Imagine that you’re a young woman in southern Africa, giving birth to the child you’ve carried for nine months. Between the pain and the pushing, you feel both excitement and dread. At the antenatal clinic several months ago, you learned that you were infected with HIV. The doctor gave you antiretroviral (ARV) drugs to prevent your child from being born with HIV. You pray that they worked.

Six weeks later, while your newborn sleeps in your arms, the clinic nurse gives you the good news. Your daughter is not infected with HIV. You burst into tears of relief and joy. But wait, not so fast. Even though your baby isn’t infected with HIV, she was exposed to both HIV and ARVs in the womb.

You learn that the term for babies like your daughter is HIV-Exposed Uninfected (HEU) infants. And HEU infants in resource-limited settings like southern Africa are two to three times more likely to die within the first two years of life than babies who weren’t exposed to HIV or ARVs. The health and survival of your little girl is still at risk. Researchers are working urgently to understand why.

Aftereffects of Success

Figuring out how to prevent pregnant HIV-infected women from passing the...
virus to their infants is one of the most inspiring success stories of the AIDS epidemic. From research done at the Harvard AIDS Initiative (HAI) and elsewhere, we have learned how to reduce mother-to-child transmission rates from 30–45% without ARVs down to as low as 1% with ARVs in resource-limited settings, even when a mother breastfeeds her infant.

In 2010, the World Health Organization (WHO) endorsed the bold goal of eliminating mother-to-child transmission of HIV by 2015. With both scientists and health policy experts focused on preventing new infant infections, there had been an assumption that ensuring that a baby remained HIV-free would safeguard the child's survival.

“It is estimated that there are approximately 1.5 million HIV+ pregnant women annually,” said Dr. Elaine Abrams, a professor of epidemiology and pediatrics at Columbia University and an expert on mother-infant HIV transmission. “With successful prevention programs, we can hope to see HIV transmission rates as low as 2–5% and perhaps as many as one million HEU infants born each year.”

Fewer and fewer infants born to infected mothers became infected with HIV. That's wonderful news. But with the number of HEU newborns surpassing a million each year, we must look closely at the health of these still-vulnerable children. An increasing body of evidence suggests that HEU babies are not like babies who have never been exposed to HIV. It's a problem we're just beginning to understand.

“With increasing success of prevention efforts, the clinical and research community are shifting attention to HEU and only now beginning to delineate the particular health issues of this growing, highly vulnerable population,” said Abrams.

There's a growing sense of urgency because we've only begun to appreciate the magnitude of this problem,” said Dr. Max Essex, Chair of HAI. “Bear in mind that until five or ten years ago, most at-risk infants weren't even protected from HIV infection.”

Many Factors

Researchers at HAI are looking closely at how and why HEU infants differ from infants who were never exposed to HIV and ARVs. The difference is likely a combination of biological, social, and economic factors. “This is a complicated question that requires thoughtful, creative research,” said Essex.

The health of a mother is critical to the health of her child. The womb of an HIV-infected woman taking ARVs is different from that of an HIV-free woman. Recent studies have found that some HEU infants fail to get a healthy immune system because the mother's immune system is compromised.

Many HIV-infected mothers, besides dealing with their own disease, tend to be more impoverished. They tend to have less access to a toilet and clean water in the home. Because HEU infants live in a household affected by HIV, they are often exposed to illness, death, and family disruptions at a young age.

The increased mortality of HEU infants is predominantly due to deaths from infectious diseases, namely complications of pneumonia and diarrhea. It is an open question whether these deaths that stem from immunological problems or from the disadvantages of being born into an HIV-affected household. It is likely a combination of both.

Growth Problems

Growth is a good indicator of overall infant health. The first 1000 days of life are the most critical time for growth and affects a person’s entire lifetime. Some researchers have found that HEU infants are more likely to have stunted growth, lagging behind in both weight and length.

“Growth is a kind of a barometer of how sturdy you're going to be if you get sick early in life,” said Dr. Kate Powis, an HAI researcher whose work focuses on improving the health of HEU infants. “Children who have lower weight or length for age face a higher risk of mortality. If they get diarrhea or pneumonia, they're more likely to need hospitalization or to die.”
Understanding why HEU infants have stunted growth and finding a solution is of utmost concern, especially in southern Africa, the epicenter of the HIV/AIDS epidemic.

What HAI Is Doing

HAI is a leader in HEU research. As Max Essex explains, “We’ve got people who know a lot about mother-to-infant transmission: how and why that occurs and how to prevent it. We also have people who know a lot about the immunology of human resistance to HIV infection and why it does or doesn’t work. A lot of that information is useful in determining what sort of mechanisms are compromised in children who didn’t get infected with HIV but are still at high risk for all these other conditions.”

In the African country of Botswana, where HAI has been working since 1996, approximately 30% of pregnant women are infected with HIV. Botswana’s Prevention of Mother-to-Child-Transmission (PMTCT) program is the most successful in Africa, with more than 95% of HIV-infected pregnant women having access to ARVs. Fewer than 4% of infants born to infected mothers become infected and the rate is expected to drop even lower, close to the 1% rate that HAI researchers have achieved in clinical trials. However, in the coming years, up to 30% of all infants born in Botswana will be born HIV Exposed Uninfected (HEU).

To address the needs of this growing group of children, HAI researchers are asking a number of important questions:

1. What are the safest drugs to prevent mother-to-child transmission of HIV for both the mother and the developing infant?
2. Which respiratory and gastrointestinal infections cause the most problems for HEU infants?
3. Can we lower the risk of HEU babies dying from infectious diseases by giving them a widely available antibiotic during their most vulnerable first 1–2 years of life?
4. What is the impact of HIV exposure versus ARV exposure?
5. How is the immune system of HEU children different from unexposed children?
6. Can poor growth patterns in HEU children be reversed?

Building on Experience

Along with Essex, Drs. Shahin Lockman and Roger Shapiro have been conducting PMTCT research at the BHP for more than a decade. The landmark Mashi and Mma Bana clinical trials made important contributions to PMTCT research. The data from those trials will help Powis conduct a retrospective analyses of 1,930 women and their infants to look at the impact of giving mothers one drug versus a triple-drug cocktail and how that affects the health and growth of a developing child.

In new research, Shapiro is following children in Botswana from birth through two years of life to try to better understand infant mortality. Lockman is looking at the neurodevelopmental outcomes and mortality of HEU children compared to unexposed children and children with HIV. In another study, Lockman and Shapiro are testing whether giving a low-cost antibiotic called co-trimoxazole will help protect against death, diarrhea and pneumonia in nearly 3,000 HEU children. Powis is hoping to launch an innovative study that compares the gut microbiome of HEU infants with unexposed infants to learn more about differences in the development of the immune system.

Time to Act

The success of WHO-sanctioned ARV treatment and PMTCT programs will continue to increase the prevalence of HEUs. This is of particular importance in southern Africa, where HEUs may represent up to 30% of infants born in areas with a high HIV prevalence. What is becoming increasingly clear is that just keeping a baby HIV-free is insufficient.

In Botswana, almost every health metric has been improving since 2002. One metric that has not shown a marked improvement is the mortality of children under five. The higher mortality rate of
HEU infants in Botswana has contributed to the plateaued under-five rate. Understanding and finding solutions to the HEU problem is essential to lowering child mortality rates, especially in sub-Saharan Africa.

As we look to the future, the number of infant HIV infections will decline, but the number of HEU infants will increase. Identifying modifiable risk factors that contribute to higher mortality among HEU children and implementing interventions to promote their health and survival should be a public health priority.

It’s hard to write a profile of someone who doesn’t complain, especially when that person encounters innumerable problems on a daily basis and has to solve them quickly and efficiently or important clinical trials will come screeching to a halt.

Dr. Anthony Ogwu, Site Leader for the Clinical Trials Unit (CTU) in Gaborone, Botswana, has impossible days at work, but you’ll only find that out by asking other people. “The obstacles are endless, but he doesn’t get frazzled,” said Molly Pretorius-Holme, Senior Research Manager of the CTU. “He really doesn’t lose his cool,” agreed Dr. Shahin Lockman, who, along with Dr. Max Essex, leads the CTU. “Anthony’s patience is—I would actually call it fortitude—it’s beyond patience.”

The Botswana CTU is funded by the U.S. National Institutes of Health (NIH). It’s part of an international network of CTUs spread across the globe to conduct HIV/AIDS research as quickly and efficiently as possible. Once the protocol of a trial is approved, it can be conducted at a number of international sites simultaneously, helping to answer pressing HIV/AIDS research questions as quickly as possible.

Ogwu is responsible for the day-to-day operations of the Gaborone CTU, which conducts multiple clinical trials concurrently. Each new study has a different protocol to learn and follow. “For the Botswana CTU to remain in existence, we have to compete with other international sites across the world,” said Ogwu. “This requires a highly motivated staff.” He supervises study coordinators, physicians, nurses, and pharmacists, as well as the recruitment and retention staff who find eligible study participants for enrollment into the ongoing clinical trials at the site.

Besides being a seasoned project manager, Ogwu is also an experienced physician. “There are a lot of administrative things to do, but I still make as much time as possible to see patients,” he said. “When the wait is long, instead of keeping patients waiting, I go out there to help clear the lines.”

Profile: Dr. Anthony Ogwu
Directing Clinical Trials

Dr. Anthony Ogwu, photo by Dave Clift
Ogwu works with other members of the leadership team to decide which future studies the Botswana CTU should participate in. Studies must be relevant to the local population. “Anthony has a great sense about which research trials are most important for Botswana,” said Essex. Ogwu is also involved in community engagement and mobilization to support current and future trials.

For any study to go forward, hundreds of items must be approved and aligned. Stakeholders include the NIH, the Food and Drug Administration (FDA), Botswana’s Ministry of Health, Institutional Review Boards (IRBs) in Botswana and at Harvard, the community, research protocol teams, and potential study participants. Once the study is underway, there is quarterly monitoring to ensure that research is conducted under strict ethical and scientific standards. The fact that the Botswana CTU is so well regarded is due, in large part, to Ogwu’s contribution.

Nigeria to Botswana

Anthony Ogwu was born in the small Nigerian village of Idumu-ogo in the southwestern part of the country. One of six children, he was raised by his mother, a nurse who constantly stressed the importance of service and respecting all people. “She told me that putting others before yourself is always the right thing to do,” said Ogwu.

He earned his medical degrees in 2002 from the University of Benin in Nigeria. A few years later, an interest in HIV/AIDS led him to Botswana, a country at the forefront of AIDS care and research in Africa at that time.

In 2005, Ogwu began working at the Botswana Harvard AIDS Institute Partnership (BHP) as a study physician. He was quickly promoted and became the study coordinator for Lockman’s groundbreaking study led by Dr. Roger Shapiro.

While working, Ogwu also received his Master’s in Public Health from the University of the Western Cape in Cape Town, South Africa. His studies in health programs and research project management had broad applicability to his daily responsibilities working on high-profile clinical trials. In 2010, Ogwu spent six months at the Harvard School of Public Health as a John L. McGoldrick Fellow in Biostatistics.

Anthony combines ethical integrity and superior clinical expertise with a research sense for what is most important. I don’t know what we’d do without him.

– Max Essex

PROMISE Trial

The Botswana CTU is part of the International Maternal Pediatric & Adolescent AIDS Clinical Trials Group (IMPAACT), which conducts multisite, international studies on the health of HIV-infected mothers, adolescents and children. Ogwu is the Site Principal Investigator in Botswana.

To date, the largest and most ambitious trial for IMPAACT is what is known as the PROMISE study. Botswana is participating in the HAART (highly active antiretroviral therapy) Standard version of the PROMISE Trial, which will determine if women who start taking ARVs during pregnancy should keep taking them indefinitely after the pregnancy or stop.

Initially no African country was selected for this trial. It was limited to sites in the U.S., South America, and Asia, where HAART was already the standard of care for pregnant women. At the time the study was being planned, most African countries used one drug rather than a three-drug HAART regimen. Botswana was in the process of rolling out HAART for HIV-infected pregnant women. The Botswana team was able to convince the PROMISE protocol committee to allow Botswana to participate in this important trial. The success of previous trials, such as Mashi and Mma Bana, was one factor. Others were the country’s evolving standard of care and the relevance of the outcome to Botswana’s population.

A total of 2000 HIV-infected women at research sites in eight countries across three continents are expected to participate in this trial. Botswana, which began enrolling women in 2010, will enroll approximately 550 of them. The trial is ongoing. Results, which should provide important answers for national prevention programs for HIV+ mothers, are expected around 2016.

In the meantime, Dr. Anthony Ogwu will be hard at work, ensuring that the PROMISE Trial and other studies conducted by the Botswana CTU are held to the highest standards.

When not at work, Ogwu enjoys spending time with his wife and two young sons. He’s involved with his church as both a preacher and a Sunday school teacher. He also runs and plays chess.

“Anthony combines ethical integrity and superior clinical expertise with a research sense for what is most important,” said Essex. “I don’t know what we’d do without him.”

“I may not be able to change the whole world,” said Ogwu, “but I can make a difference where I am.”

5
In Botswana, a third or more of pregnant women were infected with HIV. You can extrapolate to say that one in nine kids born in Botswana in that period was infected with HIV. Most of those kids would die within five to ten years. By most, I mean 90 to 95%. And most of the infected mothers would die within eight to ten years.

Starting around 2002, more and more adults in Botswana got treated with antiretroviral (ARV) drugs that would keep them alive and in reasonably good shape. Remember, the existence of programs for ARVs—what was then called the triple-drug cocktail—didn’t happen anywhere in the world until 1994 to 1996. The mortality rate for mothers with HIV dropped rapidly in relation to how rapidly the Botswana government could implement ARV programs.

Progress for infants took longer. It wasn’t until 2006 to 2009 that we recognized the best ways to prevent infant infections, even while mothers were breastfeeding.

**What part has HAI played in saving infants from HIV infection?**

**ESSEX:** We’ve done quite a lot. Even before Botswana, we were involved in Thailand. With Marc Lallemant, we published several key papers in *The New England Journal of Medicine* and elsewhere about the use of AZT and nevirapine to prevent transmission from mothers to infants.

In the 1990s, multiple drugs were shown to be more effective in the treatment of adult AIDS patients. We showed that giving multiple drugs to prevent mother-to-infant transmission *in utero* and through breastfeeding was better than the use of single drugs. That now seems pretty obvious, but it sure wasn’t then. That was a major accomplishment in preventing infant infections.

We showed that mothers could transmit HIV to their infants through breastfeeding. We then did a study to determine if giving AZT to the mother could prevent the mother from transmitting HIV to the infant and showed that it could prevent transmission quite successfully.

But the question remained about whether it was safer for HIV-infected
mothers to breastfeed or formula feed their uninfected infants. In resource-limited settings in Africa, there's often a lack of clean water and an increased risk of disease. Breastfeeding increases the risk of transmitting HIV, but also boosts a child’s immune system and helps protect against infectious disease. In the Mashi study, we compared infant feeding methods and showed that breastfeeding was at least equal overall in preventing deaths as compared to formula feeding. The Mashi study helped to establish the importance of protecting infants who are born to HIV-positive mothers, even if they're not infected with HIV.

In the Mma Bana study led by Roger Shapiro, we compared different drug regimens to prevent mother-to-child transmission of HIV though pregnancy, delivery, and breastfeeding. Our team in Botswana showed an overall infant HIV infection rate of less than 1%, the lowest rate ever for a study in Africa or among breastfeeding infants.

At this point, can we declare success for preventing mother-to-child transmission of HIV?

ESSEX: I think we can declare tremendous success from the standpoint of research discovery on how to prevent infant infections with HIV. Yes, unequivocally. Obviously, we can only declare partial though substantial success in realizing the implementation of those discoveries at the policy level in sub-Saharan Africa. There are still situations where governments or health care systems don't apply what we’ve learned to save enough infant lives.

Why are we just now recognizing that HIV-Exposed Uninfected (HEU) infants face major health challenges?

Because only recently did we have a situation where we saved enough infants from HIV infection and death to then closely examine the health of kids who were born exposed but without the virus.

If we've learned how to successfully prevent mother-to-child transmission of HIV, why are we putting time and resources into infant cure research?

ESSEX: Two reasons. First, infant cure research represents one of the best opportunities to understand cure research at all. We’re more likely to find infants with recent infections than adults. And with infants, there’s a better defined and controlled situation. You can apply research knowledge and hypotheses more efficiently to test how best to limit the infection or, hypothetically at least, eventually even eliminate the infection.

Second, remember that infants will have to be on drugs their whole lives, so possibly 60 to 70 years. Adults, if they get infected, will be on drugs only half to two-thirds as long. Looking at the expense in terms of medical care and drugs and everything else, saving infants, besides being the right and compassionate thing to do, is more logical as an investment for cost-effectiveness than anything else.

Today in Botswana, if a pregnant woman is infected with HIV, what's the outlook for her and her child?

ESSEX: Very good. We’ve seen a huge positive change. Now the mother can expect to live a fairly normal life. In most cases, the infant will be born uninfected and saved from death from AIDS. Ten to fifteen years ago nobody dreamed this would be possible.

Does that answer extend to the rest of southern Africa?

ESSEX: It should and it’s starting to. Botswana is ahead of most other countries in Africa, but fortunately, because of policies from the World Health Organization and more progressive governments, now including South Africa, other countries are starting to catch up.

HAI is dedicated to research and education to end the AIDS epidemic in Africa and developing countries. For over 25 years, HAI has been at the forefront of HIV/AIDS laboratory research, clinical trials, education, and leadership.

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Should babies infected with HIV *in utero* be put on anti-HIV drugs immediately after birth? Can very early treatment allow some children to eventually control the virus on their own? HAI researchers are helping to answer those questions.

When HIV-infected women receive antiretroviral (ARV) drugs early enough during pregnancy, their chance of passing HIV to their infants can be dramatically reduced so that nearly all babies are born HIV-free. But infants born to mothers who are not taking ARVs have a much greater chance of becoming infected.

This was the case with the so-called “Mississippi baby,” born in a U.S. clinic in 2010. When the infant was just 30 hours old, a doctor put the newborn on ARVs before knowing if the baby had HIV. Because ARVs carry a risk of harmful side effects, doctors don’t usually prescribe these drugs unless a baby has tested positive for HIV. In Mississippi, lab tests came back several days later indicating that the baby did indeed have HIV. Subsequent tests confirmed her infection.

The baby stayed on ARVs for 18 months, but stopped treatment when her mother stopped follow-up care. After five months, the baby returned to care and was tested again for HIV. Here’s where things get interesting: the baby showed no sign of HIV infection. Doctors did not restart her ARVs, but monitored her closely. The toddler celebrated her third birthday with no detectable virus. Newspaper headlines heralded a possible cure for AIDS. There was a surge of optimism in the HIV research world. Then, shortly before the child’s fourth birthday, detectable levels of HIV were found in her blood. The virus had rebounded. The girl was put back on ARVs to suppress her virus.

When the news was announced in early July, Dr. Anthony Fauci, head of HIV/AIDS research at the National Institutes of Health (NIH), issued a statement. “Certainly, this is a disappointing turn of events for this young child . . . and the HIV/AIDS research community. Scientifically, this development reminds us that we still have much more to learn about the intricacies of HIV infection and where the virus hides in the body. The NIH remains committed to moving forward with research on a cure for HIV infection.”

A cure for HIV has been maddeningly elusive. Once the virus enters the body, it quickly forms reservoirs in certain tissues, including lymph nodes, the gut, and the brain. Though ARVs work well to control the virus, they don’t eradicate it from these reservoirs. If a person stops taking ARVs, latent virus in the reservoirs begins to replicate and the virus rapidly returns. In the case of the Mississippi baby, researchers had hoped that either the reservoirs never had a chance.
to form, or that very low levels of HIV would allow the child’s immune system to control the virus and that she could stay off treatment indefinitely.

Viral rebound in the Mississippi baby was a step backward, but not all the way to the drawing board. Although cure remains the ultimate goal, researchers are now asking whether starting treatment very early in life may allow for better treatment outcomes, and possibly periods of time off treatment, even if a lasting cure is not likely. Dr. Roger Shapiro, an HAI researcher not involved with the Mississippi case, is conducting a research study on early infant treatment of HIV in Botswana. Shapiro’s earlier work made groundbreaking contributions in preventing HIV-infected mothers from passing the virus to their babies. While neonatal HIV infection has almost been eliminated in the U.S., in sub-Saharan Africa, nearly 1000 babies are born with HIV every day.

In his new study, 30 babies born with HIV will be put on treatment right after birth. “The early treatment approach depends on rapid turnaround,” said Shapiro. ARVs will only be given to babies who test positive. He hopes to get HIV test results back within 24 hours of delivery. “Our goal is to start treatment by the second day of life.”

The second big challenge confronting Shapiro and his team is giving the babies the right amount of medicine. “In terms of dosing, we don’t have a lot of knowledge about treating neonates,” said Shapiro. Drugs are mixed with syrup that’s put into a small syringe and squirted into the baby’s mouth. “Babies in the first week of life have been treated before, but it’s not common. There is some uncertainty about getting the doses right,” said Shapiro. “We are being very, very careful.”

The study also hopes to test whether children who achieve an undetectable viral level after a course of ARV treatment will be able to remain HIV-free without treatment for an extended period of time. If a child has been on treatment for 96 weeks and virus is undetectable, the young patient may stop treatment and be carefully monitored for 96 more weeks to see if the virus returns. If it does, the child will immediately restart treatment.

Prior to any treatment interruption, Shapiro and his colleagues must receive approval from a Data Safety Monitoring Board (DSMB) and two Institutional Review Boards (IRBs) to ensure that the highest ethical standards are applied and the latest scientific evidence is taken into account. If some or many of the children are able to remain off treatment for weeks, months, or even years, then we will be much closer to understanding how viral reservoirs are established and how treatment in early infancy may be different than at other times in life. And possibly closer to a cure.

As Dr. Shapiro notes, “The benefits of starting treatment early in life may be far-reaching for these children. Minimizing the amount of virus in their bodies may allow for better treatment response and more durable treatment success at times in their lives when staying on medicines may be a challenge, such as adolescence.”

“This is the culmination of our work to find solutions for infants and children impacted by HIV/AIDS,” said Dr. Max Essex, Chair of HAI. “If this work leads to strategies to cure or control HIV infection, that would make a huge difference. Children would not have to experience the lifelong health challenges associated with chronic HIV and the medicine necessary to treat it.”

Much was haphazard about the case of the Mississippi baby, but much was also learned. Though HIV eventually rebounded in one girl, that won’t necessarily be the case for all children. As NIH’s Fauci stressed, “Now we must direct our attention to understanding why that is and determining whether the period of sustained remission in the absence of therapy can be prolonged even further.”

Shapiro’s study, designed and implemented with the highest standards, will provide answers to pressing questions in pediatric AIDS research. He and his team hope to start testing newborns later this year. Preliminary results should be available in three years, with more conclusive answers in about five. Though this is a challenging trial to conduct, the outcome could have a profound positive effect on the life-long health of babies infected with HIV.
Successful Defense

Kudos to Dr. Ireen Kiwelu who, on September 24th, successfully defended her PhD thesis, “The molecular epidemiology of HIV-1 among female bar and hotel workers in Moshi, Kilimanjaro, Tanzania.” Her work was supervised by Drs. Max Essex and Vladimir Novitsky at the Harvard AIDS Initiative. Born in Moshi, Tanzania, at the base of Mt. Kilimanjaro, Kiwelu was educated in Tanzania, Denmark, England, and Norway. She returned to her hometown to work as a Senior Research Scientist at the Kilimanjaro Christian Medical Centre. ©

Next Steps: Beyond Women and Children First

No baby should be born with HIV. From work done at Harvard and elsewhere, we’ve learned how to break the chain of HIV transmission from pregnant mothers to their kids. Policy and implementation programs are quickly catching up to the science. In this issue, we feature next steps in pediatric HIV/AIDS research, including the possibility of an infant cure; the troubling mortality rates of kids exposed to HIV in the womb; and a profile of the unflappable Dr. Anthony Ogwu.