in the care of our patients as the physicians and nurses. The social workers took charge of the housing and nutritional needs of our patients so that they would not go back to homes where there was terrible food insecurity. We had to figure out how to get these patients food stamps, medical insurance, and shelter. As teammates, we served as educators for our families; we taught them how to care for their family members safely and compassionately. All of us became educators for our peers in the medical and nursing schools and for audiences both large and small in the city of New Haven and in other venues throughout the state.

Yale-New Haven Hospital has been incredibly generous. Even to this day, they provide much of the financial support and work space for the program.

***What does longitudinal follow-up look like for pediatric patients who are transitioning to adult care?***

When the number of HIV+ children began to expand, and the adult population continued to grow, we all thought it was a good idea to divide the AIDS program into adult and pediatric programs. As a pediatrician, I be-

came the director of the Pediatric AIDS Care Program. We recruited two spectacular physicians from New York, who had witnessed the beginning of the epidemic in the Bronx, to become co-directors of the adult program. The great success of antiretroviral therapy made it possible for many of our HIV+ children to survive into late childhood and even adulthood. A number of patients who are now in their early twenties were kids whose care I oversaw from the time they were born. We realized that as they continued to grow and mature, we needed to transition them into adult care. This was very difficult because many of these children and their parents had grown deeply emotionally attached to their pediatric caregivers. The pediatric staff had carried them through every conceivable crisis; we were regarded as family. They could call us whenever there were problems and we always responded to their various issues. The pediatric caregiving spaces and routines are also very different from those designed for adult care in terms of strong emotional support and physical space. The pediatric clinics do not look anything like the adult clinics; the staff are generally more cheerful and conciliatory, and the common areas are more colorful. It was difficult, but a majority of our long-term survivors have successfully transitioned to adult care at the Nathan Smith Clinic. We spend a lot of time supporting the patients through this transition process by introducing them to the nurses and doctors who will ultimately see them in the adult setting. Some of the adult staff come to the pediatric clinic, so we can all talk together. It often takes a number of months before the true physical transition takes place. Our task is to help train them to take full charge of their own care, the same as we expect of all adults.

It just occurred to me that yesterday, November 15<sup>th</sup>, was a special day. It was the day, in 1996, that the last baby infected with HIV was born at YNHH. Yesterday was his 22<sup>nd</sup> birthday and he is alive and doing reasonably well. The pediatric clinic population has dropped significantly as a result of our having eradicated mother-to-child transmission of HIV, but now, with some regularity, we're seeing small numbers of newly infected adolescents. It's so sad; we never thought this would happen. Most of these newly infected young men have become HIV+ as a result of sexual encounters with older HIV-infected men. They usually come to us early enough so that we can intervene quickly and get their viral loads down to undetectable levels through the optimal use of an ever-increasing number of antiretroviral drugs.

***What are some current obstacles, both locally and more broadly, that we are facing with regard to HIV and AIDS?***

We know that in the last five or more years the rates of mother-to-child transmission of HIV infection in the

U.S. has ranged between 1 to 2%. The vertical transmission rates used to range somewhere between 18 to 24%, depending on the part of the country. That was the baseline rate. Ever since the introduction of combination antiretroviral therapy (cART), all infected patients are treated with cART. The way in which we prescribe these drugs has become more standardized. You can easily find appropriate regimens online or in a book, even in smaller medical centers and hospitals. HIV testing has become almost universal. All of the sexually transmitted diseases, including HIV, are routinely screened during pregnancy or upon admission to some hospitals. If a woman is found to be HIV-positive, the provider can log into the CDC website for treatment options or she can also call the CDC or any state health department and they will tell you what to do. Most importantly, the provider needs to find a medical facility in which the patient can be followed with some regularity, so as to monitor for the development adverse reactions to the ARTs and to screen for potential drug resistance. It is very common over long-term treatment for patients to become resistant to some of the ARTs. So, alternative therapies have to be prescribed. Antiretroviral therapy has become complicated; there are over twenty ARTs distributed among several structural and mechanistic categories. Screening for drug resistance has become routine in this country, but has been a procedure unavailable in many parts of the world.

***You recently wrote the book: Animal Viruses and Humans, A Narrow Divide: How Lethal Zoonotic Viruses Spill Over and Threaten Us. What makes zoonotic viruses uniquely able to jump from species to species?***

There is nothing truly unique about zoonotic viruses. They are not very different from all the other viruses that exist. Many of them belong to the same species, genera and phyla as all the other viruses that we know about. Viruses become zoonotic, through a series of sequential mutations; a particular virus species or strain develops new surface antigens, mostly newly configured glycoproteins or lipids. These new structural formations allow the viruses to attach to cells in various animal species that have the appropriate receptors. It is a very random and haphazard process. Viruses are susceptible to the same kinds of mutagenic events that affect every animal or plant. Radiation and certain toxic substances can cause breaks in the DNA or RNA molecule that result in the deletion of one, two, three or a whole chain of nucleotides or in the insertion of new ones. In the influenza viruses, whole genes can swap places with one another in a process called recombination. The influenza genome is divided into eight segments, each one comprised of long nucleotide chains, each segment constitutes an entire gene. When a particular cell of the respiratory tract gets infected with one or

more strains of influenza, the genes may literally change places with one another. The only caveat is that each virion that arises from the replicative cycle must end up with eight segments; otherwise the virus cannot replicate. As viruses constantly mutate and develop new surface antigens, they may, by chance, come into contact with a cell that has complementary pre-existing receptors. The virus takes advantage of this antigen-receptor alliance, and gains entry into a mammal or bird and starts to replicate.

HIV is a good example. It is a zoonotic virus, specifically a lentivirus, a subcategory of retroviruses. There are a number of monkey and ape lentiviruses. They are RNA viruses that mutate frequently. Many of these mutations fail to be repaired in the process of replication, so the mutations stick. It is believed that the original leap of gorilla and chimpanzee viruses to humans occurred in the process of hunting or eating “bushmeat”. Once the virus gains entry to a human being, it finds a convenient home, usually on a mucous membrane.

These viruses have inhabited our planet for eons. They are not supernatural creations; they merely infect animals that ultimately have some random contact with humans in which they are able to replicate; it's that event—animal to human viral transfer—that signals the very first phase of an outbreak. The most important attribute of a successful zoonotic virus is its genetic makeup, one that favors human-to-human transmission. Preferably, the virus should be transmissible by a route in which humans commonly interact. It should be able to spread mucous membrane to mucous membrane or skin to skin like the pox viruses. The influenza viruses are among the most transmissible, it simply takes a sneeze, a cough, or the touch of a mucus-contaminated finger. Crowded urban populations and poor sanitation partner well with the spread of viruses. Most of the zoonoses I describe in my book are spread by the respiratory route, by sexual behaviors, or by ingestion of virus-laden animal flesh.

So, in summary, all zoonoses begin with a random mutation that alters the configuration of a viral surface antigen; random attachment of the altered virus to a convenient animal host cell receptor; and random association between the infected animal and a susceptible human host.

If an outbreak or an epidemic is to occur, the virus must acquire features that favor transmission from human to human.

***Why are some animals like bats and birds such good carriers of zoonotic viruses?***

Bats play important characters in my book. Many bat species live in long-term, harmonious symbiotic relationships with individual virus strains such as those belonging to the Nipah virus genus. As one example, fruit bats travel in flocks of thousands to temporarily inhabit palm



groves in Malaysia, Bangladesh, and India. They roost in trees to whose fruit and flowers they're attracted. Local groups of humans also favor the same trees. The most sought-after delicacy is stored within the tree trunks; the natives collect the delectable sap in clay buckets. The bats in the tree canopies eat the fruit and their excrement drops into the buckets below. Some bats even feed directly from the buckets. Fruit bat urine and saliva teem with Nipah virus. The epidemic begins because the humans and bats favor the same sweet, syrupy sap. Think of the exotic and odd series of sequential random events that must occur to complete this zoonotic scenario.

Migratory ducks that travel for thousands of miles along their migratory routes develop relationships with strains of avian influenza viruses, some of which have characteristics that allow them to be transmissible to humans. The ducks spread their reservoirs of viruses as they travel from country to country, and occasionally make contact with resident human populations along the way. Chickens raised by farmers in South China and other parts of Asia sometimes acquire infections caused by strains of avian influenza virus. These birds are raised in virtual industrial-sized numbers. When one of these flu strains is found to be transmissible to humans and pathogenic, tens of thousands of birds are routinely culled in order to prevent an epidemic or pandemic.

Industrial hog production operations in the United States and Asia are potential hot spots for the genesis of swine influenza outbreaks. Tens of thousands of pigs are kept in huge metal barns. Bodies rub against bodies and the animals live in their own excrement until they're slaughtered. These conditions are ripe for the genesis of epidemics. Some swine flu epidemics have also been traced to autumnal country fairs, during which time swine flu infections have spread from the pigs on display to admiring visitors who choose to pet and feed them. Swine influenza infections are sometimes fatal in pregnant women. Some such fatalities have been reported in the medical literature.

### ***How have changing ecologies led to an increase in emerging zoonotic viruses?***

As rainforests are razed to make room for arable farmland, human populations move closer and closer to the rainforest and the animals that live there. The people find new protein sources that they had not been able to successfully hunt previously. The ongoing eradication of the rainforest is considered one of the major risk factors that increases the occurrence of zoonotic spread. Climate change is another of these risk factors. Zoonoses require a perfect interplay between microenvironments and their animal inhabitants. These well-balanced environments serve the needs of their reservoir animals. Each zoonotic virus prospers and flourishes only in association with a

particular ecological niche. When we alter the environment, the local animal species have to undergo genetic change in order to accommodate to those alterations, some of which may inevitably lead to undesirable downstream events.

We have to be concerned about enormous, migrating refugee populations. There is a risk of epidemic disease outbreak when indigenous populations that have accommodated to a particular environment come in contact with new groups of people that may be carrying a pathogen to which the refugees have never before been exposed.

Warfare and tribal conflicts also serve well as cauldrons in which epidemic diseases can bubble up. The Democratic Republic of Congo is currently experiencing a prolonged epidemic of Ebola virus disease. The outbreak started months ago. Tribal warfare has plagued the DRC for a long time. When a disease outbreak begins in a war zone, everything else breaks down including the healthcare system. Wrecked roads and other forms of infrastructure make it impossible for international healthcare personnel to travel to the hot zones. Money that could best be used elsewhere is squandered to fight the war. There have been multiple Ebola outbreaks for decades in Africa; but the current one is now considered the worst. There have been hundreds of deaths already. Food and medicines cannot find their way to those who are ailing. Uganda is immediately adjacent to the Democratic Republic of Congo and there are people who are fleeing the warzone and crossing the border into Uganda. Uganda has an excellent healthcare system that has been able to identify new cases and to place those infected into quarantine. But, other adjacent countries are not as well off and there is growing concern that some people will flee to countries that do not have effective healthcare systems. Will we have another outbreak like we had in West Africa five years ago? That one was very unusual because West Africa had never seen an Ebola outbreak, so it probably had spread from adjacent countries. The epidemic ended relatively quickly, mainly because the international community did a fantastic job of placing people in quarantine and providing medical supplies and protective gear. The local population was also eager to learn preventive measures and to teach one another how to manage their households and burials safely.

Countries at risk need to have reliable infrastructure—roads that are navigable are critical, so that ambulances, trucks, and people can get from villages to health care facilities easily and quickly. Health care facilities need supplies of both clean and sterile water. Public education programs are needed so that persons at risk understand the intricacies of disease pathogenesis. Hence, in many countries, you have to start lessons with the basic principles of microbiology.

Throughout the world there appears to be constant

flow of people from rural dwelling places to urban centers. The enormous growth of cities and their inhabitants increases greatly a chance for the appearance of greater numbers of epidemics and pandemics. Crowding is a critical component of the spread of all infectious diseases, particularly those spread by the respiratory route. Gastrointestinal pathogens also favor crowding. We do not always adhere to strict handwashing rituals after sneezing, coughing, and toileting.

Zoonotic disease outbreaks will inevitably occur, either as reiterations of diseases we already know or as diseases we have not yet seen. Many outbreaks have been traced in part, to the grave inadequacies of immoral governments. When public health priorities are enacted, food, water, and basic shelter take precedence over epidemiologic investigation and communication systems. Timely communication among public health providers and first responders is a critical player in epidemic containment. In my book, I make note of the fact that almost everyone in the world has a cell phone. If we could train a set number of interested people in every country to be the initial recipients of detailed information from the hot zone, they could convey that information to responsible local public health officials and begin a chain of communication to the rest of the world.

I'm a big fan of timely information exchange and good infrastructure.