

With a vaccine and cure likely unavailable for many years, Children's Healthcare of Atlanta doctors focus heavily on existing treatments and support for their pediatric HIV/AIDS patients.





MOVING BEYOND THE STIGMA

MORE CHILDREN AND
YOUTH ARE SURVIVING
WITH HIV/AIDS



When Marilyn Richards gave birth to her daughter Suzanne, she knew that her life would change forever.* But she could not have anticipated how rough life would become. Suzanne's father had contracted HIV and then passed it without warning to Marilyn. Without experiencing physical symptoms during her pregnancy—and without obtaining HIV testing—she gave birth naturally to Suzanne, who was born with pneumonia and a collapsed lung. • “Suzanne spent most of her baby life in and out of the hospital,” Marilyn said. “They prepared me and told me that she would not survive beyond the age of 5. At age 3 she also was diagnosed with cerebral palsy.” • As Suzanne approached the age of 5, Marilyn braced herself for the worst. But, with the help of antiretroviral drugs to stave off the progression to AIDS, various orthopaedic surgeries to correct mobility problems and a completely rebuilt esophagus damaged from repeated thrush infections, Suzanne is now 18 years old. Her mother describes her as “very independent.” • Suzanne is currently a junior in high school in Atlanta, has joined the ROTC, enjoys time on the computer, has sleep-over pajama parties with girlfriends and is learning how to train her vocal cords because she wants to sing like her mom, who is a member of her church choir.

Suzanne is a success story—a child who was not expected to live but has benefitted from the newest HIV therapies. But, she also is part of an increasingly rare subgroup of the 1.1 million people living with HIV in the U.S.¹ That is because maternal HIV testing has become a standard today, sharply decreasing mother-to-child HIV transmission statistics in the U.S. to less than 2 percent.² This is due in part to increased education and awareness of rapid HIV testing (see sidebar) and the ability to treat a HIV-infected woman who is pregnant with medications and options for a Caesarean section (C-section), virtually eliminating the chance of transmission to the fetus.

These advances have been facilitated by a reduction of the stigma associated with HIV infection, at least for certain populations.

“Children often are seen as the innocent bystanders of the epidemic,” said Paul W. Spearman, M.D., Chief Research Officer and the Division Director of Pediatric Infectious Diseases at Children’s Healthcare of Atlanta and Vice Chair for Research in the Department of Pediatrics at Emory University School of Medicine. “Children usually become infected through the birth process. This happens if there is no treatment in an infected mother. But you can decrease this chance dramatically with antiretroviral therapy.”

The Centers for Disease Control and Prevention (CDC) reports that pregnant HIV-infected women who take antiretrovirals before and during birth can reduce the chance of HIV transmission from 25 percent to less than 2 percent in the U.S.² There also has been a 93 percent drop in the number of children born with HIV primarily due to the use of antiretroviral agents to prevent maternal-fetal transmission.¹ These statistics are markedly different for other countries; however, particularly in sub-Saharan Africa where prophylactic use of antiretroviral agents is not as common as in the Western world.

Dr. Spearman credits the onset of universal maternal HIV testing and the use of antiretroviral therapy with the dramatic drop in pediatric HIV.

“It has been a great advance to identify the infected mothers. If the mother’s viral load is not completely controlled, a C-section is performed,” Dr. Spearman said. “Between antiretroviral drug therapy and the occasional need for a C-section, you can decrease transmission tremendously. But, we are still seeing some pediatric patients slip through the healthcare net.”

In addition to those patients who are infected at birth, the other primary group of concern in pediatrics is adolescents who become infected through high-risk behaviors.

“We actually are experiencing a growing epidemic within the adolescent population,” Dr. Spearman said. “High-risk sexual behavior and intravenous drug use are fueling the epidemic. HIV in children is still a problem in the U.S. but it is dwarfed by what is going on in other parts of the world.”

Pediatrics turns attention to adolescents

Rana Chakraborty, M.D., Associate Professor of Infectious Disease Division at Emory University School of Medicine, who works with Dr. Spearman in the Division of Pediatric Infectious Diseases, agrees that the new focus is on adolescents and young adults. Dr. Chakraborty also is Director of the Ponce Family and Youth Clinic, one of the largest HIV pediatric clinics in the U.S., providing care to children and teens until age 25.

Dr. Chakraborty is an internationally recognized expert in designing treatment guidelines for HIV-infected children. He was recruited to Emory from St. George’s Hospital, London, where he co-directed a pediatric HIV service and served a leadership role in the Children’s HIV Association (CHIVA) of Great Britain and also the Committee on Pediatric AIDS (COPA) under the American Academy of Pediatrics (AAP).

“We began treating patients up to age 25 because we have observed an outbreak of HIV among many young people. We have seen this in many youth from inner cities and diverse ethnic groups. Many youth are men having sex with men,” Dr. Chakraborty said. “Due to the stigma and denial associated with homosexuality and HIV, they are not following up with medical treatment or taking enough precautions to protect themselves or others. Many of our patients come to the clinic very immunosuppressed, with opportunistic infections and in need of lots of care.”

Unlike Suzanne, many young people—particularly males—will go to a clinic on a few occasions and then will be lost to follow-up. And, of course, that negates the key tenets of HIV care: good follow-up and consistency in taking medications.

“Since their follow-up visits at adult clinics were erratic, the older boys and young men were often getting lost in the system,” said Dr. Chakraborty. “In our pediatric clinic, we were able to muster some of the resources to encourage these young people to follow up with us. We also have developed a youth and adolescent network with selected mentors who work to encourage other members of the clinic to maintain good adherence.”

Once children of any age are diagnosed and on therapy, they can do quite well.

“Compliance with medical therapy for HIV may be an issue, depending on the family setting,” Dr. Chakraborty said. “But, if medications are given regularly, the infant can grow up normally. The burden becomes greater as they get older and understand that they have a disease and start asking why they are taking medications. It hits home for adolescents. They tend to deny that they are mortal and take more risks. Adolescence is a very difficult time for being compliant with medications. It takes a very mature adolescent to deal well with his or her HIV diagnosis.”

An extra dose of help at Ponce Clinic

Children who are seen at the Ponce Clinic receive medical care, educational resources and social work assistance. "The families often require financial help, for example, with transportation to the clinic," Dr. Chakraborty said. "Educating the adolescent is extremely important. There are support groups with HIV-infected peers to help. They share experiences in how to deal with HIV."

The infection still carries a stigma, though Dr. Spearman said he has seen an improvement. "Among certain populations it is not as much of an issue," Dr. Spearman said. "There are places, such as at-risk populations in Africa, where it is such a stigma that people refuse to be tested. In some places and among some populations in the U.S., it is the same. However, I think the media has done a better job of discussing the issues openly in recent years and testing is readily available and more widely accepted now than ever before."

"Mothers often deal with the issues alone," said Dr. Chakraborty. "You often see that fathers are absent and mothers have difficulty coping. The result is that these teens often drift into the criminal justice system and become exploited due to their vulnerability. Many of these youth are going through life without support. We often have a 16-year-old or 17-year-old who has just come in from the streets, abused. We often discover that the parent has been virtually absent in this person's life."

These children require continuous mental health support and ongoing viral load assessment and medication adjustments. Later, for some children, the virus can become resistant and medications may become more difficult, demanding a change.

HIV research at Children's

Current treatments for HIV/AIDS have saved countless lives. Experts at Children's Healthcare of Atlanta and Emory University School of Medicine have been at the forefront in developing these antiretroviral agents.

"The virus often is being checked but it is not checked mate. Now, we want to neutralize the virus," said Raymond F. Schinazi, Ph.D., D.Sc., Director of the Laboratory of Biochemical Pharmacology at Emory University School of

The Children's HIV Association (CHIVA) of the U.K. and Ireland is focused on developing standardized care for children. Rana Chakraborty, M.D., Associate Professor of Infectious Disease Division at Emory University School of Medicine, works as part of the executive committee to help this international effort.

He points out that children who are born with HIV, at least in the U.S., have a better chance of survival with parental support and consistent treatment. Those who contract the infection as a teenager are often at greater risk.

CHIVA addresses all of these issues.

Guidelines to treat children are similar to that of adults, but with a pediatric twist. To read about CHIVA's protocols, treatment, testing, trials and guidelines, visit www.chiva.org.uk and for more information, visit the Committee on Pediatric AIDS (COPA).

Medicine. Dr. Schinazi also serves as the Frances Winship Walters Professor of Pediatrics and Chemistry at Emory University School of Medicine.

He is best known for his pioneering development of d4T (stavudine), 3TC (lamivudine), FTC (emtriva), D-D4FC (reverset), RCV (racivir) and DAPD (amdoxovir)—of which the first three are FDA-approved drugs that make up the core of HIV treatment regimens—the last three are in Phase 2 clinical development.

These innovative drugs sell more than \$2 billion per year and more than 90 percent of HIV-infected people take at least one of the drugs he invented.

"Now, I am not satisfied with just treating these patients," Dr. Schinazi said. "I am interested in curing them—trying to understand where the virus hides and how we can eradicate HIV from viral reservoirs. In some cases, antiretroviral drugs do not reach these sanctuaries. There is room for better drugs for HIV treatments but we would like to find several cures. I have focused my life on working on serious life-threatening diseases including HIV and associated infection such as hepatitis B and C."

The focus of research now

Dr. Spearman also explained the role that his laboratory has been playing in the field of HIV research.

"We are working on two distinct areas: first, we are working on understanding how the viral proteins interact with cellular pathways," said Dr. Spearman. "We may be able to find a particular human factor that the virus latches on to in order to make more viruses. There is a chance of developing new inhibitors that target these unique steps in the virus replication cycle. The more we understand how the virus copies itself, the more opportunities we have to develop a drug to interfere with the virus."

The second area of ongoing research in Dr. Spearman's laboratory is the search for an HIV vaccine. "Unfortunately, HIV vaccine development has been very difficult,"

Dr. Spearman said.

He cited a recent pivotal trial of an HIV vaccine developed by Merck & Co., which was thought to be one of the most promising in development. In 2007, the company stopped development of the vaccine, which included synthetic fragments of HIV loaded onto a genetically modified cold virus, because it failed to protect volunteers in an efficacy trial.

"It does not change the fact that we need a vaccine—and one that generates cellular immune responses and neutralizing antibodies," Dr. Spearman said. "We are still many years away from an effective vaccine."





Rapid testing has changed how people live with HIV

Testing for HIV infection is an emotional endeavor for any individual. The Centers for Disease Control and Prevention (CDC) reports that many people never return to a lab to get the results due to fear. But, with issues of stigma slowly evolving, these new rapid tests have improved the speed with which people are treated as well as overall survival.

“Rapid testing has probably changed the way we look at testing because it can be done so quickly and easily, and it helps to remove the stigma because it is more of a routine thing,” Dr. Spearman said. “It has helped a lot in that sense.”

Dr. Chakraborty noted that rapid tests have had a positive impact on pediatrics. “HIV rapid tests have a

main place in the obstetrics setting. A mother can come in unsure of her diagnosis, either late in pregnancy or about to deliver,” he said. “The clinicians need to understand that, in order to avoid mother-to-child transmission, they can present the option of a C-section birth and let the mother know not to breast-feed. After the birth, we need to give medications to both the mother and baby postnatally.”

Rapid HIV tests are easy to use and require no specialized equipment. The U.S. Food and Drug Administration (FDA) has approved six rapid HIV tests including:

- Clearview Complete HIV 1/2
- Clearview HIV 1/2 Stat Pak
- Multispot HIV-1/HIV-2 Rapid Test
- OraQuick Rapid HIV-1/2 Antibody Test
- Reveal G3 Rapid HIV-1 Antibody Test
- Uni-Gold Recombigen HIV Test

Previously geared toward eradication, Dr. Schinazi has shifted his research to focus on where the virus hides.

“We have developed models for that and are testing our hypotheses but it is going to take at least 20 years to eradicate the virus,” Dr. Schinazi said. “Once we understand how it hides, we can develop drugs to target those reservoirs.”

Dr. Chakraborty, who has helped to standardize international pediatric HIV/AIDS treatments through CHIVA (see sidebar for more information) and COPA, said that he does not anticipate big changes in the drugs available to treat children in the near future, except for those that will treat multidrug-resistant virus.

“A new class of drugs is being rolled out: integrase inhibitors in combination with other drugs will be useful for children with multidrug-resistant virus because they attack

the virus with a different mechanism,” Dr. Chakraborty said. “These still are viable after trying other drugs. There are children already benefitting from Isentress (raltegravir, the only FDA approved integrase inhibitor) used in combination with Emory University School of Medicine—invented drugs, such as Emtricitabine, but I think they will be rolled out in a bigger way in the next five years or so.”

Until there is a cure

With a vaccine and cure likely unavailable for many years, Dr. Chakraborty focuses heavily on existing treatments and support for his pediatric HIV/AIDS patients.

“The stigma associated with HIV/AIDS has evolved but again, it still exists,” he said. “There are great variations depending on the culture. Young people experience the stigma due to exterior pressures and interior forces within themselves. There is not enough study on this issue. Only in the last four to five years have we been asking the necessary questions about how to broach the problem. Many of these young people are not taking steps to protect themselves from obtaining HIV in the first place or care to prevent spreading it to others. It is a combination of denial and a feeling of invincibility amongst youth.”

The Ponce Clinic currently is recruiting young people for a research program to train them to become counselors for other pediatric and adolescent patients.

Suzanne and her mother, Marilyn, are prime candidates for this role because they have both learned to cope with this disease, an illness that has so profoundly impacted and directed their lives.

“I do not really dwell on what doctors say about the future because when Suzanne was born, they did not think she would live,” Marilyn said. “As long as we have a sense of hope and religion, as long as we pray, we believe God will work everything out. We try to live for each day and I do not try to cloud my mind on what may happen three days from now. I also would tell women that if they are pregnant, they need to get tested to avoid passing it on to their babies.”²

**Names changed to protect identity.*

Paul W. Spearman, M.D., is Chief Research Officer and the Division Director of Pediatric Infectious Diseases at Children’s Healthcare of Atlanta and Vice Chair for Research in the Department of Pediatrics at Emory University School of Medicine.

Rana Chakraborty, M.D., is an Associate Professor of Infectious Disease Division at Emory University School of Medicine, and Director of the Ponce Family and Youth Clinic.

Raymond F. Schinazi, Ph.D., D.Sc., is the Director of the Laboratory of Biochemical Pharmacology at Emory University School of Medicine and is the Frances Winship Walters Professor of Pediatrics and Chemistry. Professor Schinazi also is a Senior Research Career Scientist at the Atlanta Department of Veterans Affairs.

¹ Centers for Disease Control and Prevention. *HIV Transmission Rates in the United States*. Dec. 2008. <http://www.cdc.gov/hiv/topics/surveillance/resources/factsheets/transmission.htm>
² *Mother to Child Transmission*. April 2007. http://www.cdc.gov/hiv/topics/perinatal/resources/meetings/2007/pdf/Fogler_MTCT.pdf