MMA BANA ISSUE

We focus on the recently published results from the Mma Bana Study, a clinical trial on the prevention of mother-to-child transmission of HIV from pregnancy through breastfeeding.

STUNNING RESULTS IN PROTECTING INFANTS

The Mma Bana Study, led by Dr. Roger Shapiro, an infectious disease specialist at the Harvard AIDS Initiative (HAI), compared three different drug regimens to prevent mother-to-child transmission of HIV through pregnancy, delivery and six months of breastfeeding. In following 730 HIV-infected pregnant women in Botswana, the team showed an overall infant HIV infection rate of less than 1%. “This is the lowest rate of mother-to-child transmission ever recorded in a study from Africa or among breastfeeding infants,” said Shapiro. The results from the trial were published in The New England Journal of Medicine this June.

Of the 430,000 HIV infections in children each year, over 90% occur in sub-Saharan Africa. Over 40% of those infections occur during breastfeeding. Without intervention from antiretroviral drugs (ARVs), over 25% of infants born to HIV-positive women will become infected.

Past studies had shown that infant mortality rates were unacceptably high in Botswana and elsewhere in Africa if infants were fed with formula, rather than breast milk. Researchers were trying to determine how infants could best benefit from the immune protection of their mothers’ milk without becoming infected with HIV.

The Mma Bana (meaning “mother baby” in Setswana) Study was conducted at four clinical sites in Botswana as a collaboration between HAI and the Botswana government. The 730 HIV-positive women were given one of three different highly active antiretroviral therapy (HAART) regimens. The women began the drugs at about the third trimester of pregnancy and stayed on them through six months of breastfeeding. Their infants were tested for HIV infection/transmission at several intervals, including at birth and after six months of breastfeeding.

“All HAART regimens used in the study were found to be highly effective at suppressing HIV viral load with a 95% viral suppression in the mother at delivery and 93% throughout breastfeeding. Two of the three drug combinations (Combivir/nevirapine and Combivir/Alluvia) gave particularly impressive results—one infant infection in each group during pregnancy and no infections during birth or through breastfeeding. The third combination drug, Trizivir, resulted in three infections during pregnancy and two during breastfeeding. The overall rate of infant infections in the study was 1%.

“Until now HIV-infected mothers in Africa were faced with a choice between breastfeeding and a high risk of infecting their children with HIV, or using formula.”

‘This is the lowest rate of mother-to-child transmission ever recorded in a study from Africa or among breastfeeding infants.”

Dr. Roger Shapiro is the Principal Investigator in the Mma Bana Study, a clinical trial that compared the efficacy of several antiretroviral drug regimens to prevent mother-to-child transmission of HIV among breastfeeding women in Botswana. He recently spoke with Martha Henry, Editor of Spotlight.

The Mma Bana Study showed the lowest rate of mother-to-child transmission of HIV ever recorded in a study from Africa or among breastfeeding infants. How did your team achieve such exceptional results?

SHAPIRO: In the Mma Bana Study we were able to show the best-case scenario. We conducted a controlled trial in which the study participants received counseling,
picked up medications directly from the study clinic, and were always able to see a healthcare worker.

I think the success had a lot to do with women doing what they were asked to do, taking their medications, adhering to the study protocol. What this shows is that when women take the medicines, they work very well.

Has the problem of preventing mother-to-child transmission been solved?

SHAPIRO: We have come a long way. We now know that in Africa we can get the rates of mother-to-child transmission of HIV to the same levels as the U.S. or Europe—down to 1% or less. We know that when you give highly active antiretroviral therapy (HAART) to women and you do it properly, the drugs are extremely effective. The most exciting part is that antiretroviral drugs given to mothers prevent most HIV infections during breastfeeding.

Our findings show what is possible. This now presents a challenge to countries in the developing world and international aid agencies to make better antiretroviral regimens available and to implement effective delivery programs.

Can your results be replicated in other countries in Africa, particularly in countries that have not been as proactive on HIV/AIDS issues as Botswana or that don’t have adequate public health infrastructure?

SHAPIRO: This is an important question and always an issue when trying to replicate a clinical trial in the real world. The answer is we don’t know until we try, but we know what we can shoot for. We’re shooting for a rate of 1% or less.

I believe that is possible. We may never completely get rid of all transmissions, but getting to a rate of 1% is achievable in a program setting. Anywhere where women take these drugs, the drugs should work to prevent transmission in utero, during labor, and during breastfeeding.

How will your results be used?

SHAPIRO: They are already incorporated into the new World Health Organization (WHO) guidelines that came out in July. The new guidelines say that countries choosing the maternal HAART approach as their preferred strategy can use the same drug regimens that we used in Mma Bana to prevent mother-to-child transmission of HIV from pregnancy through breastfeeding. This strategy is effective, well tolerated, and a viable option for countries that want to use maternal HAART for prevention of mother-to-child transmission (PMTCT) while supporting breastfeeding.

Does your research mean that the pendulum encouraging women to bottle feed rather than breastfeed is swinging in the opposite direction?

SHAPIRO: Yes. What the Mma Bana Study shows is that the vast majority of infants can get the benefits of breastfeeding while also being protected from transmission of HIV.

Botswana started its formula-based PMTCT program in 1999. At the time we didn’t have a lot of data about the risks of formula feeding. Our research from the Mashi Study, published in 2006, provided some data about the higher risk of death during early infancy among formula-fed babies. There was also a nationwide diarrheal outbreak in Botswana in 2006 after heavy rains. We saw many deaths among formula-fed infants born to HIV-positive women. We think the risk from formula is two-fold: first, women may not be able to safely prepare infant formula (especially in an outbreak setting), and second, formula does not provide the protection of maternal antibodies that are present in breast milk. The Mashi Study and that diarrheal outbreak taught us that in Botswana formula feeding is not an (continues on next page)
ideal solution to the problem of HIV transmission through breast milk.

**What’s are the next steps?**

There are several “next steps” that we’re working on.

In the Mma Bana Study we found that when there were transmissions of HIV from mother to child during pregnancy, the major factors were expectant mothers starting the drugs too late in pregnancy or starting the drugs when they had a very high baseline viral load of HIV. We would like to find ways to rapidly get viral loads down for women who present late in pregnancy.

Another important question is how long HIV-positive women should breastfeed their infants. What is the optimal period? In Botswana we don’t know whether six months or a year is the right duration for breastfeeding. A year may improve infant survival, but we don’t know whether the intervention will continue to work, whether women will continue to adhere to it, or whether drug resistance will be a problem. So we’re studying six months versus twelve months of breastfeeding.

We’re also very concerned with infant mortality. We know from previous studies that HIV-exposed but uninfected kids are at higher risk of dying. These kids are more like HIV-infected kids than we might think. We want to know why kids die at a higher rate when their moms are HIV positive. Is it immunologic? Is it nutritional? Is it behavioral in some way? Nobody knows. It’s one of the questions we’re looking at. The answer may help us improve infant survival in the first year or two years of life.

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**PROFILE**

**DRS. ROGER SHAPIRO & SHAHIN LOCKMAN**

*Partners in Research & Parenting*

There are not many couples in which both husband and wife are first authors on a paper in the prestigious *New England Journal of Medicine*, but Drs. Roger Shapiro and Shahin Lockman are one of them. In addition to being researchers for the Harvard AIDS Initiative, both are also physicians specializing in infectious diseases. Together they have three sons, ages three, six and nine. And in spite of constant demands on their schedules, Shapiro and Lockman spend a significant amount of time mentoring young HIV/AIDS researchers.

Roger Shapiro was born in Hartford, Connecticut. His father, a cardiologist, and his mother, a career counselor, met on a blind date. Shapiro was a *magna cum laude* history major at Yale who then went to medical school at New York University.

Shahin Lockman was born in Columbus, Ohio. Her mother was a physician born in India to a Bahá’í mother and a Zoroastrian father. Lockman’s parents met in Heidelberg where her father, a chemist, was playing clarinet in a U.S. military band. As a child, Lockman moved with her family to Scotland and then to England and Germany. She returned to the U.S. for college and medical school at Northwestern University.

Lockman and Shapiro met in CPR class on the first day of residency at Beth Israel Hospital in Boston and began dating a year later. After residency they moved together to Atlanta to begin the Epidemic Intelligence Service, a two-year program at the Centers for Disease Control and Prevention (CDC). The couple spent a fair amount of time driving each other to the airport. Shapiro worked on food-borne and diarrheal outbreaks in Argentina and Kenya. Lockman worked on tuberculosis in Botswana. On her first visit there in 1996, another disease caught her attention. “At that point it became incredibly clear that HIV/AIDS was the fire burning down the house in southern Africa,” said Lockman, “but it wasn’t yet on the radar screen internationally how severe the epidemic was.”

Shapiro’s marriage proposal, like the rest of their lives at the time, involved a great deal of travel. Lockman flew from Botswana to meet Shapiro in Nairobi, Kenya. Together they flew to Entebbe, Uganda, took a bus to Kampala, and then another all-day bus to the far west of Uganda, stopping to help to shovel out a landslide that blocked the road. As the day was ending, they took a taxi to a pier and then a boat to an island on a deepwater lake where they were the only travelers at a tent camp. At sunset Shapiro proposed.

They got married three months later. A few days after that they started fellowships at the Partners Program for Infectious Disease in Boston and began looking for a research project. Both wanted to return to Africa to work on HIV/AIDS-related issues. They knocked on Dr. Max Essex’s door in the fall of 1998. Their timing couldn’t have been better.

Essex, Chair of the Harvard AIDS Initiative, was establishing the Botswana–Harvard AIDS Institute Partnership

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Profile: Shapiro & Lockman (continued from previous page)

(BHP). Preparations were underway for the Mabhi Study, the BHP's first clinical trial in prevention of mother-to-child transmission of HIV. Shapiro and Lockman signed on. In 1999 they moved to the Botswana village of Molepolole for a year to work on the project. “For me it was a tremendous stroke of good luck,” said Essex. “In retrospect I don’t know what I would have done without them.”

Returning to Boston in 2000, the couple continued with their research. In addition, Shapiro treated patients in the infectious disease clinic at Beth Israel Deaconess Medical Center and began working towards an M.P.H. in International Health from the Harvard School of Public Health (HSPH). Lockman treated patients at Brigham and Women's Hospital and began working towards her M.Sc. in Epidemiology from HSPH. Their first son was born in 2001. They both earned degrees from HSPH in 2003. Their second son was born in 2004. Until 2005 they continued to spend three months a year in Botswana with their children.

In 2007 the Mabhi team published key results on the study, demonstrating a way for women to avert the dangerous drug resistance that often occurs when they take antiretroviral drugs (ARVs) to prevent their infants from becoming infected with HIV. Lockman was the first author on the paper that appeared in The New England Journal of Medicine. She gave birth to her third son that same year. Shapiro was the first author of HAART’s most recent paper that appeared in NEJM on the results from the Mma Bana Trial. (See front-page article.)

When asked how they manage, Shapiro and Lockman both acknowledge the importance of their full-time nanny and say that setting priorities is crucial. Although there are always competing demands on their time, family is their number one priority. “We work well together,” said Shapiro. “Shahin is my closest colleague. We have different strengths and weaknesses, so we try to take advantage of that.” Both admit that being married to one’s research collaborator means there is no clear line between work and home life. “We are as blurred as blurred can be” said Shapiro. “We will put the kids to bed and then start talking about a study that we’re working on.” Lockman added. “We feel very fortunate to do work that we love and to do it together.”

NOW WHAT?
Applying Lessons Learned to Adult HIV Prevention

With the clear success of antiretroviral treatment to prevent HIV-positive pregnant women from transmitting the virus to their infants, researchers are now asking how lessons learned in prevention of mother-to-child transmission (PMTCT) can be applied to preventing new adult infections.

For every two patients who begin antiretroviral treatment today, five others become newly infected. According to UNAIDS, about 2.7 million people were newly infected with HIV in 2008, the last year for which global statistics are available. As Festus Mogae, the former President of Botswana, said in a 2009 address at the Harvard School of Public Health, “Prevention is now Priority Number One.”

Behavioral programs to stop the spread of AIDS, such as the ABCs (Abstain, Be Faithful, Condomize), have a dismal record of success in Africa and elsewhere.

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Now What? Adult HIV Prevention (continued from page 4)

Dr. Derek von Wissell, the Director of the National Emergency Response Council on HIV/AIDS (NERCHA) in Swaziland, the country with the highest HIV prevalence in the world, recently addressed this issue. “If you look at the increase of HIV in the country while we’ve been applying the ABC concept all these years, then it is evident that ABC is not the answer,” he said. “We need to find new ways to prevent infections.”

The Mochudi Project, HAI’s community-based HIV prevention study in Botswana, is testing a new strategy to prevent AIDS. One goal of the Mochudi Project is to identify people recently infected with HIV who have a high viral load. If people are provided with ARVs to lower their viral loads immediately, they are much less likely to spread the virus to others. “The concentration of the virus drops by a factor of 10,000 with antiretroviral treatment, resulting in 25 times the reduction of infectiousness,” said Brian Williams of the Southern African Centre for Epidemiological Modeling and Analysis at a meeting this February of the American Association for the Advancement of Science.

Antiretroviral treatment lowers the viral load of HIV in a pregnant woman to prevent her infant from becoming infected. Researchers hope this same principle will help prevent HIV-positive adults from infecting their sexual partners. Although the “test and treat” strategy for adults is gaining advocates across the globe, few clinical trials have been conducted to rigorously test the theory and most trial designs involve earlier treatment of people with late-stage infection, rather than early infections.

The Mochudi Project will contribute a significant amount of information to this growing area of research. At the end of the Mochudi trial, the worldwide HIV/AIDS community should have evidence-based answers to what are now only hypotheses. And possibly a beginning to the end of the AIDS epidemic.

MOCHUDI PROJECT LOGO CONTEST

To help foster community involvement with the Mochudi Project in Botswana, children from local schools were asked to design a logo. Pictured here are several entries. The winning entry will be published in a future issue of Spotlight.

Clockwise from right, logo designs by: Koketsa Monosi, Melita Ulaula, Othusitse Modise
Mma Bana Study (continued from front page)

and risking high infant morbidity and mortality from other diseases associated with not breastfeeding,” said senior author Dr. Max Essex, Chair of HAI. “This study provides a more satisfactory solution.”

The message is clear. Giving mothers HAART from early in the third trimester of pregnancy through six months of breastfeeding is a safe and effective strategy for preventing mother-to-child transmission of HIV while allowing for the benefits of breastfeeding. The Mma Bana findings have already influenced World Health Organization (WHO) policies for areas where formula feeding is neither safe nor feasible.

In an accompanying editorial in The New England Journal of Medicine that discussed recent clinical trials to prevent mother-to-child transmission, Dr. Lynne Mofenson of the National Institutes of Health stated, “We now have the tools to make a considerable difference in controlling the pediatric HIV-1 epidemic. A generation of children awaits our actions.”

Mma Bana Issue

In this issue we elaborate on the results of the Mma Bana Study. There is also a Q & A with Dr. Roger Shapiro, the Principal Investigator of the study, and a profile of Shapiro and his research colleague and spouse, Dr. Shahin Lockman. Also featured are entries in the Mochudi Project logo contest.

Mochudi logo design by Balosi Koditsewe