Becoming a Positive Parent: Reproductive Options for People with HIV

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As improvements in antiretroviral therapy continue to extend lifespans and enhance quality of life, more people living with HIV are hoping and planning to become parents. Roughly three-quarters of HIV positive people in the United States are of reproductive age, and multiple recent studies have found that an HIV diagnosis does little to dampen the desire to have a child.

Depending on the study, between 25% and 45% of HIV positive individuals of reproductive age report wanting to have a baby in the future, compared with about 35% in the general population.

The latest data on HIV and childbearing offers would-be parents plenty of reason to be optimistic. With optimal treatment during pregnancy and childbirth, the risk of having a baby infected with HIV drops to less than 1%. Recent studies of pregnant women on HAART suggest that pregnancy does not speed up the progression of HIV disease, and may actually slow progression in some cases. And for serodiscordant couples, advances in assisted reproductive technology can help achieve conception with minimal risk of transmission to the HIV negative partner.

Despite these promising data, however, people living with HIV may face significant challenges on the road to parenthood, including stigma and resistance among health care providers and the general public.

"There is definitely a disconnect between HIV positive men and women wanting to have kids, and there being this societal pressure not to do that," said Deborah Cohan, director of the Bay Area Perinatal AIDS Center (BAPAC) at the University of California at San Francisco.

According to an online survey conducted in 2007 by amfAR, the Foundation for AIDS Research, only 14% of Americans between 18 and 44 believe that HIV positive women should have children, despite antiretroviral therapy to prevent mother-to-child transmission. One-third of Americans said that if an HIV positive woman decided to become pregnant, they would not be at all supportive of her decision.

While no one has published a similar survey of health care providers, recent research highlights the need for more open-ended, non-judgmental conversations about HIV and childbearing. In a study of 181 HIV positive women of reproductive age from two urban health clinics, only 31% had discussed their personal plans for future reproduction with their health care providers. Of those discussions, 64% had been initiated by the woman herself, not by the provider.

"This is actually the best-case scenario of what's happening in our country," said Sarah Finocchario-Kessler, an HIV researcher from the University of Kansas who co-authored the study on provider communication. "Keep in mind that this study was done at a teaching hospital, where there were teams of people really advocating for having these types of discussions."

Health care providers in smaller clinics may be even less likely to bring up reproductive options, Finocchario-Kessler said. Infectious disease specialists may not think to ask about family planning, while gynecologists or fertility specialists may be less familiar with the specifics of HIV.

Even if a person with HIV has the courage and initiative to start a discus-

sion about future pregnancy plans, some doctors may not be prepared to discuss the topic.

"Even among providers who have a respect for the fertility rights of HIV clients, they're just not comfortable with preconception counseling," said Glenn Wagner, a behavioral scientist with the RAND Corporation who has been doing focus groups with physicians at HIV clinics in Los Angeles. "Part of it's because they just feel ill-prepared or ill-trained to do that kind of counseling. And because of the uncertainties around risk, they just avoid the subject."

People living with HIV who hope to become parents may want to independently seek out information about their reproductive options, and then search for a knowledgeable specialist to support them. This article will cover some of the latest research on how HIV affects male and female fertility, options for preventing transmission to infants and negative partners, and how pregnancy can affect HIV progression.

HIV and Fertility: A Complicated Question

Sorting out the relationship between HIV status and fertility is not an easy task. Most of the data come from population-based studies done in countries with limited resources and high HIV prevalence. In this setting, HIV infection appears to have a strong negative effect on fertility. For example, a 2002 United Nations report on fertility in sub-Saharan Africa reviewed eight population-based studies from six countries and found a 25% to 40% drop in fertility among HIV positive women compared with the general population. For every 1% of women of reproductive age infected with HIV, a country's overall birth rate fell by 0.4%.

Population-based studies don't tell the whole story, however, because they can't differentiate between behavioral causes of decreased fertility, such as fewer sexual encounters or increased condom use, and medical causes, such as problems with the sperm or egg. Because many of the behaviors that prevent transmission of HIV also prevent pregnancy, it's hard to know how much of the observed fertility drop is directly caused by the virus.

Many of the early fertility studies also failed to differentiate between asymptomatic HIV infection and progression to AIDS. Several AIDS-related opportunistic infections can affect the reproductive tract and impair fertility, and advanced disease has been linked to menstrual disorders in women and decreased sperm production in men.

But what about healthy people who are living with HIV—does being positive mean they'll have a harder time conceiving?

"There are some data that HIV can have a negative impact on fertility," Cohan said, "but most of the studies

RESOURCES FOR SAME-SEX COUPLES

Same-sex HIV positive or mixed-status couples may face additional stigma and hurdles as they try to become parents or maintain their existing families. Resources available to these parents or would-be parents include:

Lambda Legal
This national organization advocates for and represents people living with HIV and lesbian, gay, bisexual, and transgender (LGBT) people seeking to secure custody and visitation rights and to adopt children or become foster parents.
www.lambdalegal.org
866-542-8336 (toll free)

Family Equality Council
This advocacy group is dedicated to achieving social and legal equality for LGBT families through advocacy work at all levels of government. The council's website includes free publications for LGBT families and a database of local support networks across the U.S.
www.familyequality.org
617-502-8700

Growing Generations
This for-profit Los Angeles–based agency provides fee-based services to LGBT families who wish to have a child through egg or sperm donation and/or surrogate pregnancy. The company offers a program specifically for HIV positive gay couples hoping to conceive a child with a surrogate mother. A press release from the company in early 2010 reported five babies born from the surrogate program in 2009 and ten more expected in 2010.
www.growinggenerations.com
323-965-7500

have looked specifically at untreated men. It's easiest to evaluate men because you just do a semen analysis; it's more complicated to evaluate fertility in a woman."

HIV and Female Fertility

A woman's ability to get pregnant depends on a complex interplay of hormones and anatomy. The ovaries must release a mature egg at the right time each month (called ovulation), and that egg must be able to travel to her uterus through open channels called the fallopian tubes. The lining of the uterus must then be ready for the egg, once fertilized, to burrow into it, in a process called implantation.

Whether or not HIV has a direct effect on female fertility is somewhat disputed among researchers, but some think the virus may impact several of the steps described above. For instance, one study of 130 HIV positive women trying to conceive found that more than 25% had a blockage in their fallopian tubes, which could prevent a fertilized egg from getting to the uterus. These so-called tubal occlusions could be a direct effect of HIV, perhaps caused by inflammation, or they could be related to another genital tract infection such as chlamydia or gonorrhea. (HIV positive women are at higher risk of having genital tract infections, making it difficult to separate the effects of HIV from the effects of other infections.)

Women living with HIV also report a higher-than-average incidence of menstrual irregularities, including prolonged amenorrhea, or absence of a period for more than six months. Not getting a regular period often indicates that a woman is not ovulating and may have trouble getting pregnant.

Again, however, researchers are not sure whether the higher incidence of amenorrhea is due to direct effects of the virus, or to co-occurring issues such as substance abuse, high stress levels, and low body weight, which can all cause amenorrhea and are all more common in HIV positive women than in the general population. A study of 55 HIV positive women with regular menstrual cycles found normal levels of the hormones progesterone and estrogen, which are important for getting pregnant. This suggests that HIV may not have a direct effect on hormones, at least among women who get regular periods.

Recent data show that, once pregnant, healthy HIV positive women have about the same risk of miscarriage as women without HIV. In the U.S., approximately 15% to 20% of all recognized pregnancies end in miscarriage, although the true rate of pregnancy loss may be higher because many women miscarry before they know they are pregnant. One study of 352 pregnancies among HIV positive women found a 24% miscarriage rate, similar to the miscarriage rate for HIV negative women in the study.

This is in contrast to earlier research (done before most pregnant women were on HAART) that showed an increased likelihood of both spontaneous miscarriages and planned abortions among women with HIV.

HIV and Male Fertility

A few recent studies have looked at the fertility of healthy, HIV positive men undergoing treatment. For example, one group of French researchers compared semen from 191 asymptomatic HIV positive men, most of whom were on antiretroviral therapy, with 218 fertile men without HIV. After adjusting for factors such as age, frequency of sexual contact, and medical history, the researchers found that men with HIV had a smaller volume of ejaculate, fewer forward-moving sperm, and less acidic semen than the non-infected men. The researchers hypothesized that these changes were caused either by the virus itself or by antiretroviral therapy.

Some HIV medications—specifically nucleoside reverse transcriptase inhibitors (NRTIs) such as lamivudine (3TC; Epivir) and abacavir (Ziagen), which make up the combination pill Epzicom—can be toxic to mitochondria, the tiny rod-shaped structures that provide a cell with energy. Because sperm cells need a lot of energy for swimming, some researchers think that nucleoside analog drugs may impair fertility by damaging mitochondria.

To test this theory, a group of Dutch researchers looked at the semen of 34 HIV positive men who were starting combination antiretroviral therapy (ART) for the first time. They performed semen analysis before starting therapy and at 4, 12, 24, 36, and 48 weeks thereafter. Even before starting treatment, the men had a significantly lower percentage of forward-moving sperm than normal. Over the course of the study, that percentage decreased from 28% to 17%, demonstrating that HAART indeed affected the sperms' ability to swim. All other semen parameters, including volume and total sperm count, were within normal limits.

"The results of the trial are indeed remarkable," wrote HIV and fertility researcher Pietro Vernazza in an independent commentary about the study, published in the March 2008 issue of *AIDS*. "If confirmed, semen motility would be one of the most sensitive indicators of the toxicity of antiretroviral drugs."

However, Vernazza noted that although the study demonstrated a clear reduction in sperm movement, it didn't show to what extent that affected overall male fertility.

"If HAART results in reduced male fertility," Vernazza wrote, "progressively more sterile couples will seek professional advice. It therefore remains crucial that infertility clinics specialize in the treatment of HIV-infected patients and offer artificial reproductive assistance to these couples."

A 2010 study looked at 161 couples starting treatment for infertility in which one or both partners were HIV positive. Compared with an age-

matched control group of HIV negative couples, the positive couples had been struggling with infertility for a longer time before seeking treatment. Regardless of whether HIV directly impairs fertility, it's important for couples to seek reproductive assistance early, to minimize the risk of transmitting HIV to a partner during repeated attempts at conception.

Protecting an HIV Negative Partner

Serodiscordant couples are usually counseled to practice safe sex to avoid transmitting HIV to the negative partner, also known as horizontal transmission. Unfortunately for couples hoping to conceive, the barrier methods that prevent horizontal transmission also prevent pregnancy.

The risk of transmitting HIV during unprotected vaginal intercourse depends on multiple factors, including the number of sexual encounters, the viral load of the HIV positive partner, and whether either partner has other sexually transmitted infections. Observational studies suggest that transmission risk can be significantly decreased by limiting unprotected intercourse to fertile times in the female partner's cycle, treating the HIV-infected partner with antiretroviral drugs until viral load is undetectable, and treating both partners for any co-occurring genital tract infections.

A 2010 prospective cohort study of 3,381 heterosexual serodiscordant couples from seven African countries found that starting antiretroviral therapy reduced the risk of horizontal transmission by 92%. Only one of 103 cases of horizontal HIV transmission during the three-year study occurred after starting HAART. Of note, this study was part of a larger randomized controlled trial, called Partners in Prevention, which was designed to test whether the drug acyclovir (Zovirax) could prevent HIV transmission among couples in which one partner was coinfected with HIV and genital herpes. That means all HIV positive individuals in this study were also infected with herpes simplex virus 2, making them more likely to transmit HIV to their negative partners.

In another study, published in 2006, researchers reviewed all the unassisted pregnancies that occurred among serodiscordant couples with undetectable viral load from three HIV clinics in Spain and found no cases of horizontal transmission. Sixty-two couples were included in the study (with 22 HIV positive women and 40 HIV positive men), and in all cases the HIV positive partner was on HAART with a viral load below 500 copies/mL at the time of conception. Seventy-six pregnancies were recorded and 68 children were born, with one vertical (mother-to-child) transmission.

Despite these reassuring data, the researchers cautioned that the absence of detectable virus in the blood does not guarantee safe conception. Recent data suggest that plasma viral load doesn't always correlate with viral load in the reproductive tract. In a 2008 study of 145 HIV positive men enrolled in a program for assisted reproductive technology, 5% had detectable HIV genetic material in their seminal fluid, despite having had undetectable plasma viral load for at least six months prior.

Depending on which partner has HIV and whether a couple has access to a fertility center, there are several strategies that can further reduce the risk of horizontal transmission. In all cases, health care providers recommend waiting to try to get pregnant until both partners have been treated for genital tract infections and the positive partner is under optimal treatment for HIV.

If a Female Partner Has HIV

If a woman is HIV positive while her partner is negative, it's relatively straightforward and low-tech to attempt conception without risk of infection.

"Basically, it involves home insemination," Cohan said, "the good old-fashioned turkey baster technique. But obviously we don't recommend a real turkey baster, we recommend using sterile equipment instead."

First the woman figures out when she is ovulating, either by looking for changes in body temperature and cervical mucus, or by using an ovulation predictor kit purchased at a drugstore. Then her partner ejaculates into a cup or has sex while wearing a spermicide-free condom. Using a sterile syringe without a needle on it, the couple then draws up the semen and deposits it into the woman's vagina.

Success rates for serodiscordant couples using home insemination have not been published, but the technique has been used in resource-limited settings both in the U.S. and abroad. The method is also an option for lesbian couples using semen from a friend or other donor.

Couples with access to a fertility center may opt to have the procedure done in a clinic instead of at home. In this case, a sterile, flexible catheter is used to deposit the sperm into the woman's cervix, called intracervical insemination, or into her uterus, called intrauterine insemination (IUI).

Whether insemination is performed at home or in a clinic, the HIV negative male partner or sperm donor is never in contact with the positive woman's genital secretions, so there is no risk of HIV transmission, regardless of how many times the procedure is repeated to achieve pregnancy.

If a Male Partner Has HIV

If a man is HIV positive while his partner is HIV negative, the situation becomes more complicated. There are multiple options for lowering the likelihood of transmission while attempting to conceive, but none of these options is 100% risk-free. Before couples attempt to conceive, they may want to consider alternatives such as adoption or using donor sperm from an HIV negative man.

For couples who want to conceive a child with sperm from an HIV

positive partner and are willing to accept a non-zero risk of horizontal transmission, there are both high-tech and low-tech ways to reduce the likelihood of transmitting HIV to the negative partner.

The lowest-risk option is to use sperm that has been processed, or "washed," to remove the virus. HIV does not appear to infect sperm cells themselves, but instead floats as free viral particles or infects other cells present in semen. Labs that specialize in fertility treatment can isolate sperm cells from the rest of the semen, reducing the likelihood that the female partner will be exposed to HIV during fertilization.

Most labs use a process called density-gradient centrifugation to wash the sperm. Basically, a technician places a sample of semen at the top of a test tube filled with liquids of varying densities, and then spins the tube at high speed in a machine called a centrifuge. Healthy sperm end up in the bottom layer of liquid, while other cells, debris, and dead sperm get stuck in the upper layers.

In some cases, density-gradient centrifugation is combined with a second type of sperm washing called the "swim-up technique." In this case, washed sperm is placed in a dish and covered with a layer of fresh culture medium, a liquid or gel used to keep cells alive in the lab. Only healthy, forward-moving sperm will be able to swim into the new layer, leaving non-moving sperm or other cells behind.

Once sperm has been isolated from the rest of the semen, it is tested again for the presence of HIV. If no HIV is found, the sperm can be used for IUI, or for in-vitro fertilization (IVF), in which mature eggs are taken out of a woman's ovaries and combined with washed sperm in the lab. Fertilization takes place outside the woman's body, and then the fertilized embryo is put back into her uterus.

IVF may be combined with a process called intracytoplasmic sperm injection (ICSI), in which a single sperm is placed directly inside an egg; because only a single sperm in a tiny fraction of fluid is used, some researchers think that sperm washing combined with ICSI carries the absolute lowest risk of HIV transmission.

However, IVF and ICSI carry other risks. ICSI is normally used to treat men with infertility whose sperm can't independently swim to the egg; for couples with normal fertility, IVF and ICSI are more likely to result in twin pregnancy and preterm birth (see sidebar, "Sperm Washing and Intrauterine Insemination," for more information).

Cost and Access

Unfortunately, the cost of assisted reproductive services can be prohibitive for many people. One cycle of sperm washing with IUI can cost hundreds of dollars, while sperm washing with ICSI can run several thousand dollars or more per cycle. It may take several cycles for a couple to get pregnant, especially if one or both partners have other issues that may affect their fertility, such as poor sperm motility or blocked fallopian tubes. Insurance rarely covers fertility treatments, regardless of whether they are performed because of infertility or to protect a negative partner from HIV.

"The majority of patients I see do not have insurance that would cover it, and the cost to pay out-of-pocket is prohibitively expensive," said HIV specialist and obstetrician/gynecologist Jean Anderson, who runs the HIV Women's Health Program at Johns Hopkins School of Medicine.

Even if a couple has enough money to pay out-of-pocket for these services, they may have to travel away from home to find a clinic that will treat them. Although sperm washing is routinely performed before artificial insemination for couples without HIV, many clinics are not comfortable handling semen from HIV positive donors.

"What they will say is that they don't have the experience," Anderson said. "They raise theoretical concerns about potential cross-contamination and talk about needing duplicate laboratory systems."

Both the American Congress of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) state that it is unethical to deny services based on HIV status. The ASRM further warns that refusing service to an HIV-affected couple could in fact be illegal, since people with HIV are protected under the Americans with Disabilities Act, entitling them to medical services unless a physician can show "by objective scientific evidence" that treatment would pose a "significant risk" of infection.

"The way a lot of people have gotten around it is that they've developed some sort of linkage with another program that does sperm washing,

ADOPTION INFORMATION

As this article explains, there are many options available to HIV positive or mixed-HIV-status couples who want to become parents. Couples interested in adopting an infant or child may benefit from visiting the U.S. Department of Health and Human Services' online "Child Welfare Information Gateway," which offers directories of accredited adoption agencies and foster-care programs, as well as articles and fact sheets on various aspects of adoption, such as legal considerations and post-adoption support services.

Child Welfare Information Gateway—Adoption Resources
www.childwelfare.gov/adoption

SPERM WASHING AND INTRAUTERINE INSEMINATION

In the U.S., most fertility centers that serve clients with HIV will not perform IUI with washed sperm from an HIV positive donor. Instead, HIV positive couples are required to go the more expensive IVF or ICSI route, regardless of whether they need these treatments because of infertility.

This stance is based on the current recommendation from the Centers for Disease Control (CDC), which advises against using IUI with washed sperm from an HIV positive man. The CDC made this recommendation after a single case of horizontal transmission was reported in 1990, in which an HIV negative woman seroconverted after undergoing IUI with her husband's washed sperm.

Proponents of IUI argue that this case of seroconversion is no longer relevant, as the sperm had been washed using an older technique, not density-gradient centrifugation, and the viral load of the sample had not been tested before using it for IUI.

In Europe, sperm washing combined with IUI is the standard procedure for HIV positive men who do not have other fertility issues, and researchers have reported high levels of success and safety with this method. In 2007, researchers published retrospective data from the CREAThE network (Centre for Reproductive Assisted Techniques for HIV in Europe), which consists of eight fertility centers in six European countries. Together, the centers performed a total of 3,315 cycles of assisted reproduction, including more than 2,000 cycles of IUI with washed sperm, without a single case of HIV transmission.

Given these positive results, some researchers argue that the risks associated with ICSI, including a higher percentage of twin pregnancies and preterm births, make it a less desirable choice than IUI.

"We believe that the systematic use of ICSI in serodiscordant couples, where the male partner is HIV infected, is not reasonable, safe, effective, or ethical," wrote researchers from the CREAThE network in a letter to the editor of *Fertility and Sterility* in March 2009. "We believe that patients should be informed about all of the options for reducing the risk of HIV transmission and that the choice of [assisted reproductive technology] methods should be related only to the fertility status."

The CDC is currently reviewing its position on sperm washing and IUI, and new guidelines may make IUI more accessible for HIV positive couples in the near future.

so that patients will be referred," Anderson said. "But they may not be referred close by. Here in Baltimore, for instance, I have to refer people to Columbia in New York."

Until recently, laws in several states actually prohibited fertility clinics from using washed sperm from HIV positive men. For instance, California law states that tissue may not be transplanted into the body of another person until it has been tested and found negative for HIV. This measure prevented HIV positive men from accessing any kind of assisted reproductive technology until 2007, when the California senate passed an exception to allow sperm washing for HIV positive couples.

HIV positive gay men who wish to conceive a child with a surrogate mother may encounter additional challenges, as even fertility clinics that routinely serve HIV positive clients may not be willing to inseminate an unrelated surrogate with sperm from an HIV positive donor. However, at least one surrogacy agency in the United States has a program specifically for HIV positive men, and they report more than a dozen successful pregnancies in the past few years (see "Resources for Same-Sex Couples," page 44, for more information).

Pre-Exposure Prophylaxis

Because many serodiscordant couples cannot afford assisted reproductive services, or do not live near a center that provides them, doctors have been searching for less expensive options to reduce the risk of horizontal transmission among couples trying to conceive.

In addition to the recommendations for all serodiscordant couples—timing unprotected intercourse only to fertile times in the woman's cycle, treating the HIV positive partner until plasma viral load is undetectable, and treating both partners for any genital tract infections—there is some evidence that treating the HIV *negative* partner with antiretrovirals may also help prevent transmission during attempts at conception. Called pre-exposure prophylaxis (PrEP), this strategy is based on the concept that taking antiretroviral drugs prior to an HIV exposure may prevent the virus from taking hold.

The first evidence that PrEP works in humans came in 2010 from the iPrEx trial, which found a 44% drop in new HIV infections in the study group taking the antiretroviral drugs tenofovir (Viread) and emtricitabine (Emtriva), combined in the Truvada pill, compared with those taking a placebo. Furthermore, new infections were reduced by up to 73% among participants who adhered most closely to the tenofovir/emtricitabine regimen

and took the pill almost every day during the study. (For details on PrEP research, see "The iPrEx Results: Lifting Hopes, Raising Questions" in the Summer/Fall 2010 *BETA*.)

"One of the reasons that tenofovir and Truvada are being used is that, number one, they have a little longer half-life," Anderson said, "and they appear to be concentrated in the genital tract, which is the site of exposure for sexual transmission."

While these research results are certainly welcome news, one important consideration is that participants in the iPrEx study were all men who have sex with men and male-to-female transgender women. It is not yet known whether tenofovir and Truvada have the same protective effect in biologically female bodies and can help to block HIV infection during vaginal sex, and results from recent trials have been mixed.

A small study of PrEP among couples trying to conceive was presented at the International AIDS Society Conference in Sydney in 2007. This study looked at 22 heterosexual couples in which the male partner was HIV positive and on completely suppressive HAART. After testing both partners for other genital tract infections and teaching the couples how to use an ovulation predictor kit, the researchers gave the female partner two doses of tenofovir, one on the day of ovulation and one the day after. On the second day of tenofovir treatment, the couples had unprotected intercourse in the hopes of conceiving.

There were no cases of horizontal HIV transmission among the women in this study, and more than 50% of the couples became pregnant after only three acts of unprotected intercourse. However, because the risk of infection from a single act of unprotected vaginal intercourse is already comparatively low when the HIV positive partner is on completely suppressive HAART, this small study cannot prove that PrEP offers additional protection.

More recent results have been disappointing. The FEM-PrEP trial, evaluating daily oral tenofovir for HIV prevention in women in Kenya, South Africa, and Tanzania, was halted early when an interim data review showed an equal number of new HIV infections in participants taking tenofovir and participants receiving placebo pills. "At this time, it cannot be determined whether or not Truvada works to prevent HIV infection in women," the researchers reported in a press release.

Follow-up and further data analysis may clarify whether low adherence played a part in the FEM-PrEP results. In the meantime, several other large research trials of PrEP are underway around the world, including a study of 4,700 serodiscordant couples in Kenya and Uganda that should finish in 2013

The FDA has not yet approved antiretrovirals specifically for PrEP, but some doctors may be willing to prescribe these drugs for off-label use by couples wishing to conceive.

"I do talk to my patients about PrEP," Anderson said. "I have had a couple of women who have wanted to do this, and I've given them Truvada. Anecdotally, they did well, but nobody has the data yet."

Preventing Transmission from Mother to Child

Once a couple conceives, whether through assisted reproduction or timed intercourse, the focus of treatment naturally shifts from protecting the negative partner to protecting the fetus.

If a woman was negative before conceiving with an HIV positive partner, this means regular prenatal care plus HIV testing during the first and third trimesters of pregnancy. If a woman was positive before conception, or becomes HIV infected during her pregnancy, there are several effective steps that can be taken to prevent mother-to-child infection, also known as vertical transmission.

"The top question that pretty much all women ask," Cohan said, "is, 'Am I going to pass HIV on to my baby?'"

With the right treatment during pregnancy and delivery, the answer to that question is almost always no. If an HIV positive woman takes her medications religiously and maintains a suppressed viral load, particularly during the third trimester and around the time of delivery, the latest data suggest the risk of passing HIV to her baby is less than 1%.

Several large, multicenter trials in Europe have looked at the rates of vertical transmission among women on fully suppressive therapy. One of the largest studies, called the French Perinatal Cohort (EPF), looked at 5,271 mothers on antiretroviral therapy who delivered between 1997 and 2004. The overall mother-to-child transmission rate was 1.3%, with the rate as low as 0.37% among women who delivered at full term (after at least 37 weeks of pregnancy) and had a viral load below 50 copies/mL at delivery.

"To put that risk in perspective," Cohan said, "the risk of birth defects or congenital anomalies in the U.S. is about 3%. So it's about ten times less frequent than just the general population having some kind of problem with their pregnancy."

In the EPF cohort, the risk of vertical transmission increased with higher viral load, shorter duration of antiretroviral therapy, and premature delivery. Other factors associated with transmission during pregnancy include cigarette smoking, recreational drug use, genital tract infections, and having unprotected sex with multiple partners during pregnancy.

Antiretroviral Therapy during Pregnancy

Before antiretroviral therapy became available, the risk of an HIV positive mother passing HIV to her baby during pregnancy was about 25%, with additional risk of transmission during childbirth or breastfeeding.

"The antiretrovirals are just amazingly potent and effective," Cohan said. "Our role in preventing transmission ends up being us helping the woman be adherent to her regimen."

The latest clinical guidelines from the U.S. Department of Health and Human Services (DHHS) recommend combination antiretroviral therapy for all pregnant women with HIV, regardless of viral load or CD4 count. For women who did not need antiretroviral therapy for their own health before pregnancy, this may mean starting treatment for the first time. Ideally, antiretroviral therapy should begin no later than the end of the first trimester of pregnancy.

In general, the choice of therapy for pregnant women is based on the same principles that guide the choice of therapy for non-pregnant individuals, with the additional consideration of avoiding drugs that can cause birth defects or growth problems for the baby. The DHHS guidelines recommend triple-drug antiretroviral therapy with two NRTIs and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).

In most cases, the recommended NRTI regimen is AZT (Retrovir) plus 3TC (Epivir), as this drug combination has been well studied during pregnancy and is highly effective at preventing perinatal transmission. Exceptions to this recommendation include women with known AZT toxicity and women who were already on a well-tolerated, maximally suppressive regimen before pregnancy.

There are limited long-term data on the risks to the infant of being exposed to antiretroviral therapy *in utero,* but some drugs are known to be safer than others. The first group of infants born to mothers who took AZT during pregnancy have been studied for six years, and so far no negative effects have been noted. In contrast, the DHHS recommends that the NNRTI efavirenz (Sustiva) be avoided during pregnancy, especially during the first trimester, because data from animal studies and case reports show the drug may cause birth defects.

HIV and Childbirth

Because infants are exposed to high concentrations of maternal blood and vaginal secretions as they travel through the birth canal, labor and delivery is a high-risk period for transmission of HIV. In fact, studies have shown that most cases of vertical transmission happen close to labor and delivery.

To prevent transmission during childbirth, intravenous antiretroviral therapy during labor and delivery is recommended for all HIV positive women, regardless of treatment during pregnancy. Even if a woman has been on maximally suppressive therapy and has an undetectable viral load, intravenous therapy is thought to offer additional protection for the infant by acting as pre-exposure prophylaxis. In most cases, the recommended regimen is intravenous AZT plus continuation of any oral antiretrovirals the woman was taking before labor.

If a woman did not take antiretroviral therapy during pregnancy, or took therapy but was not able to get her viral load below 1,000 copies/mL, doctors may recommend an elective cesarean section before the onset of labor, usually at 38 weeks. For women who took combination antiretroviral therapy and have a viral load below 1,000 copies/mL at the time of delivery, it is unknown whether cesarean delivery offers any additional protection.

Caring for Infants Born to HIV Positive Moms

The DHHS recommends that all infants born to an HIV positive mother receive a short course of antiretroviral therapy as further protection against mother-to-child transmission. In most cases, this means a six-week course of AZT alone, although some doctors recommend combining AZT with another drug in high-risk situations, such as when the mother's HIV was not well controlled at the time of delivery (or when the mother's virus has AZT resistance mutations). In addition, infants are given drugs to prevent pneumonia caused by the opportunistic bacteria *Pneumocystis jirovecii* starting at four to six weeks of age.

Because newborns carry a high dose of their mother's antibodies at birth, all babies born to an HIV positive mother will test positive on a regular HIV antibody test. To diagnose HIV in an infant, doctors instead use a test called polymerase chain reaction (PCR), which checks the baby's blood for genetic material from the virus. PCR testing is recommended at 14 to 21 days, 1 to 2 months, and 4 to 6 months of age (or even more frequently). Two negative tests can essentially rule out HIV infection, although some doctors confirm negative status using an antibody test at 18 months, by which point maternal antibodies to HIV should no longer be present in the child's blood.

In the U.S. and other countries where clean water and infant formula are readily available, women with HIV are advised not to breastfeed their infants. Breast milk may be able to transmit HIV even when a woman's viral load is undetectable, as breast milk contains immune cells that may carry the virus. For families that cannot afford infant formula, the federally funded Women, Infants and Children Program (WIC) can provide it for free. Donated breast milk is also available through some hospitals and "milk banks."

Keeping Mom Healthy: Pregnancy and HIV Progression

Preventing mother-to-child transmission is only one of the major goals of perinatal HIV care; the other main objective is to protect mom's health during and after pregnancy.

In the early days of the AIDS epidemic, women with HIV were advised not to get pregnant, not only because

of the risk of vertical transmission, but also because pregnancy was thought to negatively impact HIV disease. During pregnancy, the body automatically scales back its immune response to keep the mother's immune system from attacking the developing fetus. This reduction in immune response includes decreased activity of T-cells, which normally protect against viruses and opportunistic infections and are targeted by HIV.

Early research looking at the impact of pregnancy on untreated HIV suggested that pregnancy either hastened disease progression or had no effect. In observational studies done in developing countries, pregnancy appeared to predict immune system decline, while several studies in Europe and the United States found no effect.

However, a more recent study of HIV positive women on HAART found that pregnancy was actually associated with a decreased risk of disease progression, defined as the occurrence of an AIDS-defining illness or death. Published in the *Journal of Infectious Diseases* in 2007, the study followed 759 HIV positive women who received care at a particular HIV clinic between 1997 and 2004. After adjusting for age, baseline CD4 count, and viral load, women who became pregnant were significantly less likely to progress to AIDS or death. The apparent protective effect of pregnancy was dose-dependent, as women who became pregnant more than once during the study were even less likely to progress.

Of course, an observational study like this one cannot prove that pregnancy caused the difference in disease progression, because differences in immune status before getting pregnant could also explain the results. Indeed, women who got pregnant during the study tended to be younger and healthier than those who didn't, although the researchers took those differences into account in their analysis.

"Given the beneficial effect of pregnancy on disease progression despite several methods to control for confounding factors," the authors wrote, "one must entertain possible physiologic explanations."

One possibility is that the immunologic changes that occur during pregnancy also slow viral replication. Pregnancy causes a shift in the type of signaling molecules, called cytokines, that are released by T-cells. While some T-cells become less active, others become more active, and this temporary activation may be responsible for the observed protective effect of pregnancy.

In contrast to the positive impact of pregnancy, some researchers have noticed a "rebound effect," where a woman with well-controlled HIV suddenly gets sick during the postpartum period. This effect may be due to postpartum depression, the high levels of stress women often experience while taking care of a newborn, and/or decreased adherence to medication. Without the immediate risk of mother-to-child transmission as a motivator, women may be more likely to stop following their antiretroviral drug regimens.

"One of the things we really struggle with at our clinic is helping women not just take antiretrovirals during pregnancy, but also continuing them postpartum," Cohan said. "While we have had the *rare* case of perinatal HIV transmission since the HAART era began, we have had several women who have died in the first few years postpartum because they stopped taking their meds."

Because the health of a child is influenced by the health of his or her parents, good HIV care after birth is a critical component of obstetric care. Depending on individual health status, women may be advised to continue taking their pregnancy antiretroviral regimen, to switch to a different combination of drugs, or to stop taking antiretrovirals altogether.

HIV and Parenting: "A Sign of Success"

Perspectives on HIV and childbearing have changed significantly since the early days of the epidemic.

In 1994, the Ethics Committee for the American Society of Reproductive Medicine (ASRM) published guidelines regarding patients with HIV who requested reproductive assistance. In that statement, the committee expressed concern about HIV transmission to partners and children, as well as hesitation regarding the ethics of offering reproductive assistance to people who might not live long enough to see their children grow up. Physicians were urged to "counsel couples about the consequences of using potentially infected sperm, and to discuss the options of donor sperm, adoption, or not having children."

In 2010, the ASRM committee published a revised statement with a very different message: "To the extent it is economically and technically feasible, [assisted reproductive technology] providers should widen access to HIV-infected patients who desire to procreate in a manner that minimizes the risk of viral transmission to their partners and offspring."

Improving access to reproductive care for HIV positive people may take some time and effort on the part of the medical community. Until more insurance companies cover fertility services for people with HIV, many serodiscordant couples will not be able to access the lowest-risk options like sperm washing. And some providers may still feel uncomfortable with harm reduction techniques like timed intercourse and pre-exposure prophylaxis.

But now that there's clear data that people with HIV can have healthy, HIV negative children without infecting their partners or jeopardizing their own health, researchers say there's no excuse for avoiding the subject.

"If people want to have children, they know how to do it—unprotected

sex will work," Finocchario-Kessler said. "It's really a decision for the medical community, to be involved and have the chance to reduce transmission, or to totally step back and close our eyes to it. That alternative actually puts people at greater risk of transmission, which was our fear in the first place."

Hopefully, the next decade will bring improved access to fertility services as well as new, lower-cost options like pre-exposure prophylaxis. At Johns Hopkins, Anderson said she's already seen a significant shift in the way that her colleagues think about HIV and childbearing.

"As HIV has evolved into really a chronic disease, I think people are changing their opinions slowly but surely," she said. "To me, it's a sign of success that people with HIV are really considering this. It means that they're feeling better, they're living longer, and they're healthier. They know that we have been successful for the most part in preventing perinatal transmission, and they're feeling more hopeful about the future."

Hadley Leggett, MD, is a freelance medical writer in the San Francisco Bay Area.

Selected Sources

Barreiro, P. and others. Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes* 43(3):324–26. November 1, 2006.

Bujan, L. and others. Decreased semen volume and spermatozoa motility in HIV-1-infected patients under antiretroviral treatment. *Journal of Andrology* 28(3):444–52. May/June 2007.

Bujan, L. and others. Lack of clinical and scientific evidence to justify the systematic use of ICSI in HIV-serodiscordant couples wishing to conceive where the male partner is infected. *Fertility and Sterility* 91(3):e1–2. March 2009.

Bujan, L. and others. Safety and efficacy of sperm washing in HIV-1 serodiscordant couples where the male is infected: results from the European CREAThE network. *AIDS* 21(14):1909–14. September 12, 2007.

Blumenthal, S. *Women, HIV, and Stigma: Results from a National Survey.* amfAR Briefings. March 31, 2008. www.hivlawandpolicy.org/resources/download/194.

Cejtin, H. Gynecologic issues in the HIV-infected woman. *Infectious Disease Clinics of North America* 22(4):709–39. December 2008.

Cohan, D. The fruits of our success: conception and HIV discordant couples. 48th Annual Meeting of the Infectious Diseases Society of America. Vancouver. October 21–24, 2010. Symposium 140, Presentation 1393.

Donnell, D. and others. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 375:2092–98. June 12, 2010.

Ethics Committee of the American Society for Reproductive Medicine. Human immunodeficiency virus and infertility treatment. *Fertility and Sterility* 94(1):11–15. March 16, 2010.

Finocchario-Kessler, S. and others. Do HIV-infected women want to discuss reproductive plans with providers, and are those conversations occurring? *AIDS Patient Care and STDs* 24(5):317–25. May 2010.

Finocharrio-Kessler, S. and others. Understanding high fertility desires and intentions among a sample of urban women living with HIV in the United States. *AIDS and Behavior* 14(5):1106–14. October 2010.

Goldman, B. IAS 2007 study summaries: an interview with Pietro Vernazza, MD. July 25, 2007. www.thebodypro.com/content/confs/ias2007/art42636.html?mb84o.

Grant, R. and others. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine* 363(27):2587–99. December 30, 2010.

Marcelin, A. and others. Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1 RNA in blood plasma. *AIDS* 22(13):1677–79. August 2008.

Massad L. and others. Pregnancy rates and predictors of conception, miscarriage and abortion in U.S. women with HIV. *AIDS* 18(2):281–86. January 23, 2004.

Matthews, L. and Mukherjee J. Strategies for harm reduction among HIV-affected couples who want to conceive. *AIDS and Behavior* 13(Supplement 1):5–11. June 2009.

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. May 24, 2010: 1–117. http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.

Tai, J. and others. Pregnancy and HIV disease progression during the era of highly active antiretroviral therapy. *Journal of Infectious Diseases* 196(7):1044–52. October 7, 2007.

Van Leeuwen, E. and others. Assisted reproductive technologies to establish pregnancies in couples with an HIV-1-infected man. *Netherlands Journal of Medicine* 67(8):322–27. September 2009.

Van Leeuwen, E. and others. Effects of antiretroviral therapy on semen quality. *AIDS* 22(5):637–42. March 12, 2008.

Vernazza, P. HAART improves quality of life: should we care about the quality of spermatozoa? *AIDS* 22(5):647–48. March 12, 2008.

Warszawski J. and others. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS* 22(2):289–99. January 11, 2008.

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