Mother-to-Child HIV Transmission: National and International Progress and Challenges

According to estimates by the World Health Organization (WHO), approximately 700,000 children were infected with HIV in 2003, with greater than 95% of these infections occurring in resource-poor nations. Conversely, new HIV infections in children are becoming increasingly rare in many parts of world, most notably wealthy nations.

The vast majority of children with HIV acquire the infection through mother-to-child transmission (MTCT) of the virus, which can occur in utero, during labor and delivery, and while breastfeeding (estimates of the timing of MTCT are illustrated in Figure 1). In the absence of any intervention, the risk of MTCT is 15% to 30% in non-breastfeeding populations. In the setting of breastfeeding, the risk increases by 5% to 20%, to a total of 20% to 45% (De Cock, 2000).

The risk of MTCT can be reduced to below 2% by employing interventions that include antiretroviral therapy given to HIV-infected women during pregnancy and labor, as well as to exposed infants during the first weeks of life; the avoidance of breastfeeding; and delivery by elective Caesarean section. With all of these approaches, there are numerous questions and considerations. In turn, PRN invited Dr. Elaine Abrams—a Columbia University pediatrician involved in both national and international programs focused on curtailing MTCT of HIV—to put these questions and considerations into context for the PRN membership and readers of The PRN Notebook.

Risk Factors for MTCT

Many studies conducted over the past decade have demonstrated that women with advanced HIV disease are at the highest risk of transmitting HIV, both during pregnancy and while breastfeeding. High HIV-RNA levels in blood, low CD4+ cell counts, and an AIDS diagnosis are

FIGURE 1. Estimates of Timing of Mother-to-Child HIV Transmission in the Absence of Antiretroviral Treatment

<table>
<thead>
<tr>
<th>Time of Exposure</th>
<th>Number Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;14 week</td>
<td>1</td>
</tr>
<tr>
<td>14–34 week</td>
<td>4</td>
</tr>
<tr>
<td>36 week through Labor</td>
<td>12</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>8</td>
</tr>
<tr>
<td>76 Uninfected</td>
<td>25</td>
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<tr>
<td>36 week through Labor</td>
<td>10</td>
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<tr>
<td>Intrapartum</td>
<td>6</td>
</tr>
<tr>
<td>Breast Feeding</td>
<td>16</td>
</tr>
<tr>
<td>64 Uninfected</td>
<td>36</td>
</tr>
</tbody>
</table>

all markers of MTCT risk. HIV-RNA levels in genital fluids, most notably at the time of labor and delivery, are also associated with an increase in transmission risk. “These are the primary maternal factors associated with an increased risk of transmission,” Dr. Abrams explained. “Additional maternal factors to consider include genetic influences, underlying sexually transmitted diseases, and behavioral factors, such as smoking, the health of sexual partners, and intravenous drug use.”

As for obstetrical factors, Dr. Abrams explained that prolonged rupture of membranes, defined as longer than four hours, has been associated with an increased risk of transmission. Caesarean section has been shown to be protective if electively done prior to the onset of labor. “C-sections remain protective in the context of antiretroviral therapy given for perinatal prevention, particularly zidovudine monotherapy. This procedure is recommended in the United States for HIV-positive pregnant women with viral loads greater than 1,000 copies/mL. However, C-sections may not have an added benefit when viremia is very low or undetectable as a result of using combination antiretroviral therapy.”

Infants born prematurely are also at higher risk for infection. “It was initially believed that HIV infection of the fetus led to premature delivery,” recalled Dr. Abrams, “but it appears the premature babies are at greater risk for infection during labor and delivery, compared to babies who reach full term.”

Guidelines in the United States and most European countries have strongly warned against breastfeeding among new HIV-positive mothers. However, in many parts of the world, where the benefits of breastfeeding are weighed heavily against the risks, it remains a major issue. “It has been estimated that there are about ten cases of infection for every 100 women who breastfeed for a year and that the risk of transmission is pretty constant throughout the duration of breastfeeding,” Dr. Abrams explained. “And much like the transmission of HIV in utero or around the time of labor and delivery, maternal factors—such as high viral load and low CD4+ cell counts—can increase the risk of transmission while breastfeeding.”

The U.S. Standard of Care: PACTG 076 and Beyond

The MTCT story in the United States—and most resource-rich countries—is one of great success. According to the United States Centers for Disease Control and Prevention (CDC), there were fewer than 100 cases of AIDS reported in children in the United States in 2000, compared with over 400 cases reported annually at the peak of the epidemic (1991 through 1994). “This really signifies what have been enormous successes in MTCT prevention in settings where resources are available,” Dr. Abrams added. In New York, where cases of HIV infection of newborns have been easier to document in response to mandatory newborn testing requirements, Dr. Abrams said that only 24 cases of new HIV infections among children were reported to the Department of Health in 2001. “These aren’t new AIDS cases, this is the number of children with new HIV infections,” she stressed. “In 2003, I think there were fewer than 20 cases throughout the state. Pretty remarkable, especially when you consider the prevalence of HIV infection in New York State.”

One of the greatest breakthroughs in the history of MTCT prevention research were the results of PACTG 076, a randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of zidovudine in reducing MTCT of HIV (Connor, 1994). HIV-infected pregnant women 14 to 34 weeks’ gestation with CD4+ counts above 200 cells/mm³ who had not received antiretroviral therapy during the current pregnancy were enrolled. The zidovudine regimen included antepartum zidovudine (100 mg orally five times daily), intrapartum zidovudine (2 mg/kg given intravenously over one hour, then 1 mg per kilogram per hour until delivery), and zidovudine for the newborn (2 mg per kilogram orally every six hours for six weeks). Infants with at least one positive HIV culture of peripheral blood mononuclear cells (PBMCs) were classified as HIV-infected.

From April 1991 through December 1993, 477 pregnant women were enrolled. During the study period, 409 gave birth to 415 infants. HIV-infection status was known for 363 births (180 in the zidovudine group and 183 in the placebo group). Thirteen infants in the zidovudine group and 40 in the placebo group were HIV-infected. The proportions infected at 18 months, as estimated by the Kaplan-Meier method, were 8.3% in the zidovudine group and 25.5% in the placebo group. This corresponded to a 67.5% relative reduction in the risk of HIV transmission.

In August 1994, a U.S. Public Health Service (USPHS) task force issued recommendations for the use of zidovudine for the reduction of perinatal HIV transmission. And in July 1995, the USPHS issued recommendations for universal prenatal HIV counseling and testing—with consent— for all pregnant women in the United States. “Prior to the results of PACTG 076, there was a lot of debate among many in the field regarding the value of actually diagnosing HIV during pregnancy,” Dr. Abrams commented. “How would these results help the mother? And what did these results provide to the child? This study really changed the equation and showed us that, if we were able to diagnosis HIV during pregnancy, there was potentially some great benefit to an HIV-positive woman’s child that could be gained. And over the last decade, we’ve seen a real move towards mandatory counseling and voluntary testing. More recently, there’s been increasing movement toward using rapid testing in labor for women who come to delivery not knowing their status.”

Data are also available regarding the use of combination antiretroviral therapy as a component of MTCT prevention. In an open-label, nonrandomized study of 445 pregnant women with HIV infection in France, lamivudine was added at 32 weeks’ gestation to standard zidovudine prophylaxis (Mandelbrot, 2001). Lamivudine was also given to the infant, in addition to zidovudine. The transmission rate in the zidovudine/lamivudine group was 1.6%. In comparison, the transmission rate in a historical control group of women receiving only zidovudine was 6.8%.
Prior to the use of combination antiretroviral therapy, studies were performed to determine the value of cesarean delivery in decreasing the risk of perinatal HIV transmission, either with or without concurrent use of zidovudine. In this meta-analysis, using data from 15 prospective cohort studies involving more than 7,800 mother-infant pairs, the rate of perinatal transmission among women undergoing elective C-section delivery was significantly lower than that among women undergoing nonelective C-sections (C-sections performed after the onset of labor or rupture of membranes) or vaginal delivery. Among the 559 women undergoing elective cesarean delivery who did not receive zidovudine, the perinatal HIV transmission rate was 10.4%. Among the 5,385 women undergoing other modes of delivery (The European Mode of Delivery Collaboration, 1999). Combining zidovudine therapy with elective C-sections reduced perinatal transmission to approximately 1%, compared to 4% among those undergoing other methods of delivery (acog Committee Opinion Scheduled Cesarean Delivery and the Prevention of Vertical Transmission of HIV Infection, 2001).

**FIGURE 3. Elective Cesarean Delivery and Risk of MTCT**

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The Global Challenge: The Quest for Effective and Resourceful Options

“IN SITTING BACK AND THINKING ABOUT THE GREAT SUCCESSES WE’VE had in this country, it was also apparent to us that the mtct situation in resource-rich countries is only the tip of the iceberg,” Dr. Abrams said. “We recognized the need to focus on resource-poor countries. However, it wasn’t likely that the intensive care and therapy we provide to pregnant women in this country could easily be provided to HIV-infected pregnant women in these other parts of the world. In turn, alternative strategies have been very much sought after.”

Many developing countries have not been in a position to implement the pACTG 076 regimen because of its complexity and cost. In turn, one of the first efforts to capitalize on the effectiveness of zidovudine in a resourceful manner was to investigate the safety and efficacy of short-course zidovudine administered during late pregnancy and labor (see Figure 4).

In a randomized, placebo-controlled trial, HIV-infected pregnant women at two Bangkok hospitals were randomly assigned to receive either placebo or zidovudine (300 mg bid) from 36 weeks’ gestation and every three hours from the onset of labor until delivery (Shaffer, 1999). Mothers were given infant formula and asked not to breastfeed. Three-hundred ninety-seven women were randomized and 393 gave birth to 395 infants. The median duration of antenatal treatment was 25 days, and the median number of doses during labor was three. Of 392 babies with at least one PCR test available, 55 tested positive: 18 in the zidovudine group and 37 in the placebo group. The estimated transmission risks were 9.4% in the zidovudine group and 18.9% in the placebo group. Women in the zidovudine group had a mean decrease in viral load of 0.56 log_{10} copies/mL and approximately 80% of the treatment effect was explained by lowered maternal viral concentrations at delivery. There was no statistically significant difference in the adverse event rates between the two groups.

Short-course zidovudine was also evaluated in a safety and efficacy study involving HIV-positive women in Abidjan, Côte d’Ivoire, all of whom would be breastfeeding after delivery (Wiktor, 1999). From April 1996 to February 1998, all consenting HIV-positive pregnant women attending a public antenatal clinic were enrolled at 36 weeks’ gestation and randomly assigned to receive either placebo or zidovudine, 300 mg bid until the onset of labor, followed by 300 mg every three hours until delivery. The study was closed in February 1998, when favorable results from the Bangkok study became available (reported above). Two-hundred eighty women were enrolled (140 in each group). The median duration of the
prenatal drug regimen was 27 days and the median duration of labor was 7.5 hours. Among babies with known infection status at age three months, 30/115 (26.1%) babies in the placebo group and 19/115 (16.5%) in the zidovudine group were documented to have HIV infection. The estimated risk of transmission in the placebo and zidovudine groups were 21.7% and 12.2% at four weeks and 24.9% and 15.7% at three months. The long-long regimen, 4.7% for the long-short regimen, and 8.6% for the short-long regimen. The rate of in utero transmission—documented using PCR testing at birth—was significantly higher in the two groups employing shorter maternal treatment (5.1%) than in the two groups employing longer maternal treatment (1.6%).

In conclusion, short-short zidovudine quickly proved to be inferior to the long-long regimen and led to a higher rate of perinatal HIV transmission. Conversely, the long-short, short-long, and long-long regimens had equivalent efficacy. However, the risk of in utero transmission associated with the short-long regimen was of major concern to the investigators. “The extent of suppression of in utero transmission depends on the duration of antiretroviral treatment during the later part of pregnancy,” the authors summarized in their New England Journal of Medicine report. “We suggest that to improve prevention programs that currently use a short course of zidovudine, the best option would be to implement the long-short regimen. The seven additional weeks of maternal treatment will prevent an important fraction of in utero transmissions and at a minimal extra cost, given that most women will have already received counseling and undergone HIV testing.”

FIGURE 4. Short-Course Zidovudine for Prevention of MTCT

Because many developing countries lack the necessary resources to implement mother-to-child transmission programs employing the zidovudine dosing schedule used in PACTG 076, there are ongoing efforts to capitalize on the effectiveness of zidovudine in a resourceful manner, including short-course zidovudine administered during late pregnancy and labor. The results of two clinical trials are reported here. The bars labeled Thailand illustrate the results of a placebo-controlled trial in which HIV-infected pregnant women at two Bangkok hospitals were randomly assigned to receive either placebo or zidovudine (300 mg bid) from 36 weeks’ gestation and every three hours from the onset of labor until delivery (women were told not to breastfeed after delivery). The estimated transmission risks were 9.4% in the zidovudine group and 18.9% in the placebo group, representing a 50% reduction in the perinatal HIV transmission rate. The bars labeled Côte d’Ivoire illustrate the results of a clinical trial in which HIV-positive pregnant women attending a public antenatal clinic in Abidjan were enrolled at 36 weeks’ gestation and randomly assigned to receive either placebo or zidovudine, 300 mg bid until the onset of labor, followed by 300 mg every three hours until delivery. The estimated risk of transmission in the placebo group was 26.1%, compared to an estimated risk of transmission in the short-course zidovudine group of 16.5%.

Source: Shaffer, 1999; Wiktor, 1999

Nevirapine to the Fore

Throughout its development for the treatment of HIV infection, nevirapine (Viramune)—Boehringer Ingelheim’s non-nucleoside reverse transcriptase inhibitor (NNRTI)—was being eyed carefully by experts in the field of perinatal HIV care. Compared with zidovudine, nevirapine is considerably more potent in vitro and capable of suppressing HIV replication in vivo much more effectively and quickly. It is rapidly absorbed when taken orally, entering the bloodstream and halting viral replication almost immediately. It has a considerably long half-life: 61 to 66 hours in pregnant women and 45 to 54 hours in infants. Nevirapine has been documented to cross the placental barrier in concentrations sufficient to reduce HIV replication. In turn, a hypothesis was born: that a short course of nevirapine therapy—a single oral dose administered to an HIV-infected pregnant woman at the onset of labor, along with a single oral dose given to the newborn—would be a simpler and more cost-effective approach to reduce perinatal HIV transmission, particularly in the absence of perinatal care, compared to short- and long-course zidovudine treatment.

To evaluate this approach, investigators at Makerere University in Kampala, Uganda—in collaboration with researchers at Johns Hopkins University School of Medicine—conducted HIVNET 012, a clinical trial comparing the safety and efficacy of short-course nevirapine or zi-
doxovudine during labor and the infant’s first week of life (Guay, 1999). From November 1997 to April 1999, the study team enrolled 626 HIV-infected pregnant women at Mulago Hospital in Kampala. The women were randomly assigned to receive either nevirapine 200 mg orally at the onset of labor (and 2 mg/kg to the infants within 72 hours of birth) or zidovudine 600 mg orally at the onset of labor and 300 mg every three hours until delivery (and 4 mg/kg orally twice daily to the infants for seven days after birth). Nearly all infants (98.8%) were breastfed, and 93.6% were still breastfeeding at age 16 weeks.

The estimated risks of perinatal HIV transmission in the zidovudine and nevirapine groups were, respectively, 10.4% and 8.2% at birth, 21.3% and 11.9% by eight weeks of age, and 25.1% and 13.1% by 16 weeks of age—a reduction in perinatal transmission, favoring short-course nevirapine over short-course zidovudine, by 47%. Additional follow-up data indicated that the reduction in transmission was maintained: after 18 months, the estimated risk was 25.5% in the zidovudine group and 15.7% in the nevirapine group.

“HIVNET 012 was an extremely important study,” commented Dr. Abrams. “It helped galvanize efforts to set up simple and cheap perinatal prevention programs in some of the poorest parts of the world. Since this study was published, the Elizabeth Glaser Pediatric AIDS Foundation, working with governments, healthcare providers, ministries, provinces, and individuals—a whole assortment of groups and individuals—has actively set up programs using single-dose nevirapine in more than 17 countries. They estimate that more than a million women have received single-dose nevirapine since these programs went into effect. We’ve also seen many governments develop national plans to roll out single-dose nevirapine for perinatal prevention.”

While the results of HIVNET 012 solidified the importance of nevirapine as an agent to help prevent perinatal HIV transmission, the infection rates were still higher than those seen in PACTG 076 and significantly higher than the transmission rates seen today in the United States in association with the use of combination antiretroviral therapy. In turn, the PACTG group—responsible for the study evaluating varying courses of zidovudine in HIV-infected pregnant women and infants discussed above—conducted a second study (dubbed PACTG-2) to examine whether adding a single dose of nevirapine to a short-course zidovudine could help further reduce MTCT HIV transmission rates (Lallement, 2004).

Between January 2001 and February 2004, the study randomized 1,844 HIV-positive women to one of three treatment groups: zidovudine alone, started at 28 weeks’ gestation and continued through labor, delivery, and to the infant for six weeks after birth (placebo-placebo group); zidovudine plus single-dose nevirapine (200 mg) given to the woman at the onset of labor but not the infant (nvp-placebo group); or zidovudine plus single-dose nevirapine given to the woman at the onset of labor and to the infant after birth (NVP-NVP group). All women formula-fed their infants after delivery. An interim analysis conducted in May 2002, involving the first 629 infants born in the study, demonstrated a significant reduction in vertical transmission in all NVP-treated mothers. In turn, the placebo-placebo group was dropped.

In the intent-to-treat analysis conducted in May 2002, a significant reduction in vertical transmission was seen in the NVP-NVP group compared with the placebo-placebo group (1.1% vs. 6.3% transmission rate respectively). In the NVP-placebo group, the rate was 2.1%. As for the final intent-to-treat analysis, the transmission rate among those in the NVP-NVP group was 2.0%, compared to a transmission rate of 2.8% in the NVP-placebo group. Results were similar in the as-treated analysis.

“What’s so important about these transmission rates in this non-breastfeeding population is that they parallel what we’re seeing in the U.S. and Europe, using much more complicated regimens with much more frequent and greater toxicities,” Dr. Abrams said. “This combined regimen does offer a more simplified and less toxic regimen that we can move forward with in resource-poor areas.”

### Nevirapine Resistance

Unfortunately, the news is not entirely rosy when it comes to nevirapine for the prevention of perinatal HIV transmission. Data from various studies have demonstrated relatively high rates of NNRTI resistance developing in women receiving single-dose nevirapine, which has raised a number of questions about the long-term clinical and public health consequences of nevirapine use in this setting (see Table 1).

At least two studies presented at the XV International AIDS Conference, held this past summer in Bangkok, described the incidence and persistence of NNRTI-resistant HIV following single-dose nevirapine therapy. The first study was a prospective evaluation of 623 women-infant pairs receiving single-dose nevirapine in South Africa (Morris, 2004). After six weeks, blood samples were analyzed for evidence of nevirapine resistance.

### TABLE 1. Rates of Nevirapine Resistance in Women after MTCT Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Resistance (%)</th>
<th>Time of Sample</th>
<th>Mutation Frequency</th>
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</thead>
<tbody>
<tr>
<td>HIVNET 006</td>
<td>Single-dose nevirapine</td>
<td>20%</td>
<td>6 weeks postpartum</td>
<td>K103N (3/3)</td>
</tr>
<tr>
<td>HIVNET 012</td>
<td>Single-dose nevirapine</td>
<td>25%</td>
<td>6 to 8 weeks postpartum</td>
<td>K103N (19/21)</td>
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<td></td>
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<td></td>
<td></td>
<td>Y181C (5/21)</td>
</tr>
<tr>
<td>PACTG 316</td>
<td>Antiretroviral therapy* plus</td>
<td>15%</td>
<td>6 weeks postpartum</td>
<td>K103N (9/14)</td>
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<tr>
<td></td>
<td>single-dose nevirapine</td>
<td></td>
<td></td>
<td>Y181C (3/14)</td>
</tr>
<tr>
<td>HIVNET 023</td>
<td>Single-dose nevirapine</td>
<td>28%</td>
<td>8 weeks postpartum</td>
<td>K103N (8/10)</td>
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<tr>
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<td></td>
<td>Y181C (2/10)</td>
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<tr>
<td>SAINT</td>
<td>Two doses of nevirapine</td>
<td>67%</td>
<td>4 to 6 weeks postpartum</td>
<td>K103N (62%)</td>
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<td></td>
<td></td>
<td></td>
<td>Y181C (45%)</td>
</tr>
<tr>
<td>PHPT-2</td>
<td>Zidovudine plus single-dose</td>
<td>20%</td>
<td>12 days postpartum</td>
<td>K103N (21%)</td>
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<td></td>
<td>nevirapine</td>
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<td>Y181C (2%)</td>
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</table>

\* Women in PACTG 316 study also received zidovudine, zidovudine/lamivudine, or other drug combinations with and without protease inhibitors.
follow-up data from discussed above, mutations, and the detection of combination antiretroviral therapy—as compared with one multivariate analysis, a viral load at or above the median at the beginning of therapy, with several factors: a viral load at or above the median at the beginning of therapy, a CD4+ count below the median of 174 cells/mm³, and has been reported to be 5.5 to 7.3 times more common in women than men, and has been reported in pregnant women (Public Health Service Task Force, 2004). Other studies have found that hepatic adverse events with systemic symptoms—predominantly rash—were 3.2-fold more common in women than men.

The degree of risk for hepatic toxicity varies with CD4+ cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy discussed in the Recommendations, women with CD4+ counts greater than 250 cells/mm³ were 9.8 times more likely than women with lower CD4+ cell counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity. Higher CD4+ cell counts have also been associated with increased risk of severe nevirapine-associated skin rash.

In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality is quite rare (~0.04% to 0.4%). Severe or life-threatening rash occurs in approximately 2% of patients receiving nevirapine.

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen, it is unknown if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs. Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity, it’s very important for clinicians caring for women re-
ceiving nevirapine during pregnancy to be aware of this potential complication and conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases, particularly during the first 18 weeks of therapy. Nevirapine should also be used with caution in pregnant antiretroviral-naive women who are being started on combination antiretroviral therapy for the purpose of preventing perinatal HIV transmission, but who have CD4+ cell counts that would not otherwise indicate that they require therapy for their own health.

Conclusion

IN CONCLUDING HER TALK, DR. ABRAMS STRESSED THAT THERE HAVE BEEN great advances in the medical establishment’s understanding of the risks, mechanisms, and prevention of perinatal transmission. With this knowledge comes priorities. For Dr. Abrams and her colleagues, the first priority is simple enough: to ensure that adequate treatment is provided to all sick women during pregnancy. “Women who are eligible for combination antiretroviral therapy, under any circumstances, absolutely must have access to therapy during pregnancy, at the time of labor and delivery, and in the early postpartum period.” This, she argues, will have a number of important effects. First, the risk of nevirapine resistance will be much lower, as these women will remain on combination therapy. Second, as is illustrated in this article, women with more advanced HIV disease are at the highest risk of MTCT HIV transmission. By treating them, it has been widely hypothesized that marked reductions in the rate of MTCT HIV transmission will follow. “This is a big leap and it’s going to take a lot of work,” Dr. Abrams added. “But it should be a major priority as the global rollout begins.”

The second priority should be to maintain MTCT prevention programs using single-dose nevirapine. “These are often the first programs established in settings that really have never provided any form of HIV care and have virtually nothing to offer women and their families,” Dr. Abrams said. “We have to look at these programs as a starting point... as a way to train people... as a way to begin offering communities some focus on care and treatment, while also being able to decrease the rate of perinatal HIV transmission. With this groundwork, programs can be built up to a point where they can offer more comprehensive services to women who are eligible for more complex regimens that are more efficacious than single-dose nevirapine.”

References


