S1 For whom the bell tolls
Howard Minkoff

S3 Reducing the risk of mother-to-child human immunodeficiency virus transmission: past successes, current progress and challenges, and future directions
Mary Glenn Fowler; Margaret A. Lampe; Denise J. Jamieson; Athena P. Kourtis; Martha F. Rogers
There have been major advances with the prevention of mother-to-child human immunodeficiency virus transmission, and this paper summarizes the successes and current challenges and provides suggestions for future directions.

S10 Recent trends in the incidence and morbidity that are associated with perinatal human immunodeficiency virus infection in the United States
Matthew T. McKenna; Xiaohong Hu
Population-based data sources regarding the incidence and morbidity that are associated with perinatal human immunodeficiency virus infection are improving and indicate that prevention efforts have been enormously successful.

S17 Utility of antenatal HIV surveillance data to evaluate prevention of mother-to-child HIV transmission programs in resource-limited settings
Omotayo Bolu; Abhijeet Anand; Andrea Swart zendruber; Wolfgang Hladik; Lawrence H. Marum; Abdullahi Ahmed Sheikh; Aseged Woldu; Shabbir Ismail; Agnes Mahomva; Stacie Greby; Keith Sabin
This paper describes the utility of antenatal surveillance for monitoring and evaluating prevention of mother-to-child human immunodeficiency virus (HIV) transmission programs in resource-limited countries with generalized HIV epidemics.
S26 Recommendations for human immunodeficiency virus screening, prophylaxis, and treatment for pregnant women in the United States
Denise J. Jamieson; Jill Clark; Athena P. Kourtis; Allan W. Taylor; Margaret A. Lampe; Mary Glenn Fowler; Lynne M. Mofenson

The 25 year history of US recommendations for human immunodeficiency virus screening, prophylaxis, and treatment of pregnant women is summarized, highlighting the relevance for practitioners.

S33 Use of enhanced perinatal human immunodeficiency virus surveillance methods to assess antiretroviral use and perinatal human immunodeficiency virus transmission in the United States, 1999-2001
Norma S. Harris; Mary Glenn Fowler; Stephanie L. Sansom; Nan Ruffo; Margaret A. Lampe

The results of this study demonstrate that mother-infant pairs who received all 3 arms of antiretroviral therapy had the lowest infant human immunodeficiency virus infection rates.

S42 International recommendations on antiretroviral drugs for treatment of HIV-infected women and prevention of mother-to-child HIV transmission in resource-limited settings: 2006 update
Halima Dao; Lynne M. Mofenson; Rene Ekpini; Charles F. Gilks; Matthew Barnhart; Omotayo Bolu; Nathan Shaffer

We reviewed the evidence and summarized the new 2006 World Health Organization recommendations on antiretroviral drugs for the treatment of women who are infected with the human immunodeficiency virus and for the prevention of the transmission of the human immunodeficiency virus from mother to child.

S56 Use of single-dose nevirapine for the prevention of mother-to-child transmission of HIV-1: does development of resistance matter?
Michelle S. McConnell; Jeffrey S. A. Stringer; Athena P. Kourtis; Paul J. Weidle; Susan H. Eshleman

Nevirapine resistance has been detected after single-dose nevirapine, and there is concern about the effectiveness of subsequent nevirapine-based treatment in HIV-infected women; data on the impact of single-dose nevirapine on subsequent treatment and pregnancies are reviewed.

S64 Infant human immunodeficiency virus diagnosis in resource-limited settings: issues, technologies, and country experiences
Tracy L. Creek; Gayle G. Sherman; John Nkengasong; Lydia Lu; Thomas Finkbeiner; Mary Glenn Fowler; Emilia Rivadeneira; Nathan Shaffer

This paper provides a description of challenges, progress, and recommendations for infant human immunodeficiency virus (HIV) diagnosis in resource-limited settings with high HIV prevalence.

S72 Rapid human immunodeficiency virus-1 testing on labor and delivery in 17 US hospitals: the MIRIAD experience
Denise J. Jamieson; Mardge H. Cohen; Robert Maupin; Steven Nesheim; Susan P. Danner; Margaret A. Lampe; Mary Jo O’Sullivan; Mayris P. Webber; Jeffrey Wiener; Rosalind J. Carter; Yvette Rivero; Mary Glenn Fowler; Marc Bulterys

Routine rapid testing during labor provides a feasible, acceptable, and accurate way to identify human immunodeficiency virus–infected women before delivery.
SUPPLEMENT (continued)

S83 Approaches for scaling up human immunodeficiency virus testing and counseling in prevention of mother-to-child human immunodeficiency virus transmission settings in resource-limited countries
Omotayo O. Bolu; Virginia Allread; Tracy Creek; Elizabeth Stringer; Fatu Forna; Marc Bultery; Nathan Shaffer
This paper provides a summary of approaches and recommendations for scaling up human immunodeficiency virus testing and counseling in prevention of mother-to-child transmission settings in resource-limited countries.

Stephanie L. Sansom; Norma S. Harris; Ramses Sadek; Margaret A. Lampe; Nan M. Ruffo; Mary Glenn Fowler
The number of new perinatal human immunodeficiency virus infections in funded states decreased by 56%, achieving Centers for Disease Control and Prevention goal of a 50% reduction in incidence by 2005.

S96 Cesarean delivery for HIV-infected women: recommendations and controversies
Denise J. Jamieson; Jennifer S. Read; Athena P. Kourtis; Tonji M. Durant; Margaret A. Lampe; Kenneth L. Dominguez
Cesarean delivery to prevent mother-to-child transmission of human immunodeficiency virus is safe, effective, and relatively cost-effective; accordingly, cesarean delivery rates among human immunodeficiency virus–infected women have increased dramatically.

S101 Prevention of mother-to-child transmission services as a gateway to family-based human immunodeficiency virus care and treatment in resource-limited settings: rationale and international experiences
Elaine J. Abrams; Landon Myer; Allan Rosenfield; Wafaa M. El-Sadr
Viewing preventing the mother-to-child transmission as a gateway to family-based human immunodeficiency virus care and treatment will help strengthen ties between the 2 programs.

S107 Site-specific interventions to improve prevention of mother-to-child transmission of human immunodeficiency virus programs in less developed settings
Tabitha Sripipatana; Allison Spensley; Anna Miller; James McIntyre; Gloria Sangiwa; Frederick Sawe; David Jones; Catherine M. Wilfert
This article discusses site-specific interventions to increase the uptake of prevention of mother-to-child transmission programs based on experiences in sub-Saharan Africa. Lessons learned can apply to many resource-constrained settings.

S113 Prevention of human immunodeficiency virus-1 transmission to the infant through breastfeeding: new developments
Athena P. Kourtis; Denise J. Jamieson; Isabelle de Vincenzi; Allan Taylor; Michael C. Thigpen; Halima Dao; Timothy Farley; Mary Glenn Fowler
This paper focuses on current and planned research trials on strategies to prevent breastfeeding transmission of human immunodeficiency virus from mother to infant worldwide.
Young, seropositive, and pregnant: epidemiologic and psychosocial perspectives on pregnant adolescents with human immunodeficiency virus infection
Linda J. Koenig; Lorena Espinoza; Krystal Hodge; Nan Ruffo
Population-based and cohort data are examined to document prevalence and psychosocial characteristics of pregnant, HIV-infected adolescents, highlighting the need for aggressive transmission risk reduction and pregnancy prevention interventions for HIV-infected youth.

The missing link: documentation of recognized maternal human immunodeficiency virus infection in exposed infant birth records, 24 United States (jurisdictions, 1999-2003)
Allan W. Taylor; Nan Ruffo; Judy Griffith; Athena P. Kourtis; Jill Clark; Michael Lindsay; Donata Green; Denise J. Jamieson
Recognized maternal human immunodeficiency virus infection remained undocumented in 4 of exposed infant medical records; these infants had increased risk of inadequate prophylaxis and human immunodeficiency virus infection.

Consultation needs in perinatal HIV care: experience of the National Perinatal HIV Consultation Service
Jessica A. Fogler; Shannon Weber; Ronald H. Goldschmidt; Megan R. Mahoney; Deborah Cohan
This study provides an overview of the consultation needs of providers who care for HIV-infected pregnant women and HIV-exposed infants in the United States.
For whom the bell tolls

Howard Minkoff

Any man’s death diminishes me, because I am involved in Mankind; And therefore never send to know for whom the bell tolls; it tolls for thee.

John Donne

In June of 1981, a description of the first cases of what are now called AIDS was published in MMWR. That report established the Center for Disease Control and Prevention’s (CDC) reputation for tracking the epidemic, a reputation (as reflected in this supplement) that has since solidified and expanded. It also led to a less fortunate idée fixe in the American conscience: that AIDS is an epidemic that only infects “others,” i.e., marginalized populations. In the first years of the epidemic, those others were gay males, but later, drug users and members of minority groups joined them. Today, the others are infected people in the developing world.

In fact, the spread of human immunodeficiency virus (HIV), in general, and mother-to-child transmission of HIV, in particular, has bifurcated into two unique epidemics; one in countries with access to highly active therapies, and a much larger one in parts of the world where access to treatment is sporadic at best. The parallel tracks of these epidemics, and the strategies that need to be tailored to the unique circumstances of each are the subjects of this supplement. The message reflected in the surveillance data from the United States is clear. Remarkable advances have already occurred and, from the perspective of mother-to-child transmission of HIV, further progress may focus on simplifying protocols as much as amplifying benefits. The protocols in question are not limited to those detailing drug regimens, although efforts to reduce pill burdens and side effects proceed apace. They also apply to protocols for identifying HIV-infected women in the first instance. The message from the CDC and American College of Obstetricians and Gynecologists (ACOG) is unambiguous: it is time to opt out of the opt-in strategy for prenatal testing. It is also time to expand and expedite peripartum rapid testing for women with no prenatal care. Those women are at particularly high risk and, as more and more women with regular care are identified, they will disproportionately bear the children in the United States who acquire HIV at birth.

The story in the developing world is more complex and more desperate. However, those adjectives were apt descriptors of the AIDS epidemic in the United States in its earliest years. The same commitment that started to change the course of the epidemic in the United States—to learn about and confront the illness—can certainly have a salutary effect in the developing world, and there are reasons for cautious optimism. The infusion of $15 billion over 5 years through The President’s Emergency Plan for AIDS Relief (PEPFAR) program (even with some potentially counterproductive earmarks) presents many opportunities to bring treatments to locales that heretofore had minimal access. In this supplement, the roadmap to progress in the developing world can start to be discerned. The core strategies mirror some that formed the basis for progress in the United States over the last 20 years, i.e., surveillance and testing.

In considering the twin HIV epidemics, it would be easy for readers of the American Journal of Obstetrics & Gynecology to focus solely on American women. Accordingly, they might accept as their charge assuring that their patients benefit from the relative bounty of American medicine, that proper medications are prescribed, and that potential toxicities are monitored. However, in holding to this narrow definition of patient care, clinicians would be ignoring the overwhelming epidemic that threatens millions overseas, as well as the less common issue of limited access to therapy in parts of our own country. Thus while they may be providing ethical care in their offices, it would be an ethics writ small.

In that regard it is worth considering one fact that has held true since AIDS was first described: it is a prism through which the social conscience of individuals is refracted. Since the early 1980s, there have been those who saw AIDS as a reason to discriminate, and others who saw it as a reason to fight discrimination. Today, events in Africa may provide a similar litmus test. The killings in Darfur, for example, test our social consciousness. However, Sudan is not the only country on that continent where lives are being laid waste. At this moment, millions of men, women, and children are in mortal peril from HIV. Our obligation to those people does not derive merely from our common humanity, though that alone should suffice. We must also recognize, and appreciate, that what we are now learning about mother-to-child transmission and how, for example, we should treat American women identified as HIV-infected while in labor, is derived from research being performed in Africa. This supplement reinforces the reality that we are interconnected in this epidemic.

Thus, clinicians should reflect on their obligation to look beyond proper prescribing practices if they want to attain the highest ethical standard of their profession. Several American and European medical organizations have jointly published what they referred to as a physician charter describing the ob-

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0002-9378/free
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doi: 10.1016/j.ajog.2007.05.014
llications of professionalism, including social justice, noting that, “physicians should work actively to eliminate discrimination in health care, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category.”8 To achieve that end, physicians may need to bring their advocacy out of the hospital and into the broader world. Physicians trained in obstetrics and gynecology and versed in the medical arts may feel ill prepared to advocate for the social change required to promote optimal health for their patients. But societal impediments, whether they be the loss of insurance by women in the postpartum period, or the failure of managed care organizations to allow needed procedures or medications, can confound the best of medical plans. No illness is more illustrative of the intertwining of the health of a society with the health of its citizens than HIV, and none has greater need of advocacy at home and abroad. Physicians must start to recognize that the mantle of altruism with which society vests them comes at a cost. They need not be polished lobbyists. But whether by volunteering their time, contributing money, or agitating on behalf of their patients, they need to bring the suasion of the white coat to bear on these important health issues.

Finally, for highlighting the interrelationships between the epidemic at home and abroad, as well as for the remarkable job they have done in laying the groundwork for changing the course of the epidemic in the United States, a debt of gratitude is owed to the Public Health Service. Although thousands of physicians and scientists have participated in that work, there are a few contributors to this supplement whose dedication to combating this epidemic for more than 20 years have been particularly remarkable. For those extraordinary efforts, I would like to end by acknowledging the indefatigable commitment to the health of women and children of Mary Glenn Fowler, Mary Jo O’Sullivan, Lynne Mofenson, and Martha Rogers.

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2. McKenna MT, Hu X. Recent trends in the incidence and morbidity that are associated with perinatal HIV infection in the United States.
Reducing the risk of mother-to-child human immunodeficiency virus transmission: past successes, current progress and challenges, and future directions

Mary Glenn Fowler, MD, MPH; Margaret A. Lampe, RN, MPH; Denise J. Jamieson, MD, MPH; Athena P. Kourtis, MD, PhD, MPH; Martha F. Rogers, MD

In the global human immunodeficiency virus (HIV) pandemic, prevention of mother-to-child transmission (PMTCT) in the United States and Europe has been one of the major success stories. Prior to effective perinatal HIV interventions, about 1 in 4 babies born to HIV-infected women became infected; whereas today an HIV-infected pregnant woman in the United States or Europe receiving highly active antiretroviral therapy (HAART) and with an undetectable viral load has only about 1-2% chance of transmitting HIV to her infant.1 In international resource-limited settings, simplified, shorter-course antiretroviral regimens have also been shown in perinatal HIV clinical trials to reduce transmission among breast-feeding HIV-infected women, although with less efficacy than HAART. However, translation of the findings from most of these research studies into successful national PMTCT programs and ministry of health policies has not been optimal.

U.S. EXPERIENCE

In 1992, at the peak of the U.S. perinatal epidemic, close to 2000 babies in the United States became HIV infected, whereas currently fewer than 200 infants become HIV infected annually (see related article is this issue by McKenna et al). The dramatic success in reducing perinatal HIV transmission across the United States was due in large part to the rapid translation of research trial findings into practice. This was achieved through the combined leadership of the U.S. Public Health Service, effective partnerships of city and state health departments with university perinatal researchers and health care providers at tertiary care centers, and the strong support of national organization partners. In 1985, 2 years after the first case of pediatric acquired immunodeficiency syndrome (AIDS) was described in the United States, the Centers for Disease Control and Prevention (CDC) recommended that HIV-infected women in the United States should not breast-feed, which was one of the first preventive steps that substantially reduced the risk of perinatal transmission in the United States.2 Currently the vast majority of HIV-infected women in the United States avoid breast-feeding by the use of formula.

In the United States, a major breakthrough in PMTCT occurred in 1994 with the announcement of the Pediatric AIDS Clinical Trial Group Protocol 076 results.3 This double-blinded, randomized, placebo-controlled trial, which included an intensive regimen of oral zidovudine (ZDV) given prenatally, intrapartum, and postpartum, decreased perinatal transmission risk by two thirds when compared with placebo. Based on these findings, the US Public Health Task Force quickly recommended that all pregnant women should be offered HIV testing and that those women who were identified as HIV infected should be given ZDV according to the PACTG.
076 regimen. Widespread implementation of these recommendations led to sharp decreases in perinatal HIV transmission. Furthermore, since the late 1990s, most HIV-infected women in the United States have been prescribed combination regimens, which further reduced the risk.

Elective cesarean delivery was shown to be associated with a 50% reduction in transmission in both a randomized European trial and a large metaanalysis; and in 2000 the American College of Obstetricians and Gynecologists (ACOG) recommended that all women with HIV viral loads greater than 1000 copies per milliliter be counseled with regard to the benefit of cesarean delivery (see related article is this issue by Jamieson et al). However, these interventions have failed to reach certain high-risk groups. For example, to implement these interventions, both an HIV-infected pregnant woman and her health care provider must know her HIV status.

The Mother-Infant Rapid Intervention at Delivery (MIRIAD) study attempted to reach these women with unknown HIV status by demonstrating that rapid HIV testing in labor and delivery units was feasible, acceptable, and accurate. The MIRIAD study, which was conducted in 17 hospitals in 5 urban areas, reported findings demonstrating that offering rapid HIV testing in labor and delivery settings to women whose HIV status was still unknown was feasible and deliverable. It was also demonstrated that based on these rapid test results, peripartum antiretroviral interventions to reduce the risk of transmission could then be successfully provided (see related article is this issue by Jamieson et al). Furthermore, a critical policy event occurred in 2003 when the CDC issued a Dear Colleague letter supporting routine rapid testing at labor and delivery for pregnant women whose status was still unknown (see related article in this issue by Sansom et al).

In addition, after the results of the MIRIAD study were announced, ACOG also issued guidelines to its fellows supporting routine rapid testing at labor and delivery for women whose status was still unknown. The CDC also developed and distributed a model protocol on rapid HIV testing at labor/delivery to provide hospitals and clinicians with implementation guidance for rapid HIV testing at labor/delivery and carried out a series of regional workshops for key hospitals to provide hands-on assistance to their staff in developing their hospital site-specific implementation plans.

Since 1999 Congress has provided substantial funding to support perinatal HIV prevention programs in high-prevalence states. These targeted federal funds have helped jump-start and sustain states’ perinatal HIV prevention efforts and include funding support for social marketing; development of information and educational materials, expanding voluntary HIV screening to all pregnant women seen in antenatal settings; and rapid testing during labor/delivery for pregnant women whose status was still not known (see related article in this issue by Sansom et al).

The chronology of events leading to increased uptake of HIV testing among pregnant women and interventions for HIV-infected pregnant women are shown in Table 1.

**Remainng Gaps and Challenges in Perinatal HIV Prevention Efforts in the US**

Despite the dramatic reductions in perinatal HIV and pediatric AIDS seen over the past decade, babies in the United States are still becoming HIV infected. Some of the ongoing issues and program gaps include practitioners who continue to offer HIV testing only to those women they consider at high risk despite CDC recommendations for routine HIV screening for all pregnant women unless they decline; lack of retesting to identify the subset of women who test negative early in pregnancy but then seroconvert in later pregnancy; limited resources focused on developing interventions that reduce the risk of primary HIV infection among adolescent females and adult women; and limited overall funding for perinatal HIV prevention programs at the state and community level.

**International Experience in PMTCT**

Internationally, following the results of PACTG 076, a number of randomized trials were undertaken to see whether simpler short-course regimens deliverable in resource-limited settings could also significantly reduce the risk of perinatal HIV transmission. The first of these studies’ results were announced in 1998 and included 2 CDC short-course ZDV trials in Thailand and West Africa in which pregnant women were given either oral ZDV or placebo from 36 weeks through labor/delivery. In the Thailand CDC trial in which HIV-infected women did not breast-feed and infants were formula fed, the findings reported...
in 1998 were that this short-course ZDV regimen reduced transmission by 50%, whereas in the West African setting of Côte d’Ivoire and where HIV-infected women breast-fed, 3-month transmission was reduced by 37%.19,20

Results from other short-course trials quickly followed. The PETRA study21 was a 4-armed study that compared use of 2 drugs, ZDV and 3TC, with placebo. The findings were that the longest arm of the PETRA trial, in which HIV-infected pregnant women received ZDV/3TC from 36 weeks through delivery and 1 week postpartum and their newborns also received 1 week of ZDV/3TC, was highly efficacious at 6 weeks when compared with placebo with a 67% reduction in HIV transmission.

In Uganda, a simpler regimen tested in the HIVNET 012 trial22,23 used a single dose of nevirapine (SD NVP) given to the mothers at labor onset and to their newborns. This regimen was found to be highly efficacious and deliverable. It reduced transmission by 42% when compared with an ultrashort course of ZDV given at labor onset and for 1 week postpartum to mothers and their newborns. Building on the 2 successful regimens, a study in Thailand24 combined the short-course ZDV regimen from 28 weeks’ gestation with SD NVP plus 1 week of ZDV to the infant and reduced transmission to 2%. This combined, 2-drug strategy in Thailand among non-breast-feeding women was found to be as effective in reducing transmission as the HAART interventions being used in the United States and Europe. When used in breastfeeding settings in West Africa, the regimens of ZDV or ZDV/3TC in the last trimester plus SD NVP at labor and to the newborn demonstrated a transmission rate of about 6-9%.25 (see also related article is this issue by Kourtis et al).

Based on the results of these trials, international agencies and donor groups including the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), the United Nations Children’s Fund (UNICEF), The Bill and Melinda Gates Foundation, the Elizabeth Glaser Pediatric AIDS Foundation, and US and European governments provided funding for implementing and scaling up these short-course interventions in resource-limited settings (see related articles is this issue by Bolu et al and Sripipatana et al). A chronology of major international milestones relevant to PMTCT is summarized in Table 2.

### Table 1: Chronology of events: perinatal HIV prevention in United States

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
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<tbody>
<tr>
<td>1983</td>
<td>First case of pediatric AIDS in United States described</td>
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<tr>
<td>1985</td>
<td>CDC issues first guidelines for prevention of perinatal HIV transmission including the recommendation that HIV-infected women in United States should not breast-feed</td>
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<tr>
<td>1992</td>
<td>Number of reported pediatric AIDS cases peaks in the United States</td>
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| 1994       | - PACTG 076 trial findings reported, which indicate a two thirds reduction with an intensive regimen of ZDV given to the mother from the second trimester, intravenously at labor and for 6 weeks to the newborn.  
- Food and Drug Administration licenses ZDV for perinatal HIV prevention indication  
- US Public Health Service recommends implementation of ZDV regimen for all HIV-infected pregnant women |
| 1995       | CDC recommends voluntary counseling and testing for all pregnant women and offering the ZDV regimen to all HIV-infected women |
| 1998       | Institute of Medicine report released, which recommends universal HIV screening with right of refusal for all pregnant women |
| 1999       | Congress provides targeted funding for perinatal HIV prevention efforts in high prevalence states |
| 2001       | Revised CDC Counseling and Testing Guidelines for Pregnant women supports reducing barriers to offering of perinatal HIV testing to ensure routine universal testing and offering rapid HIV testing at labor/delivery for women whose HIV status is still unknown |
| 2002-2003  | CDC reports high uptake of screening of pregnant women using opt-out strategy. Dear Colleague Letter issued recommending opt-out strategy to optimally support routine universal testing of pregnant women. |
| 2006       | CDC Revised Recommendations for HIV Testing in Health Care Settings released recommending an opt-out strategy with routine HIV screening of all pregnant women as part of the routine panel of prenatal tests, a second test in the third trimester for women in areas or facilities with elevated incidence of HIV or who are known to be at high risk for HIV, and rapid HIV testing for women whose HIV status is not known at labor/delivery. Additionally, opt-out testing recommended for: all patients aged 13-64 y (annually for those likely to be at high risk for HIV); women as a component of preconception care and all patients with tuberculosis or seeking treatment for a sexually transmitted disease. |

### International Trials Aimed at Reducing Transmission among HIV-Infected Women Who Breast-feed

Current international trials are directed at maximally reducing the risk of transmission among breast-feeding HIV-infected women in resource-limited settings in which breast-feeding is the norm and in which not breast-feeding is associated with high infant mortality. A number of different trials are currently
Results from these trials will be available during the period of breast milk exposure. Strategies being assessed include the following: (1) use of 2 antiretrovirals such as short-course zidovudine/lamivudine or ZDV plus SD NVP at labor/delivery; (2) maternal HAART during the last trimester of pregnancy, at labor, and for up to 6 months following delivery with a goal of minimizing maternal viral load in plasma and breast milk; (3) interventions directed at protecting the infant during 3-6 months of exclusive breastfeeding followed by early weaning; and (4) active or passive immune strategies that boost infant immune responses during the period of breast milk exposure. Results from these trials will be available over the next several years and should provide guidance on the most effective strategies to reducing the risk of transmission during breast-feeding.

**Current Challenges and Program Gaps Internationally**

Despite the impressive efficacy of the short-course PMTCT regimens in research clinical trial settings, the translation into public health policy in resource-limited international settings has been disappointingly slow, compared with the rapid widespread implementation seen from the mid-1990s in resource-rich settings. This is due to a variety of factors including weak and crumbling health care infrastructure in some settings, lack of integration of PMTCT programs into maternal child health services, limited donor funding support, PMTCT drug and HIV test kit stockouts, the fact that many women in resource limited settings deliver at home or outside medical facilities in which PMTCT services are available, and competing public health priorities in the context of limited overall health care funding available in resource-constrained countries in Africa and Asia.

Other challenges include lack of male involvement in HIV testing including couple testing (see related article is this issue by Abrams et al); issues of disclosure by women of their HIV status that may prevent HIV-infected women from receiving appropriate antiretroviral interventions for both PMTCT and their own treatment; and competition for limited resources setting up artificial and unnecessary

### TABLE 2

<table>
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<th>Date</th>
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<tr>
<td>2000</td>
<td>US presidential monies made available to support PMTCT. Activities in 15 resource limited international countries. Gates Foundation provides CTA funding to Elizabeth Glaser Pediatric AIDS Foundation to launch use of SD NVP regimen. Boehringer Ingelheim and Abbot provide SD NVP and determine rapid HIV test kits to support scaling up of PMTCT through the AXIOS donation program.</td>
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<tr>
<td>2000</td>
<td>WHO UNAIDS recommends use of any of 3 options for PMTCT: SC regimens (ZDV, ZDV/3TC) from 36 weeks and SD NVP and exclusive breast-feeding with early weaning for HIV-infected women in situations in which use of breast milk substitutes is not safe, sustainable, or affordable</td>
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<tr>
<td>2003 to present</td>
<td>US Presidential Emergency Funding for AIDS Relief provides substantial funding for treatment and prevention activities to 15 countries, rolling in PMTCT activities</td>
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<tr>
<td>2004</td>
<td>Renewal and expansion of CTA funding for PMTCT under PEPFAR initiative</td>
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<tr>
<td>2004</td>
<td>Combined SC ZDV and SD NVP results published from Thailand demonstrating further reduction in transmission to 2% with this combined regimen among formula-fed infants. In West Africa, 6 week transmission rates of 4-6% were reported in programs using a similar regimen (SC ZDV/3TC + SD NVP or SC ZDV + SD NVP) from 32 weeks in a population in which some women breast-feed. WHO recommends SC ZDV plus SD NVP as the first-line regimen for PMTCT among women who do not require HAART for their own care; and HAART for HIV-infected pregnant women who meet WHO treatment criteria</td>
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<tr>
<td>2005</td>
<td>MASHI trial from Botswana finds reduced HIV transmission but overall similar infant HIV-free survival similar because of more deaths from other causes in trial comparing mother-infant pairs randomized with either formula from birth and 1 month of infant ZDV prophylaxis versus exclusive breastfeeding for 6 months and 6 months of infant ZDV</td>
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<tr>
<td>2006</td>
<td>WHO convenes expert consultations on infant feeding to consider consequences of early weaning and consultation on early infant diagnosis to aid early initiation of antiretroviral treatment for infants and children. Also releases updated recommendations for use of antiretrovirals among pregnant women</td>
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CTA, Call to Action; PEPFAR, Presidential Emergency Funding for AIDS Relief; SC, short course.
tensions between HIV prevention and care/treatment programs.

Lack of family-planning services has been another major programmatic gap area. In settings with high HIV prevalence rates among women of reproductive age, combined with high rates of unintended pregnancy, there is an urgent need for programs that integrate family planning and PMTCT programs. Unfortunately, PMTCT programs often lack the funding, organizational structure, and technical expertise to provide comprehensive contraceptive services for HIV-infected women. High rates of unintended pregnancy among participants in antiretroviral treatment programs have recently been reported and highlight this gap in services. Efforts must be made to make contraceptive services easily accessible to HIV-infected women in care and/or on antiretroviral therapy by closely linking contraceptive counseling and services to PMTCT programs.

Likewise, although simple, inexpensive drug regimens for PMTCT are available, there are still barriers to widely implementing and national scaling up of these regimens because of inadequate funding, sociocultural, and institutional barriers. Currently it is estimated that less than 10% of HIV-infected women in sub-Saharan Africa receive any antiretrovirals during pregnancy or delivery. In addition, as concerns are raised about reduced efficacy of simplified regimens such as single-dose nevirapine, compared with more intense regimens as well as the possible effect of transient nevirapine resistance on later treatment outcomes, the medical community has increasingly recommended more complex regimens for perinatal prophylaxis (see related article is this issue by McConnell et al). Particularly, efficacious and sustainable interventions for prevention of HIV infection during the postnatal breast-feeding period are urgently needed.

And finally, the optimal strategy for infant feeding of HIV-infected mothers in resource-limited settings has yet to be delineated. Balancing the benefits of breast-feeding in settings with unsafe water, poor hygiene, and lack of affordable nutritional substitutes for breast milk against the risk of postnatal HIV transmission to the infant is complex. The issue of HIV and the best infant feeding choice has also been a continuing dilemma for international agencies, ministries of health and HIV-infected mothers in resource-limited settings in which use of breast milk substitutes is not culturally acceptable, feasible, affordable, safe, or sustainable. Recent data presented at a 2006 WHO consultation on HIV and Infant Feeding underscore the risk of increased infant gastroenteritis morbidity and overall infant mortality associated with early breast-feeding cessation and the introduction of contaminated complementary foods.

**Future Directions for PMTCT in the US and Internationally**

In the United States, the translation of PMTCT research into practice has been one of the major successes in public health efforts to prevent HIV infection. However, lessons from experiences with other diseases such as tuberculosis demonstrate that when successful public health efforts are taken for granted, the gains may be temporary. To sustain achievements, not only do the efforts that led to the declines in perinatal HIV transmission need to continue, but ongoing surveillance of the scope and breadth of perinatal transmission in the United States needs to be strengthened. Recent CDC recommendations that HIV screening should be a routine part of health care and a key component of preconception care should be supported and implemented, increasing the likelihood of HIV-infected women learning their status prior to pregnancy so that they can make informed choices about pregnancy and take full advantage of life-saving interventions.

Even in the event of screening prior to pregnancy, all women should be offered testing early in prenatal care for every pregnancy. To support this goal, CDC is launching the One Test, Two Lives campaign in the United States to encourage obstetrical providers in all settings to offer early HIV testing as a routine, opt-out practice for their pregnant patients and to counsel them to accept an HIV test in the event of an initial decline. The campaign offers a full suite of information and materials, both for providers and their patients. (For more information about One Test, Two Lives or free materials for your practice, visit the campaign website at www.cdc.gov/1test2lives or contact the National Prevention Information Network at www.cdcnpin.org or 800-458-5231.)

Clinical management of HIV-infected pregnant women is increasingly complex (see related article is this issue by Jamieson et al), and obstetric clinicians need education and support to provide medical care, particularly to women who have a positive rapid HIV test during labor and delivery. The Health Resources and Services Administration and the CDC jointly support the National Clinical Consultation and Referral Service’s Perinatal Hotline (see related article is this issue by Fogler et al). Ongoing and expanded education and resources for obstetric clinicians are needed especially as rapid HIV testing for women in labor with unknown HIV status becomes the standard of care.

Whereas there are highly effective antiretroviral interventions for PMTCT, similar interventions are not yet available to prevent primary HIV infection in women. Studies of vaccines, antiretroviral prophylaxis, and microbicides have yet to demonstrate efficacy in preventing HIV in women, although some promising possibilities are actively being explored. Until HIV is controlled in women, the promise of eliminating perinatal HIV transmission is unlikely to be realized.

In international settings, effective strategies to make breast-feeding safer for HIV-exposed infants through the first year of life are urgently needed. Trials currently underway include maternal HAART during breast-feeding and extended infant antiretroviral prophylaxis, and immune-based strategies. A preventive infant HIV vaccine, if proven efficacious, would be an optimal approach to both reducing the risk of breast-feeding...
transmission of the HIV virus during the first year of life while providing the infant with adequate nutrition and the continued protection of breast milk against other infectious causes of morbidity and mortality. This strategy has the benefit of reducing the risk of HIV acquisition while maintaining breast milk as a source of life-saving nutrition.

In conclusion, as documented throughout this supplement, much progress has been made in PMTCT of HIV both in the United States and internationally. However, the challenges of complete elimination of new perinatal HIV infections will depend on not only PMTCT interventions worldwide but also effective primary HIV prevention interventions among adolescents and young adults.

REFERENCES


Recent trends in the incidence and morbidity that are associated with perinatal human immunodeficiency virus infection in the United States

Matthew T. McKenna, MD, MPH; Xiaohong Hu, MS

A cornerstone of prevention and public health practice is the ongoing, systematic collection, analysis, evaluation, and dissemination of data that describe and monitor health events such as disease incidence and prevalence and the determinants of these outcomes. All data sources and formal evaluations to date suggest that the prevention of the transmission of human immunodeficiency virus (HIV) from mother to infant (perinatal transmission) in the United States has been very successful. This success has been achieved through the implementation of guidelines for the identification of HIV-infected women through testing, the provision of comprehensive preconception (including contraceptive services) and perinatal care, the administration of antiretroviral therapy to the mother during pregnancy and delivery, and the administration of antiretrovirals to the HIV-exposed newborn infant. However, despite documented decreases in perinatally associated acquired immunodeficiency syndrome (AIDS) cases since the apex of this epidemic in 1992, enumeration of the number of infected infants has relied on indirect statistical techniques rather than systematic public health reports of such cases. The most recent national estimate from the Centers for Disease Control and Prevention (CDC) was calculated for the year 2000 and indicated that between 280 and 370 HIV-infected infants were born that year. That report was analyzed national surveillance data that had been reported to the Centers for Disease Control and Prevention to elucidate the impact of recent clinical and public health efforts to further decrease the number of human immunodeficiency virus (HIV) infections and resulting morbidity caused by perinatal transmission. Long-term trends in pediatric (ages, 0-13 years), perinatal acquired immune deficiency syndrome (AIDS) cases were analyzed by log-linear Poisson regression for the period 1992-2004. Estimates for the number of perinatal HIV infections that occurred during the more recent period of 2001-2004 were developed by extrapolation from the 33 states with ongoing HIV (non-AIDS) reporting to the entire United States with the use of a probabilistic model. The number of pediatric perinatal AIDS cases that were identified decreased from 858 in 1992 to only 41 in 2004. These declines were consistent across demographic and regional subgroups. Data on the number of perinatal HIV infections suggests ongoing declines throughout the early years of the 21st century from 277 (95% CI, 224-346) in 2001 to 138 (95% CI, 96-186) in 2004. The incidence and morbidity associated with perinatal HIV infection continue to decline. To ensure that existing prevention efforts continue to achieve control of these infections, consistent methods of public health surveillance must be instituted throughout the entire United States.

Key words: HIV, perinatal, surveillance, United States

We analyzed national surveillance data that had been reported to the Centers for Disease Control and Prevention to elucidate the impact of recent clinical and public health efforts to further decrease the number of human immunodeficiency virus (HIV) infections and resulting morbidity caused by perinatal transmission. Long-term trends in pediatric (ages, 0-13 years), perinatal acquired immune deficiency syndrome (AIDS) cases were analyzed by log-linear Poisson regression for the period 1992-2004. Estimates for the number of perinatal HIV infections that occurred during the more recent period of 2001-2004 were developed by extrapolation from the 33 states with ongoing HIV (non-AIDS) reporting to the entire United States with the use of a probabilistic model. The number of pediatric perinatal AIDS cases that were identified decreased from 858 in 1992 to only 41 in 2004. These declines were consistent across demographic and regional subgroups. Data on the number of perinatal HIV infections suggests ongoing declines throughout the early years of the 21st century from 277 (95% CI, 224-346) in 2001 to 138 (95% CI, 96-186) in 2004. The incidence and morbidity associated with perinatal HIV infection continue to decline. To ensure that existing prevention efforts continue to achieve control of these infections, consistent methods of public health surveillance must be instituted throughout the entire United States.
from state to state. The stigma that is associated with the HIV infection has engendered concerns that governmental registries that contain the names of HIV-infected persons might lead to discrimination and that apprehension about such reporting could be a deterrent to being able to recruit persons for HIV testing. As a result, many state health departments have found it politically difficult to establish such reporting systems for HIV infection. However, systematic surveys of persons who are at risk of HIV have demonstrated consistently that fear about disease reporting is not among the most commonly identified deterrents, and testing rates have not declined in areas that have implemented name-based reporting for this condition. Therefore, throughout the late 1990s and into the 21st century, more states began to implement such data collection systems.

By 2001, 33 states had established name-based HIV-infection reporting systems that provide data that can be processed and analyzed by the CDC. These areas report 70% of the perinatally associated AIDS cases in the United States. The availability of data from areas with the most burden of perinatal HIV transmission provides an opportunity to use more direct methods to estimate the number of perinatally acquired infections occurring in the United States and to review recent trends in the morbidity that is associated with HIV.

**Methods**

**Data source**

The data used for this analysis are from the national reporting system for HIV/AIDS. The analysis includes records of AIDS and HIV cases reported and maintained by the CDC through December of 2005. The details of the methods and operations that are used to compile the data that is entered into this system have been described in more detail elsewhere. Briefly, all states and the District of Columbia have mandated that healthcare providers (including physicians, laboratories, hospital and clinic personnel, and in some cases insurance companies) submit case reports to appropriate local public health authorities on all persons who are diagnosed with AIDS with the use of a standard case definition. These reports include identification of information about the patient that includes the name and usually the address of the case. Data from the reports are then forwarded to the CDC after the personal-identifying information is removed from the case record.

In 1999 CDC published guidelines for the operation of HIV reporting systems that included criteria for the evaluation of the systems and a standardized case definition for HIV, non-AIDS infections in adults, adolescents, and children who are infected through perinatal exposure. However, unlike AIDS reporting for which local surveillance records included the patient’s name in all areas, many jurisdictions used identifiers other than the name of patients who were diagnosed with HIV infections that had not progressed to AIDS. Formal evaluations of these systems by the CDC indicated that the data from these systems were not sufficiently accurate to use for epidemiologic or other public health purposes. Therefore, the CDC continues to exclude data for HIV non-AIDS cases from areas that use identifiers other than names in the national dataset.

As of 2001, 33 states had established name-based HIV reporting systems that included the submission of reports on children who were found to be infected through perinatal exposure to HIV. These states were Alabama, Alaska, Arkansas, Arizona, Colorado, Florida, Idaho, Indiana, Iowa, Kansas, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nebraska, Nevada, New Jersey, New Mexico, North Carolina, North Dakota, New York, Ohio, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, West Virginia, Wisconsin, and Wyoming. In the construction of a statistical model to estimate the total number of perinatal infections in the United States, data regarding children who were infected with HIV through perinatal exposure and in whom AIDS later developed are included from all states, and only data from the 33 areas with name-based reporting are included on cases that have not progressed to AIDS.

**Model structure for estimating infections by birth year**

Table 1 shows the assumptions, data sources, and estimated uncertainty that are associated with each component of the model that was used to compute the national estimates. The fundamental assumption underlying this approach is that the number of new infections that were acquired in the areas with name-based reporting contributes to the national total by the same proportion as the number of childhood (age, <13 years) perinatal AIDS cases from those areas contributes to the total number of perinatally acquired AIDS cases in children who live in the entire United States. We used the proportion of all perinatal AIDS cases that were reported in the United States and that were reported from these 33 states over the 5-year period, 2001-2005. Therefore, the number of cases that were reported for a single birth year was multiplied by the inverse of the proportion of perinatal AIDS cases that were reported from the areas with name-based reporting. During this period, black children constituted 70% (Table 1) of case reports, even though only 12%-15% of all children who were born in the United States during this period were from this racial group. This disparity reflects the extraordinary racial disparity in HIV infections among women generally. Therefore, the estimates were developed for race-specific strata and aggregated to derive an overall national total.

Although a higher proportion of diagnosed HIV and AIDS cases are reported than for most other infectious diseases, there is ample information to demonstrate that not all cases are reported to health departments. In particular, the exclusion or confirmation of a diagnosis of perinatally acquired HIV in an exposed infant is very complex because such newborn infants usually possess maternal antibodies against HIV. Therefore, the confirmation of a diagnosis of perinatal infection can be delayed, and children who are infected may never
be reported to the health department. We adjusted for delays in reporting by calculating the proportion of cases that were reported in each year after 2001 through 2005 among the infected children who were born in 2001. For years of birth subsequent to 2001, the number of cases who were born and reported as infected was inflated by the inverse of the proportion of the total number of cases that were reported for 2001 over a period of time equivalent to the period between the birth year and 2005. For example, according to the December 2005 CDC data, 94% of infections among children who were born in 2001 were reported by the end of 2004. Therefore, the number of observed cases who were born in 2002 was multiplied by the inverse of 0.94 to adjust for the anticipated reporting delay. Finally, some cases are never reported to the health department. There are no recent data on the completeness of reporting specifically for perinatal cases. However, formal evaluations to estimate underreporting for the overall number of newly diagnosed patients demonstrate that approximately 15% of HIV and/or AIDS cases would not be reported to the health department during a period similar to that of this analysis.17,23 Therefore, we further inflated all estimated case counts by the inverse of 0.85 to adjust for this undercounting phenomena (Table 1).

**Statistical analysis**

AIDS case counts were available from all 50 states and the District of Columbia. These counts were compiled by year of diagnosis and were adjusted for reporting delay with standard methods that have been developed by the CDC.24 AIDS case counts were not adjusted for underreporting. Trends were assessed after 1992 (the apex of the number of cases) by the calculation of regression coefficients with the use of linear Poisson regression that was based on the annual case counts from 1992-2004.25 Differences in coefficients that were calculated for the diagnosis year were assessed with the standard errors for these coefficients from the models and the calculation of Z tests for pairwise comparisons or the logit test for homogeneity for categories with >2 groups (eg, race/ethnicity and region of the United States).25,26 To estimate the annual percent of decline (APD) during this period the regression coefficients were transformed using the formula: \( e^\beta - 1 \times 100\% \), where \( \beta \) is the coefficient for the year of diagnosis.

The HIV infection computation model was constructed based on a probabilistic method used frequently in economic analyses.27 Data and computations were entered and executed in Excel (Microsoft Corporation, Redmond, WA) spreadsheets. The uncertainty that was associated with each input was quantified with the use of a plausible probability distribution (eg, Poisson for count data or the binomial distribution for proportions) or by the identification from the literature of minimum, most likely, and maximum values for the input estimate and the assumption of a triangular distribution that was defined by these 3 values. See Table 1 for the details of each estimate entered into the model. The software package @RISK (version 4.5; Palisades Corporation, Ithaca, NY) was used to simulate 1000 results for each output estimate by sequentially drawing independent values from the input distributions and conducting the

### Table 1: Variable values, sources for the values, and the probability distributions used in the model to estimate the number of infants infected with HIV in the United States by year, 2001-2005

<table>
<thead>
<tr>
<th>Variable</th>
<th>Source</th>
<th>Probability distribution</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants infected through perinatal exposure</td>
<td>33 States with HIV infection reporting, 2001-2005</td>
<td>Poisson</td>
<td>White* = 42, Black = 289, Hispanic = 72, Other = 12</td>
</tr>
<tr>
<td>Proportion of all HIV-infected infants in the United States that occurred in the 33 states</td>
<td>Proportion of perinatally AIDS cases in the United States that occurred in the 33 states, 2001-2005</td>
<td>Binomial</td>
<td>White = 54/84* (64), Black = 277/381 (.73), Hispanic* = 76/107 (.71), Other = 4/13 (.31)</td>
</tr>
<tr>
<td>Reporting completeness: proportion of infected infants that were reported to the surveillance system within 4 years after birth</td>
<td>Evaluations of completeness of the HIV reports17,23</td>
<td>Triangular</td>
<td>Value = .85, Range = .70-.99</td>
</tr>
<tr>
<td>Reporting delay</td>
<td>Proportion of all infants who will be reported within 4 years of the birth year, based on 2001 birth cohort (see Table 2)</td>
<td>Binomial</td>
<td>Proportion reported within: Year of birth, .24, 1 Year after birth, .70, 2 Years after birth, .89, 3 Years after birth, .94, 4 Years after birth, 1.00</td>
</tr>
</tbody>
</table>

* White and black patients are non-Hispanic. The “other” category includes Native American, Asian, Pacific Islander patients and patients whose ethnicity is unknown.
† The race-specific ratios are the number of perinatal AIDS cases that were reported in the 33 states with HIV infection divided by the number of AIDS cases in the entire United States.
necessary calculations. Monte Carlo techniques were used to conduct the sampling. The distribution of the values for each output estimate reflects the overall uncertainty that is associated with the input values. Ninety-five percent confidence intervals (95% CI) were derived by the identification of the 2.5 and 97.5 percentile values for the distribution of computational results from the @RISK simulations.

**Results**

**Trends in perinatal AIDS cases from 50 states and the District of Columbia**

The number of perinatal AIDS cases peaked in all 50 states and the District of Columbia in 1992. From 1992 through 2004, 4805 perinatal AIDS cases were diagnosed in children <13 years old. However, there was a 95% decrease from 1992, when 858 cases were diagnosed, to 2004 when only 41 cases were diagnosed (Figure A). This represented a 22% year over year decline for this metric (95% CI, 22-24).

Cases among black children constituted 67% of the total for entire period. There was little annual variation in this proportion (Figure B). Correspondingly, there was also little variation in the APD in any of the 3 major racial and ethnic groups (Figure B; black, 21 cases [95% CI, 18-24]; white, 23 cases [95% CI, 20-26]; Hispanic, 22 cases [95% CI, 19-25]). Among Asian and Pacific Islanders (data not shown in the Figure because of small numbers), there was also a significant decline (APD, 18; 95% CI, 5-26), even though only 33 cases were diagnosed over the entire period. Only 16 cases were diagnosed among Native American patients, which resulted in an imprecise assessment of the overall trend (APD, 7; 95% CI, 5-18).

Notable regional differences in trends existed in the United States (P < .05, for homogeneity). These regions are defined by the National Center for Health Statistics. In the south (APD, 20; 95% CI, 18-23) and northeast (APD, 24; 95% CI, 21-27) United States, comparable numbers of cases were diagnosed during the 13 years that were analyzed, and the declines were similar (Figure C). However, the western (APD, 19; 95% CI, 15-22) and midwestern (APD, 18; 95% CI, 13-22) United States had fewer cases and smaller relative declines in the case counts.

There were no notable differences in the magnitude or trends in case counts between male and female patients during this period (Figure D).

**Perinatal HIV infection cases in 33 states with name-based reporting**

The number of HIV infection cases that was attributed to perinatal exposure in the 33 states that reported data to the CDC is displayed on the basis of the year of birth and the year the cases were reported to the surveillance programs (Table 2). The presence of maternal antibodies to HIV in the newborn infant complicates the diagnosis of perinatal HIV infections; unless repeated viral detection tests (eg, polymerase chain reaction for RNA or DNA) are positive, the current case definition requires as many as 18 months to diagnose infection definitively on the basis of the results of standard antibody tests. Therefore, a substantial number of infants who were born in 2001 were not reported until 2005 (ie, 10 cases). However, trends in the number of cases by year of birth can be inferred by the assessment of the diagonal cells from left to right. For exam-
Number of perinatally infected infants by year of birth in the year of the report to the national database among 33 states with HIV infection report that have reported since 2001

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>Year of report</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td></td>
<td>39</td>
<td>74</td>
<td>31</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td>—</td>
<td>29</td>
<td>50</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td>—</td>
<td>—</td>
<td>25</td>
<td>34</td>
<td>27</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>25</td>
<td>33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n</th>
<th>N (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>162</td>
</tr>
<tr>
<td>2002</td>
<td>109</td>
</tr>
<tr>
<td>2003</td>
<td>86</td>
</tr>
<tr>
<td>2004</td>
<td>58</td>
</tr>
</tbody>
</table>

*C. confidence interval

Total number of actual cases reported in birth cohort from 33 states (n).

Data from 33 states with HIV infection that were reported were extrapolated to the entire United States (N). Estimates include adjustments for delays in reporting and underreporting of cases.

Comment

These results, based on the most extensive data available to date regarding the direct population-based reporting of HIV infection and morbidity, suggest that the incidence of perinatally acquired HIV infection continues to decline in the United States. The trends in perinatally acquired AIDS are more difficult to interpret because the observed decreases could result from improved treatment of infected infants that forestalls the development of the sequelae that are associated with HIV. However, in conjunction with the data on infections from the growing number of areas such as New York State that have a history of substantial incidence and morbidity from this route of infection, it appears that the AIDS trends arise from both a decrease in infections and a potential success in slowing disease progression. There were statistically significant regional differences observed in the AIDS trends. However, the absolute differences in these geographic trends were modest (range, 18%-24% per year). Smaller declines occurred in areas with smaller numbers of cases. This may reflect a statistical “floor” whereby the relative rate of change decreases because the number of events becomes small and further reductions can be difficult. The continued decline in annual perinatal HIV infections reflect a dynamic that was first observed in the mid 1990s when the CDC estimated that the number of children who had been born with HIV had fallen from a high of 1650 in 1991 to 480 in 1996. By 2000 the CDC estimated that the number decreased further to between 280 and 370 infections.

The estimated decrease in perinatal HIV infections could arise through 1 or some combination of mechanisms. The first is a decrease in the number of births to HIV-infected women or better prevention efforts among HIV-infected women who become pregnant and deliver. The number of births could have declined either because of a decrease in birth rates among these women or a decrease in the population of infected women. The latter explanation is unlikely because survival among HIV-infected women continues to improve and despite evidence of recent modest declines in the number of new diagnoses in this group, the overall prevalence in women continued to increase during the early years of the 21st century. This growing prevalence was identified by the CDC in 2000 as the major reason that the number of perinatal infections could be reduced only by another one-third, even if all women who delivered were provided optimal antiretroviral therapy. However, data from New York State, where essentially all newborn infants are tested for HIV by the health department, demonstrate that the number of births to infected women decreased by 60% from 1990 through 2003, which suggests that at least in 1 high morbidity area declining birth rates among HIV-infected women is making a major contribution to the decrease in perinatal HIV cases.

The second possible explanation that perinatal HIV infections continue to decrease is improvement in the provision of appropriate antiretroviral therapy to HIV-infected women who become pregnant and deliver. Such treatment is contingent on the identification of these women before or during pregnancy through HIV testing. CDC surveillance data from 28 states with name-based reporting of infants who were born to HIV-infected women (ie, HIV exposure...
reporting) during the period 2001-2004 demonstrated that the proportion of infected mothers that was reported in these areas who were diagnosed before or at delivery was quite high at 93%. This is consistent with data from 24 states that participated in the CDC Enhanced Perinatal Surveillance system in which, from 1999-2001, the proportion of infected mothers who were diagnosed during or before delivery was 94%, and approximately 80% of women received antiretroviral prenatally or during the intrapartum period.

Establishing the specific determinants of the trends in perinatal incidence would require more comprehensive information about birth trends in HIV-infected women and the patterns of care in these women. Federal funding for anonymous antenatal seroprevalence surveys in the United States is prohibited currently by Congress. Therefore, the only feasible source of information for the elucidation of the determinants of perinatal infections has to be derived from monitoring perinatally exposed newborn infants. The CDC currently supports 10 states and the cities of Chicago and Philadelphia and Puerto Rico to continue the Enhanced Perinatal Surveillance program. This system collects extensive information regarding treatment of the mother and infant before and after delivery (special Surveillance supplement). In addition, the CDC, the Council of State and Territorial Epidemiologists, and the American Academy of Pediatrics recommend that children who are born to HIV-infected mothers should be reported and followed for infection and potential long-term effects of exposure to HIV and antiretroviral. However, because >90% of these children will not be infected, there are concerns about privacy that make the universal implementation of these recommendations unlikely.

Without universal perinatal HIV exposure reporting, population surveillance of perinatally infected children will remain the fundamental metric for the definition of the status and success of efforts to prevent this route of transmission. Direct HIV infection reporting data from only 33 states could be used in this analysis. The imprecision of the case counts for more recent years was further exacerbated by the fact that definitive determination of the infection status for a newborn infant who was perinatally exposed to HIV can require up to 18 months of monitoring. Therefore, estimates of the number of newly infected newborn infants in any temporally proximate period must be adjusted for inevitable delays in diagnosis and reporting to public health officials. Further complicating this issue is the small number of these infections, which makes the statistical extrapolations dependent on a limited set of small counts. Hence, strong confidence that these declines reflect success in prevention will require observation for several more years. However, as of July of 2006, 45 states had legal authority to conduct name-based HIV infection surveillance, and the recent federal legislation reauthorizing the Ryan-White act essentially has required states to implement HIV reporting to receive this federal funding for treatment and care of HIV-infected patients. Therefore, the precision and validity of these numbers should improve rapidly over the next several years and provide critical inputs for focusing resources to sustain and augment prevention efforts that already have proved successful and ameliorate problems when they are identified.

ACKNOWLEDGMENT

The authors acknowledge the commitment, skill, and tireless work of the state and local HIV/AIDS Surveillance Coordinators who collect and vigorously protect the privacy and confidentiality of the data that were used in this analysis.

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Utility of antenatal HIV surveillance data to evaluate prevention of mother-to-child HIV transmission programs in resource-limited settings

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In many resource-limited countries with generalized HIV epidemics, defined as HIV prevalence greater than 1% among pregnant women,1 HIV sentinel surveillance is conducted in antenatal clinics (ANCs). About 70% (range 30-90%) of women in resource-limited countries make at least 1 ANC visit during pregnancy.2 ANC sentinel surveillance has been used widely for more than 2 decades to estimate the HIV prevalence in the general population and to monitor the impact of HIV prevention programs. Unlinked anonymous testing (UAT) is the most common strategy used for ANC sentinel surveillance. With UAT, leftover blood routinely collected from women at the first antenatal care visit is stripped of all identifiers and tested for antibodies to HIV.1 Testing is unlinked and anonymous; therefore, informed consent is not obtained and test results cannot be provided to participants.

Programs for the prevention of mother-to-child HIV transmission (PMTCT) are also conducted in antenatal clinics and target the same group, pregnant women, as ANC sentinel surveillance. With increased funding and attention,3,5 and in line with the goal of the United Nations General Assembly Special Session on AIDS in 2001 to reduce mother-to-child HIV transmission by 50% by 2010,6 many resource-limited countries have begun expanding PMTCT programs, although global PMTCT coverage is still low at 8%.7,8 Expansion of PMTCT services increasingly includes clinics at which ANC sentinel surveillance is conducted, resulting in increased availability of HIV testing data from both PMTCT programs and ANC sentinel surveillance in the same clinic population.

Operational similarities and distinctions between PMTCT programs and ANC sentinel surveillance are outlined in Table 1. In summary, HIV testing in PMTCT programs is voluntary; with all ANC clients either routinely recommended HIV testing with a right to refuse testing ("opt-out") or required to specifically request to be tested ("opt-out") or required to specifically request to be tested.
in”). Therefore, the acceptance or uptake for HIV testing varies widely by clinic and country. Ideally, the HIV test is offered at the first ANC visit, because many women may make only 1 ANC visit during pregnancy, although this does not always happen on that first visit because of the lack of resources. The HIV test is usually performed within the PMTCT clinic or a related laboratory. Women who accept testing have an opportunity to receive their results and benefit from PMTCT interventions, including antiretrovirals for PMTCT and prevention, treatment, care, and support services for themselves and their families. Typically, PMTCT programs enter individual data into ANC registers and logbooks, which are aggregated as a monthly or quarterly report and sent to the Ministry of Health at the district and national levels, where they are compiled.

In contrast, ANC sentinel surveillance consecutively samples leftover blood routinely collected for various pregnancy tests on all new ANC attendees until the target sample size is reached. Unique identifiers, such as name and hospital number, are removed before the HIV test is done. HIV testing is usually performed outside the clinic, usually in a central reference laboratory, with strong quality assurance measures. For each sampled ANC surveillance client, individual data, such as age, parity, and gravidity, are abstracted or transcribed into individual data forms without identifiers, entered electronically, and analyzed. The Figure shows the flow chart for conducting ANC surveillance within a PMTCT service site.

There have been recent evaluations of the utility of PMTCT program data for the purpose of surveillance because of ethical concerns about the inability to provide UAT-based test results and services to ANC clients; the introduction of rapid syphilis testing with limited access to leftover blood; and the larger number of PMTCT sites and sample sizes, compared to ANC surveillance. However, the limited published results to date suggest that whereas PMTCT program data often include large numbers of women, their data quality, availability, and the uptake of PMTCT HIV testing must be considered when using them for surveillance. The variable HIV testing uptake in PMTCT programs may compromise the use of PMTCT data for ANC sentinel surveillance because not all ANC attendees accept to be tested for HIV.

On the other hand, given the uneven quality of PMTCT clinic data, the varying uptake of PMTCT services and the increasing availability of PMTCT services at ANC sentinel surveillance sites, it is useful to assess whether ANC sentinel surveillance data can be used to evaluate how PMTCT programs perform at the first ANC visit. Some countries have added PMTCT variables into their ANC sentinel surveillance data forms. These data can provide information on whether the HIV prevalence among

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**TABLE 1**

Comparison of PMTCT programs and ANC sentinel surveillance

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PMTCT program</th>
<th>ANC sentinel surveillance system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To provide PMTCT interventions to pregnant women based on their HIV status</td>
<td>To document HIV prevalence and monitor trends among pregnant women</td>
</tr>
<tr>
<td>Type of site</td>
<td>Antenatal clinics, labor and delivery wards, and postdelivery units</td>
<td>Antenatal clinics</td>
</tr>
<tr>
<td>Number of sites and representativeness</td>
<td>Goal in most countries: to cover all ANC clinics and delivery wards</td>
<td>Systematic, convenience sample, usually with goal to achieve geographic representation</td>
</tr>
<tr>
<td>Timing</td>
<td>Year round</td>
<td>Annual or biennial for about 3-4 months</td>
</tr>
<tr>
<td>Clients tested for HIV (sample size)</td>
<td>HIV testing is usually offered to all pregnant women attending ANC. Acceptance of HIV test is voluntary. HIV test uptake varies by site.</td>
<td>Sample size is calculated on the basis of an estimated HIV prevalence. Typically 200-500 first time per pregnancy ANC attendees per clinic</td>
</tr>
<tr>
<td>Data collection</td>
<td>Varies across sites. Typically individual data include age, parity, HIV counseling, tested, posttest counseling, HIV test results, syphilis status: receipt of PMTCT interventions including ARVs are entered into a register or log book. The data are aggregated or summarized into a monthly or quarterly report.</td>
<td>Uniform across sites. Typically collects individual data on special abstraction form including demographics, gravidity, parity, syphilis status, HIV test results from UAT testing.</td>
</tr>
<tr>
<td>Data quality</td>
<td>Variable</td>
<td>Often high-quality data</td>
</tr>
<tr>
<td>Quality assurance (QA) and quality control (QC) for HIV testing</td>
<td>Variable</td>
<td>Often high-quality QA/QC protocols</td>
</tr>
<tr>
<td>Written protocols for data collection</td>
<td>Variable</td>
<td>Always</td>
</tr>
<tr>
<td>Provision of services</td>
<td>Yes, including posttest counseling, provision of test results, PMTCT interventions, provision or referral to ARV treatment and care and support services</td>
<td>No</td>
</tr>
</tbody>
</table>
women who participate in PMTCT or accept HIV testing (ie, acceptors) is lower or higher, compared with HIV prevalence in women who do not participate in PMTCT or refuse HIV testing as part of PMTCT services (ie, refusers). These data are not available from routine PMTCT records and can help countries estimate the number of HIV-positive women not identified by the PMTCT program and the related lost impact (ie, number of infant infections that could have been averted if all HIV-positive mothers were identified in the PMTCT program). This information can be useful for planning and setting PMTCT service targets. However, the experiences in using these data have not been documented. Presented here are case studies of efforts to use ANC sentinel surveillance data to monitor and evaluate PMTCT programs and a discussion of approaches to using ANC sentinel surveillance to enhance and plan PMTCT programs.

**Materials and Methods**

We analyzed data from Ethiopia, Kenya, and Zimbabwe. Ethiopia and Kenya added PMTCT variables to their ANC sentinel surveillance data form. Variables added were whether the client sampled for ANC sentinel surveillance accepted to participate in the PMTCT program (Ethiopia) or whether the client was offered an HIV test through the PMTCT program and the PMTCT-related HIV test result (Kenya). Zimbabwe does not collect PMTCT data as part of surveillance, but we were able to utilize the HIV prevalence estimates from ANC sentinel surveillance sites and the annual PMTCT program data for this analysis.

Using the ANC sentinel surveillance data from sites with PMTCT services, we estimated the overall burden of disease based on the HIV prevalence among all new ANC clients enrolled in surveillance. For Kenya and Ethiopia, we estimated the percentage of new ANC clients who participated or tested for HIV under the PMTCT program as well as the pooled and the median (interquartile range) HIV prevalence among clients who accepted PMTCT, compared with prevalence among those who were not offered PMTCT services or HIV testing or who refused the HIV test.

Both the pooled and median HIV prevalence data are presented for several reasons. The pooled data are appropriate for use when limiting the interpretation only to the sentinel sites sampled, and is also useful in calculating infant infections averted. The median prevalence accounts for outlying larger clinics and has been used for years by sentinel surveillance to extrapolate to the general population, which we did not do here for Kenya and Ethiopia but show for comparative purposes. We calculated the number of additional infant HIV infections that could have been averted among HIV-positive women not identified by PMTCT (ie, women not offered PMTCT services or HIV testing or who refused the HIV test as part of PMTCT).

For the calculation of infant infections averted or that could have been averted, we multiplied the number of HIV-positive women by 35%, the standard estimated percentage of HIV-positive women who will transmit the virus to their infants without PMTCT interventions in resource-limited settings. Next, we multiplied the result by 41%, the efficacy of single-dose nevirapine (SDNVP) to prevent mother-to-child HIV transmission. SDNVP was the main antiretroviral (ARV) prophylaxis regimen for PMTCT in these countries during the reported surveillance rounds. The results from Kenya and Ethiopia were extrapolated from the 3-month surveillance period to a year to determine number of infections that could be averted in a year at these sites.

Zimbabwe does not collect PMTCT data on its surveillance form, but we used the 2004 PMTCT program summary data and ANC surveillance data from the 19 sentinel surveillance sites. We multiplied the HIV prevalence from the ANC surveillance data with the number of new ANC attendees in all PMTCT sites in 2004 to get an estimate of the number of HIV-positive pregnant women attending all PMTCT sites. We compared the estimated number of HIV-positive pregnant women based on surveillance data with the actual number of HIV-positive women identified through the PMTCT program to estimate the percentage of HIV-positive women who were not identified (not tested for HIV) by the PMTCT program. Based on our assumption of 35% transmission risk and 41% SDNVP efficacy, we estimated the number of infant infections that

*Sites with both PMTCT and ANC sentinel surveillance.

1. In some settings, not all women are offered HIV test for PMTCT due to lack of resources e.g. staff, test kits, thus their HIV status is unknown at the time of first visit.

2. Socio-demographic and PMTCT information on first time attendees, irrespective of whether they accept or refuse or were not offered PMTCT HIV testing are abstracted onto surveillance form.
could have been averted among women not identified or missed by the PMTCT program in 2004.

**Results**

**Kenya**

In Kenya, ANC sentinel surveillance is conducted annually.20 Pilot programs for PMTCT began in 1999 and national scale-up began in 2002. In 2001, 3 of 35 sentinel surveillance sites offered PMTCT services. By 2005, there were more than 1100 PMTCT sites in Kenya, and all sentinel surveillance sites (n = 43) offered PMTCT services, which includes routinely recommending HIV testing to ANC clients with a right to opt out. Between 2004-2005, the following PMTCT variables were added to the sentinel surveillance data form: whether HIV testing was offered; whether the client accepted the test; and the PMTCT-related test result.18

During the 2005 survey period (approximately 3 months), a total of 13,026 women were consecutively sampled for ANC sentinel surveillance at the 43 sites. Of these, 9690 (76%) were offered and accepted HIV testing under the PMTCT program; 2988 (23.6%), either refused testing or were not offered HIV testing; and there were 348 women with missing data.

The overall pooled HIV prevalence from the ANC sentinel surveillance was 7.3%. The HIV prevalence was 5.4% among those who were not offered testing or refused the test, compared with 8.0% among women who accepted HIV testing from the PMTCT program (Table 2). Similarly, the median HIV prevalence among acceptors was higher than among refusers and women not offered testing. (Table 2). Of all HIV-infected women in the ANC sample, 17.3% (162/939) were not HIV tested as part of PMTCT during the surveillance period.

Based on the data and assumptions depicted in Table 2, 329 HIV-positive women would be expected to transmit the virus to their infants and 135 infant infections would have been averted if all HIV-positive women had received SDNVP at dual sites (ie, sites with both PMTCT and sentinel surveillance).

**Ethiopia**

In Ethiopia, ANC sentinel surveillance is conducted biennially for a period of approximately 3 months. Ethiopia’s 2005 ANC sentinel surveillance data collection form included 1 PMTCT variable: whether the enrolled client participated in PMTCT (ie, agreed to be referred to receive PMTCT services). ANC sentinel surveillance was conducted at 43 rural and 36 urban sites. Of these, 36 (12 rural and 24 urban) had PMTCT services. These 36 sites with ANC sentinel surveillance and PMTCT services included 12,316 of the 28,572 women (43%) sampled by the national ANC surveillance system.

The percentage of clients participating in PMTCT at the 36 sites was 47% (58% among rural; 41% among urban sites). The remaining 53% of women were either not offered PMTCT services because of lack of availability of service (11%) or refused PMTCT participation (42%). As shown in Table 2, the overall pooled HIV prevalence from the ANC sentinel surveillance was 7.4%. The prevalence was higher, 8.2% (536/6542), among women who did not participate or for whom services were not available, compared with 6.4% (370/5774) among women who participated in PMTCT. Similarly, the median HIV prevalence among refusers and women not offered testing was higher than among acceptors (Table 2). Of all HIV-infected women in the ANC sample, 59% were missed by the PMTCT program at the time of surveillance.

Based on the data and assumptions depicted in Table 2, 317 HIV-positive women were at risk of transmitting the virus, and an estimated 130 infant infections could have been averted if all HIV-positive women had received SDNVP. Given that 17% of the HIV-positive women did not test under PMTCT, we estimate that an additional 23 infant HIV infections could have been averted had the women’s serostatus been identified and they had received SDNVP. Extrapolating to a full year, about 93 infant HIV infections that should have been averted occurred at the 43 sites.

**Zimbabwe**

In Zimbabwe, ANC sentinel surveillance is conducted biennially, with the most recent survey in 2004. In that year, the ANC sentinel surveillance included 19 antenatal clinics (7 urban, 5 periurban, and 7 rural), all of which provided PMTCT services. In total, 800 of 1383 antenatal clinics throughout the country offered PMTCT services in 2004, but only 265 offered comprehensive PMTCT services (HIV counseling, on-site testing, and SDNVP). The remaining clinics provided basic ANC services including information on PMTCT and referral to a clinic with services for an on-site HIV test and SDNVP or transport of blood for off-site HIV testing and SDNVP provided to HIV-positive clients.

We used ANC surveillance prevalence estimates to estimate prevalence among new ANC clients attending PMTCT sites because the 2004 ANC sentinel survey in Zimbabwe did not collect PMTCT information on the surveillance data forms. Table 3 shows the application of the 2004 HIV prevalence estimates from ANC sentinel surveillance for monitoring the PMTCT program in Zimbabwe. The HIV prevalence was multiplied by the number of new ANC attendees in all PMTCT sites (sites that provided any PMTCT service including clinics that could refer pregnant women to clinics with PMTCT) to provide an estimate of the number of HIV-positive pregnant women attending ANC in all PMTCT sites. By comparing this number to the number of HIV-positive women identified through the PMTCT program, we estimated that approximately half of the HIV-positive women attending PMTCT sites in Zimbabwe in 2004 were tested for HIV. By using a 35% transmission risk and 41% SDNVP efficacy, we estimated that 12,162 HIV-positive women attending PMTCT sites but not identified by
### TABLE 2

#### Estimating HIV-positive women not identified through PMTCT in Kenya and Ethiopia in 2005 using ANC surveillance

<table>
<thead>
<tr>
<th></th>
<th>Kenya</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Median site %</td>
<td>Interquartile range</td>
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<tr>
<td><strong>ANC surveillance sites</strong></td>
<td>43</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td><strong>New ANC attendees enrolled in ANC surveillance sites</strong></td>
<td>13026</td>
<td></td>
<td></td>
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<tr>
<td><strong>Dual sites</strong>*</td>
<td>43</td>
<td>100%</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>New ANC attendees enrolled in surveillance at dual sites</strong></td>
<td>13026</td>
<td>100%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Accepted PMTCT or HIV testing as part of PMTCT</strong></td>
<td>12678</td>
<td>76.4%</td>
<td>84.2%</td>
<td>53.2%-99.3%</td>
<td>12316</td>
<td>46.9%</td>
<td>44.3%</td>
<td>24.8%-72.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Refused PMTCT participation, HIV testing, or service not offered</strong></td>
<td>12678</td>
<td>23.6%</td>
<td>15.8%</td>
<td>0.7%-46.8%</td>
<td>12316</td>
<td>53.1%</td>
<td>55.7%</td>
<td>27.4%-75.2%</td>
<td></td>
</tr>
<tr>
<td><strong>HIV prevalence among all clients enrolled at dual sites</strong></td>
<td>13026</td>
<td>7.3%</td>
<td>5.3%</td>
<td>3.7%-8.4%</td>
<td>12316</td>
<td>7.4%</td>
<td>7.7%</td>
<td>2.5%-10.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Accepted PMTCT or tested for HIV in PMTCT</strong></td>
<td>9690</td>
<td>8.0%</td>
<td>5.1%</td>
<td>0.0%-8.5%</td>
<td>5774</td>
<td>6.4%</td>
<td>7.0%</td>
<td>2.4%-11.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Refused PMTCT, HIV testing, or service not offered</strong></td>
<td>2988</td>
<td>5.4%</td>
<td>4.7%</td>
<td>1.4%-6.8%</td>
<td>6542</td>
<td>8.2%</td>
<td>7.9%</td>
<td>2.1%-11.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Proportion of HIV-positive women missed by PMTCT</strong></td>
<td>939</td>
<td>17.3%</td>
<td>15.4%</td>
<td>0.0%-52.4%</td>
<td>906</td>
<td>59.2%</td>
<td>52.8%</td>
<td>25.6%-80.6%</td>
<td></td>
</tr>
<tr>
<td><strong>Potential infant infections that can occur with 35% transmission risk in all HIV-positive women (number HIV-positive × 0.35):</strong></td>
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<td></td>
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<td></td>
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<tr>
<td><strong>3-mo surveillance period</strong></td>
<td>329</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Extrapolated to 1 y</strong></td>
<td>1316</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Infant infections that could be averted with use of SDNVP with 41% efficacy (potential number of infant infections × 0.41):</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>3-mo surveillance period</strong></td>
<td>135</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Extrapolated to 1 y</strong></td>
<td>540</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Infant infections not averted among HIV-positive women missed by PMTCT (missed × infant infections that could be averted with SDNVP):</strong></td>
<td></td>
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<td></td>
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<tr>
<td><strong>3-mo surveillance period</strong></td>
<td>23</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Extrapolated to 1 y</strong></td>
<td>93</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

* Sites with both ANC sentinel surveillance and PMTCT service.
the program would have averted an additional 1746 infant HIV infections in 2004 if they had received SDNVP.

**Comment**

These case studies demonstrate the utility of ANC sentinel surveillance data for PMTCT programs in ANCs. The inclusion of simple PMTCT variables in the ANC sentinel surveillance data forms in Ethiopia and Kenya provided an effective tool to monitor and evaluate PMTCT programs in ANCs during the first antenatal visit of pregnant women. All sentinel surveillance sites in Kenya and Zimbabwe now have PMTCT services, providing an opportunity to directly compare the surveillance and PMTCT program data.

There are several advantages to collecting PMTCT-related variables in ANC surveillance. PMTCT is a high-impact program as measured by the number of infant HIV infections that can be averted. The estimates calculated from the number of HIV-positive women tested through UAT but not identified by PMTCT because they refused either PMTCT participation or HIV testing or were not offered PMTCT services permits a measure of the potential number of infections that could have been averted with a fully successful program at current sites. Adding these variables also allows for an estimate of HIV prevalence among refusers, women not offered HIV testing, or HIV-positive women not participating in PMTCT, and can be used by policy makers and clinic managers to determine which ANC sites are missing HIV-positive women who might benefit from PMTCT services.

Because the data can be stratified at the clinic level, it can help PMTCT program managers decide on where to intensify efforts. This kind of evaluation cannot be performed with routine PMTCT program data because HIV prevalence among those not offered or refusing PMTCT is not known. Assuming that ANC surveillance sites are representative of the larger number of clinics and general population, the estimates of the number of women missed and infections not averted can be generalized to all PMTCT sites if the HIV testing uptake is performed with routine PMTCT program data because HIV prevalence among those not offered or refusing PMTCT is not known. Additionally, the ANC HIV surveillance estimates can be applied to the number of annual births to estimate the infant HIV infection burden nationwide and also the potential for preventing infant infections. This analysis can be done with each surveillance round to document trends in PMTCT uptake among HIV-positive women.
Another benefit is the capacity to compare the prevalence among those who accept HIV testing under PMTCT and those who either refuse or who are not offered the test. HIV prevalence was higher in those who were not offered or refused HIV testing in Ethiopia. Conversely, in Kenya, prevalence among acceptors or women participating in PMTCT is higher, which is similar to findings in the literature, and which may reflect an increasing awareness and acceptance of the benefits of PMTCT services.

Additionally, HIV testing performed under the PMTCT program can be compared with HIV testing conducted under UAT sentinel surveillance, which is often done in a central reference laboratory. If the testing algorithms are similar in PMTCT program and ANC surveillance and all test results are available, this type of comparative analysis can be done. Kenya collects the related PMTCT test results on the surveillance form, but not all results were available in 2005 and thus not presented in this paper. The comparison of the 2 HIV test results (done under PMTCT and UAT) for each client can provide some information on the quality of test done by the PMTCT program and used for improvement.

The difference between HIV test acceptance in Ethiopia and Kenya (48% vs 81%) may be attributed to Ethiopia’s opt-in testing strategy in contrast to Kenya’s opt-out strategy. The opt-out approach to HIV testing results in greater acceptance and uptake for PMTCT. Ethiopia is currently transitioning to the opt-out policy and should consider similar analyses of the data a year after this new policy takes effect to evaluate its impact on HIV testing uptake; prevalence between participants and nonparticipants of PMTCT services; and the impact on aversion of infant HIV infection.

Although Zimbabwe did not collect PMTCT data during ANC surveillance, PMTCT and ANC sentinel surveillance data sets were compared, permitting the estimation of the number of HIV-positive pregnant women attending ANC and the percentage of HIV-positive women not identified by the PMTCT program. As ANC surveillance becomes more robust, population-based estimates and extrapolations to program data will become more accurate. Ideally, countries should include PMTCT variables on their ANC surveillance forms; however, at sites at which this is not available, the type of analysis presented here for Zimbabwe can provide useful estimates.

There are a number of limitations to these analyses. Although ANC surveillance sites have been used for decades to provide information on trends and serve as a reasonably robust and representative sample for estimating HIV prevalence among pregnant women, sites are conveniently selected and are not a true random sample. For Zimbabwe, we extrapolated the prevalence to all PMTCT sites because we had the HIV testing uptake data; however, we realize that heterogeneity of HIV prevalence at all sites and knowledge of HIV prevalence at each site are preferred. In addition, some women who were not HIV tested by the PMTCT program during the surveillance period might already have a documented HIV-positive status. Furthermore, others may have been tested at subsequent ANC visits, which could bias the analyses toward an underestimate of PMTCT uptake and an overestimate of infant infections that could have been averted. We relied on multiple assumptions and were unable to extrapolate to all PMTCT sites because data on HIV testing uptake for each site were unavailable. The variable from Ethiopia, “participation in PMTCT,” is vague and does not provide

### TABLE 4

<table>
<thead>
<tr>
<th>Proposed questions for UAT form</th>
<th>PMTCT variable to add to the form</th>
<th>Monitoring and evaluation indicator</th>
</tr>
</thead>
</table>
| Was the woman offered HIV testing under the PMTCT program? | Offered HIV testing in PMTCT:  
⇒ Yes, no, no PMTCT | Proportion of women offered HIV testing  
Proportion of women not offered HIV testing |
| Did the woman accept HIV testing? | Accepted HIV testing in PMTCT:  
⇒ Yes, no | HIV prevalence in women who accepted testing  
HIV prevalence in women who refused testing  
HIV prevalence in test refusers as compared with test acceptors  
Sociodemographic characteristics of women who refuse HIV testing  
Proportion of HIV-positive women missed by the PMTCT program  
Number of preventable infant HIV infections |
| What was the PMTCT HIV test result? | PMTCT HIV test result (only if rapid HIV test is done on site):  
⇒ Positive, negative, indeterminate, don’t know | External quality assurance for laboratory testing in PMTCT when test result is compared with UAT HIV test result |
detailed information on the number of women who actually agreed to the test. More accurate results can be obtained if countries utilize more specific variables like those from Kenya. Despite these limitations, these estimates provide important and useful guidance for monitoring and evaluating PMTCT programs.

**Recommendations**

Comparing ANC sentinel surveillance and PMTCT program is relatively simple and can provide important information. Countries should be encouraged to incorporate PMTCT variables in ANC sentinel surveillance. We suggest several PMTCT variables and their related indicators (Table 4). These recommendations are in line with recent recommendations from the World Health Organization Regional Office for Africa’s Technical Network Group on sexually transmitted infections and HIV surveillance, which will be released in mid-2007.

We also recommend that countries should prioritize PMTCT implementation at ANC sentinel surveillance sites. This will ensure that ANC clients sampled for UAT are given the opportunity to learn their HIV status and receive appropriate services. However, efforts should be taken to ensure that the protocols for implementing ANC sentinel surveillance are retained when PMTCT programs are introduced. Anecdotal evidence suggests that introduction of PMTCT programs at ANC sentinel sites creates additional work for staff and can cause confusion in sampling, which can bias the HIV prevalence results. Additional resources with improved supervision, training, and support during the duration of ANC sentinel surveillance will aid in preventing sampling confusion and the risk of related bias.

Using ANC sentinel surveillance to monitor PMTCT should not undermine routine PMTCT program monitoring systems. PMTCT program managers should improve the quality of routine PMTCT data collection systems through training and proper staff supervision. As the PMTCT data quality improves and HIV testing uptake continues to increase with more countries implementing an opt-out testing strategy, evaluations should be conducted to determine how well the PMTCT program data can complement or replace the ANC sentinel surveillance data.

At this time, ANC sentinel surveillance continues to play an important role in monitoring the HIV epidemic in many countries. ANC sentinel surveillance can be used to monitor, evaluate, and enhance PMTCT programs by including PMTCT variables in ANC surveillance data collection forms or by comparing both data sets and performing simple analyses as shown in the Zimbabwe example in which we were able to compare data from surveillance and PMTCT program. We propose that these types of analyses be used to evaluate PMTCT uptake; estimate the number of HIV-positive women missed by the PMTCT program at first ANC visit; assess HIV prevalence among acceptors and refusers; and estimate PMTCT program impact and missed program impact (ie, the potential number of infections that could have been averted). This would also require consideration of the efficacy of various ARV regimens for PMTCT that are increasingly available in many of these countries. The findings from the country case studies can be followed up over time to determine improvement in PMTCT programs and used by policy makers to guide PMTCT scale-up and program planning.

**Acknowledgment**

The authors acknowledge the input and support from the Ministry of Health officials from Kenya, Ethiopia, and Zimbabwe who provided the data for the analysis and Jelaludin Ahmed of the Centers for Disease Control and Prevention Ethiopia, who provided technical input, support, and guidance on this paper. In addition, the authors thank Dr Theresa Diaz, Dr Nathan Shaffer, Ray Shareshi, and Meade Morgan (Centers for Disease Control and Prevention/Global AIDS Program Atlantaj and Dr Garcia Celaje, Jesus Maria, and Dr Peter Ghys (World Health Organization/Geneva) for their technical reviews, suggestions, and comments.

**References**


Recommendations for human immunodeficiency virus screening, prophylaxis, and treatment for pregnant women in the United States

Denise J. Jamieson, MD, MPH; Jill Clark, MPH; Athena P. Kourtis, MD, PhD, MPH; Allan W. Taylor, MD, MPH; Margaret A. Lampe, MPH, RN; Mary Glenn Fowler, MD, MPH; Lynne M. Mofenson, MD

R ecommendations regarding human immunodeficiency virus (HIV) screening, prophylaxis, and treatment of pregnant women have evolved considerably in the United States over the last 25 years, reflecting changes in the epidemic and the science of prevention. Not long after acquired immunodeficiency syndrome (AIDS) was first described in 1981, the possibility of mother-to-child transmission of the new syndrome was proposed.1 Scientific consensus that gathered to support this theory included reports of infants with AIDS who had not had significant contact with their mothers after delivery, which suggested that infection had occurred before or during birth.2 Even though significant gaps still exist in our knowledge of the exact timing and mechanisms of mother-to-child transmission of HIV, substantial evidence has accumulated to document the risk of mother-to-child transmission, and concerted research efforts have brought about a dramatic decrease in such transmission, at least in the industrialized world, with interventions such as combination antiretroviral prophylaxis, cesarean delivery, and avoidance of breastfeeding.3 In addition, the treatment of HIV disease during pregnancy has changed considerably, with an increasing proportion of women receiving highly active antiretroviral therapy throughout pregnancy.3 This article describes the evolution of US recommendations for HIV screening, prophylaxis, and treatment of HIV-infected women that have contributed to this remarkable public health success in the arena of mother-to-child HIV transmission.

The Evolution of the Centers for Disease Control and Prevention (CDC) HIV Screening Guidelines for Pregnant Women

The CDC released its first set of recommendations for HIV testing of pregnant women in 1985.4 These recommendations acknowledged that the only available strategy for reducing the risk of perinatal transmission was pregnancy prevention and that the benefits of knowing one’s HIV status were few, given the lack of treatment options. The 1985 recommendations identified certain groups of women who were at high risk for HIV infection who should be counseled regarding HIV and offered testing. These groups included women with signs and symptoms of infection,
intravenous drug users, women who were born in countries with a higher burden of heterosexual transmission of HIV, sex workers, and sex partners of men at increased risk. Nonpregnant women with positive test results could be encouraged to delay pregnancy. However, women who were already pregnant could be offered only additional medical and support services to manage opportunistic infections and psychologic concerns and be advised not to breastfeed their infant because of the potential for transmission of HIV through breastfeeding. These guidelines did not endorse routine testing of all women or counseling and testing among women who were considered not at high risk. This recommendation was motivated by concern about the interpretation of test results in low prevalence populations (ie, the repercussions of false positive results in an environment in which considerable stigma and fear surrounded a diagnosis of HIV infection).

Only a few years passed, however, before it became apparent that risk-based screening was failing to identify substantial numbers of infected women. Many physicians and public health officials believed that being able to notify a woman of her HIV status was important enough to justify expanded screening beyond defined risk groups, despite the few options for treatment of a woman’s own disease or prevention of perinatal transmission.

In 1994, 1 of the most significant breakthroughs in the history of the HIV/AIDS epidemic was announced. On February 21, 1994, the Pediatric AIDS Clinical Trials Group (PACTG) announced results of a randomized, double-blinded clinical trial, PACTG 076, that had demonstrated that a 3-part regimen of zidovudine (starting in the second trimester of gestation and continuing in labor and to the infant for 6 weeks after birth) was effective in lowering the risk of perinatal HIV transmission by approximately two-thirds. In addition to being effective, zidovudine was found to be safe in this setting, with no serious or short-term side effects of zidovudine therapy detected for women or their infants when compared with placebo.

The announcement of an intervention that offered significant protection against HIV infection for infants was a turning point for perinatal HIV prevention strategies. Although stigma and discrimination against persons with HIV and AIDS were still present, there were now real benefits to learning one’s HIV status. Treatments for the protection of an individual’s health had been available for several years, and now prophylaxis could be provided to pregnant women to lower the risk that they would pass the virus to their children.

In response to this development, the CDC developed new recommendations for HIV testing among pregnant women in 1995. For the first time, the US Public Health Service recommended routine HIV counseling and voluntary testing for all pregnant women. Increasing scientific data on the safety and effectiveness of zidovudine for prevention of mother-to-child HIV transmission and some advances in advocacy and protections for persons who were infected with HIV had shifted the balance of benefits and risks. However, these guidelines maintained a strong emphasis on the provision of counseling before and after testing, specific informed consent, and the voluntary nature of testing. The recommendations stated that pretest counseling should include information on HIV risk behaviors, the risk of mother-to-child transmission if the woman were infected, and the availability of therapy to reduce this risk. Provisions were also included to ensure that women who declined testing, or declined treatment if positive, were not denied care or subjected to discrimination. After the receipt of positive HIV test results, the guidelines stated that women should receive posttest counseling that included an explanation of the clinical implications of a positive test result, information about HIV-related medical and other intervention services, the risk for mother-to-child HIV transmission and ways to reduce this risk, the prognosis for infants who become infected, reproductive options, recommendations to abstain from breastfeeding, and an assessment of the potential for negative psychologic and social effects that result from HIV infection.

In 1996, Congress passed the Ryan White CARE Act, which provided funding for testing and treatment and additional strategies to combat the HIV/AIDS epidemic. A provision of this legislation called on the Institute of Medicine to conduct an evaluation of state efforts to reduce mother-to-child HIV transmission and an analysis of the existing barriers to further reductions in transmission in the United States. The committee found that, despite considerable efforts to implement the US Public Health Service recommendations, the number of children who were born with HIV remained too high, often because of lack of timely diagnosis of maternal HIV infection. Their central recommendation was to implement universal HIV testing with patient notification as a routine component of prenatal care, a strategy referred to as “opt-out” testing. They stressed that extensive pretest counseling had proved to be a barrier to providing testing for many providers. Incorporating HIV testing into the standard panel of prenatal tests could increase the number of women who were offered testing, while still ensuring notification to the patient that testing would be done and preserving her option to decline. Associated recommendations that were designed to increase the proportion of pregnant women who were tested for HIV included educating prenatal providers on the value of HIV testing, adoption of professional recommendations and performance measures to encourage testing, improvement of care for HIV-infected persons, maintenance of federal funding for perinatal prevention of HIV, and collection of appropriate surveillance data.

As a result of the Institute of Medicine report, several professional groups, including the American College of Obstetricians and Gynecologists and American Academy of Pediatrics, issued new guidelines that supported the recommendations of the Institute of Medicine and endorsed universal HIV testing with patient notification as a routine component of prenatal care. The CDC convened consultations to discuss these rec-
ommendations and published revised recommendations for HIV screening of pregnant women in 2001 that replaced the 1995 recommendations. The revised recommendations emphasized that HIV testing should be a routine part of prenatal care and recommended simplification of the testing process to reduce barriers to testing but maintained a strong commitment to the voluntary approach to HIV testing. These guidelines also recommended the provision of pretest counseling, with a preference for face-to-face counseling, but allowed for the possibility of written or electronic formats.

In 2002, a CDC assessment of prenatal HIV screening rates was published that found that testing rates were generally lower in jurisdictions with laws that mandated pretest counseling and specific written consent before an HIV test (the “opt-in” approach) and were generally higher in areas with opt-out testing. After the publication of this study, the CDC issued a “Dear Colleague” letter that endorsed the practice of routinely incorporating HIV testing in the standard panel of tests for all pregnant women with the option to decline. In 2006, the most recent CDC recommendations for HIV testing were published. Recommendations regarding HIV screening for pregnant women were incorporated into general recommendations for all adults and adolescents, and opt-out HIV screening was recommended for all adults aged 13-64 years who seek care in healthcare settings, including pregnant women. The 2006 guidelines codified and strengthened the recommendation for opt-out screening in pregnant women.

The 2006 recommendations also strengthened the CDC’s recommendation for rescreening during pregnancy. A second HIV test during pregnancy was first mentioned in the 1995 guidelines, which recommended that women who test negative early in pregnancy and continue to practice high-risk behavior should be retested during the third trimester. The recommendations for a second test during pregnancy were repeated in the 2001 guidelines, which again recommended retesting in the third trimester (before 36 weeks of gestation) for women who had tested negative but remained at high risk for acquiring HIV. This recommendation was also strengthened by adding a caveat that routine universal retesting could be considered in healthcare facilities with high HIV prevalence among women of child-bearing age. After the publication of these recommendations, new analyses demonstrated that a second HIV test during the third trimester is as cost-effective as other commonly accepted health interventions, even in populations with relatively low HIV prevalence. In addition, emerging research from New York has suggested an increasing proportion of infants with perinatal HIV infection are born to women who acquire HIV infection during pregnancy. These findings support expanded recommendations for a second HIV test in the third trimester. Although the latest recommendations continue to note that a second screen may be considered in all areas, a second test is recommended specifically for all women in 22 states with elevated HIV incidence, for women who are served in facilities in which prenatal screening reveals a prevalence of at least 1 per 1000, and for women who are at high risk of acquiring HIV infection.

Before the release of the 2001 recommendations, new research demonstrated reductions in the risk of mother-to-child HIV transmission, even if antiretroviral prophylaxis was not given during pregnancy and could only be given during labor and/or to the newborn infant. Therefore, the 2001 guidelines also recommended that women with unknown status at labor and delivery should be tested promptly to allow for intrapartum and neonatal antiretroviral prophylaxis, if positive. Testing could be accomplished either by expedited standard testing (with return of results within 12 hours) or preferably with rapid testing, which could be done at the bedside, to allow the prompt initiation of antiretroviral prophylaxis in women with a positive HIV test while still in labor. However, at the time the guidelines were published, only 1 rapid test was available commercially in the United States.

Since 2001, several additional rapid tests have been approved by the Food and Drug Administration (FDA) for use in the United States, and additional research has described the acceptability and accuracy of rapid testing during labor and delivery. The Mother-Infant Rapid Intervention at Delivery study found that rapid testing is feasible and accurate and delivers timely results for women in labor. The 2006 recommendations specifically recommend the use of a rapid HIV test for screening women who arrive in labor with unknown or undocumented HIV status and reiterate recommendations to initiate antiretroviral prophylaxis to prevent mother-to-child HIV transmission based on the rapid test result, without waiting for confirmatory results. These recommendations are also reflected in the most recent guidance from the American College of Obstetricians and Gynecologists.

US Public Health Service Guidelines for Prophylaxis and Treatment of HIV-Infected Pregnant Women

Within 2 months of the release of the results from the PACTG 076 trial, interim guidance was issued by the US Public Health Service that supported the use of zidovudine as described in the PACTG 076 protocol. On June 6-7, 1994, the US Public Health Service convened a workshop of invited guests that included representatives from the medical, scientific, public health, and legal communities to develop recommendations for the use of zidovudine to reduce perinatal HIV transmission and to provide guidance for clinicians and public health professionals in interpreting the results of the PACTG 076 trial. Based on feedback from this workshop, the US Public Health Service Task Force, which was composed of obstetric and pediatric HIV experts and federal agency representatives, issued more extensive guidance for the use of zidovudine to reduce perinatal HIV transmission.
were notable for several features that are still reflected in the current 2006 guidelines, such as (1) the inclusion of clinical situations, later termed clinical scenarios, that present hypothetic clinical scenarios with discussion and recommendations to help clinicians with decision-making and (2) the clear distinction between prophylaxis to prevent perinatal transmission as opposed to treatment for the benefit of the woman’s own health. The guidelines emphasize that pregnancy should not be a reason to defer antiretroviral therapy when it is needed. Although there is a need for antiretroviral prophylaxis for the prevention of transmission to the infant and although issues that are related to potential drug toxicity to mother and fetus affect the choice of antiretroviral drugs that are used for treatment, these concerns should be dealt with in the context of assuring optimal treatment to preserve the mother’s health.

In January 1998, updated guidelines were issued that included more general recommendations for the use of antiretroviral drugs in pregnancy, expanding the previous guidelines’ focus on zidovudine. By this time, there were 11 FDA-approved antiretroviral drugs, and these powerful new drugs were being used in highly active drug combinations. The title of the document now included “maternal health”, which reflected further emphasis on considerations beyond mother-to-child HIV transmission to address issues for the pregnant woman’s own health. After publication of these guidelines, the Public Health Service Task Force began meeting by monthly conference calls to review new evidence and regularly update the recommendations. The guidelines, which are now updated several times a year, are posted on a website so that revised guidelines can be disseminated more rapidly. Each time the guidelines are posted, the changes that are new since the last revision are highlighted so that the reader can quickly review the most recent changes. The guidelines also contain hyperlinks that link the reader to other parts of the guidelines and supplemental information.

The current Public Health Service guidelines have evolved considerably over time. They now contain information on >20 antiretroviral drugs, the FDA pregnancy category and information on placental passage, dosing and pharmacokinetics during pregnancy, and animal carcinogenicity and teratogenicity studies. Most of the approved antiretroviral drugs are FDA pregnancy category B or C. However, efavirenz is category D, which indicates that there is evidence of human fetal risk. Severe central nervous system defects, which were consistent with abnormalities that have been seen in animal studies, have been reported in 4 infants after first trimester exposure of efavirenz-containing regimens. Therefore, efavirenz should be avoided during the first trimester. Because efavirenz is a relatively popular choice for combination regimens and because more than one-half of pregnancies in the United States are unintended, it is critical that women who take efavirenz be counseled regarding the risks. Women who are planning to become pregnant should strongly consider the use of regimens that do not contain efavirenz or other drugs with teratogenic potential.

Current recommendations for treatment of HIV infection in pregnant women are the same as those for the initiation of treatment in nonpregnant individuals; in the United States, treatment is recommended for all individuals with a CD4 cell count of <200/mm³ or an AIDS-defining illness and should be considered for individuals with a CD4 cell count of <350/mm³. Standard treatment for nonpregnant and pregnant women is highly active antiretroviral therapy with ≥3 drugs. For HIV-infected pregnant women who do not require therapy for their own health, antiretroviral drugs are recommended for the prevention of mother-to-child transmission. In the United States, combination therapy with highly active antiretroviral therapy is also recommended for all pregnant women with HIV RNA levels of >1000 copies/mL. For women with HIV RNA levels of <1000 copies/mL, the 3-part PACTG 076 zidovudine prophylaxis regimen can be used alone or in combination with other antiretroviral drugs. Table 1 provides a summary of recommendations for the treatment and prevention of mother-to-child HIV transmission for pregnant HIV-infected women in different clinical scenarios.

After pregnancy, it is recommended that, if the woman does not meet criteria for treatment in nonpregnant women, consideration should be given to discontinuing therapy after delivery. In most cases, all drugs should be stopped simultaneously. One exception is when drugs with long half-lives (such as nonnucleoside drugs like nevirapine) are used in combination with drugs with considerably shorter half-lives (such as nucleoside analogue drugs [eg, zidovudine or lamivudine]). In the case of a nevirapine-containing regimen, consideration should be given to continuing the dual nucleoside analogue drug component of the regimen for a period of time (ie, 3–7 days) after discontinuation of nevirapine to reduce the risk of the development of nevirapine resistance, although the optimal duration of time to continue the dual nucleosides is not known.

As noted earlier, highly active combination therapy is now the norm for both nonpregnant and pregnant women, and because of the complex nature of the management of HIV infection, it is recommended that a specialist with experience in the treatment of pregnant women with HIV infection be involved in their care. The guidelines now also include a table that summarizes the pharmacokinetic data and general concerns in pregnancy and makes recommendations about the suitability of each antiretroviral drug in pregnancy by categorizing each agent as (1) a recommended agent, (2) an alternate agent, (3) insufficient data to recommend use, and (4) not recommended. Although antiretroviral prophylaxis and treatment regimens have evolved rapidly and have become increasingly complicated, it is interesting to note that zidovudine is still the mainstay of perinatal prevention efforts, >10 years after the results of PACTG protocol 076 were released. It is still recommended that zidovudine be included in antiretroviral regimens for pregnant women whenever possible.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1–infected woman of childbearing potential</td>
<td>HAART as per US treatment guidelines</td>
</tr>
<tr>
<td>HIV-1–infected woman who receives HAART and becomes pregnant</td>
<td>Continue current HAART regimen; discontinue drugs with teratogenic potential</td>
</tr>
<tr>
<td>HIV-1–infected pregnant woman with antenatal plasma HIV-1 RNA of ≥1000</td>
<td>HAART (ideally contains zidovudine) consider delaying initiation until after</td>
</tr>
<tr>
<td>copies/mL who does not currently receive antiretroviral therapy</td>
<td>the first trimester</td>
</tr>
<tr>
<td>HIV-1–infected pregnant woman with antenatal maternal plasma HIV-1 RNA</td>
<td>Zidovudine given antepartum after the first trimester and as continuous</td>
</tr>
<tr>
<td>of &lt;1000 copies/mL, who does not currently receive antiretroviral therapy</td>
<td>infusion* during labor OR HAART (ideally contains zidovudine) consider delaying</td>
</tr>
<tr>
<td></td>
<td>initiation until after the first trimester plus zidovudine given as continuous</td>
</tr>
<tr>
<td></td>
<td>infusion* intrapartum; discontinue HAART after delivery (if regimen includes</td>
</tr>
<tr>
<td></td>
<td>drug with long half-life such as NNRTI, consider stopping NRTIs 3-7 days after</td>
</tr>
<tr>
<td></td>
<td>stopping NNRTI, although limited data exist)</td>
</tr>
</tbody>
</table>

Continued on page S31.
Antiretroviral drug resistance is another topic that has received considerable attention in the pregnancy guidelines in recent years, with sections specifically addressing incidence, prevalence, impact, management, and prevention of drug resistance in pregnancy and indications for and the significance of resistance testing. Resistance testing is recommended for all pregnant women who are not currently receiving antiretroviral drugs before the initiation of therapy or prophylaxis and for those women with persistent viral replication while receiving antiretroviral treatment to optimize antiretroviral drug choice and to provide the most effective and durable regimen in women who need treatment and greater preservation of future treatment options in women receive antiretroviral prophylaxis. The development of resistance during pregnancy may have clinical importance for both the pregnant woman and her infant. The development of drug resistance is a problem for drugs for which a single mutation may be associated with resistance (eg, nonnucleoside drugs such as nevirapine and efavirenz and lamivudine or emtricitabine), when the drug is used in the context of a non-suppressive antiretroviral regimen. In contrast, for drugs in which multiple mutations are required before resistance occurs (such as zidovudine), prolonged use as single-drug prophylaxis is generally required before resistance occurs; the development of zidovudine resistance was rare in PACTG 076. Because the development of drug resistance is 1 of the major factors that leads to HIV therapy failure, resistance that develops during pregnancy may have life-long implications for the woman. In addition, if the woman transmits resistant virus to her infant, future treatment options for the infant may be limited. Because there are few drugs with adequate safety data in pregnancy, a general principle in obstetrics is to minimize fetal exposure to drugs. Therefore, early on, monotherapy and dual therapy were used extensively for prophylaxis in pregnant women with the aim of reducing the mother-to-child transmission risk without exposing the fetus to multiple drugs. However, the use of antiretroviral regimens that do not fully suppress viral replication can be associated with the development of resistance. Thus, current recommendations in the United States are for the use of highly active combination therapy with 3 drugs for pregnant women with ongoing viral replication (HIV RNA, ≥1000 copies/mL) who do not require therapy for their own health.

In addition to summarizing information about antiretroviral drugs, the guidelines also include extensive discussion of the preferred mode of delivery for HIV-infected women. This expanded scope of the recommendations is reflected in the current phrase, interventions to reduce perinatal HIV-1 transmission, which replaced the phrase antiretroviral drugs in pregnant women in the older title of the guidelines. In addition to the 4 clinical scenarios that summarize the recommendations for use of antiretroviral drugs, the guidelines also include 4 scenarios regarding the mode of delivery. Other recent revisions to the

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**TABLE**

Recommendations for antiretroviral drug use and prevention of mother to child HIV transmission in pregnant HIV-infected women in the United States

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| HIV-1–infected woman who has received no antiretroviral therapy before labor | Several effective regimens are available to choose from:  
(1) Woman: zidovudine given as continuous infusion* during labor; infant: zidovudine for 6 weeks  
OR  
(2) Woman: zidovudine + lamivudine every 12 hours during labor; infant: zidovudine + lamivudine for 1 week  
OR  
(3) Woman: single-dose nevirapine (Note: If delivery is imminent (<1 hour), do not give the maternal intrapartum nevirapine because of insufficient time to reach adequate level in the infant; infant: single-dose nevirapine at 48-72 hours of age (Note: If mother did not receive intrapartum nevirapine, then give infant nevirapine at birth and 48-72 hours)  
OR  
(4) Combination zidovudine + nevirapine: woman: zidovudine given as continuous infusion* during labor, plus single-dose nevirapine at onset; infant: single-dose nevirapine plus zidovudine for 6 weeks. |
| Infant born to HIV-1–infected woman who has received no antiretroviral therapy before or during labor | Zidovudine given for 6 weeks to the infant (started within 6-12 hours of birth)  
OR  
Some clinicians may choose to use zidovudine in combination with additional drugs, but appropriate dosing for neonates is defined incompletely and the additional efficacy of this approach in reducing transmission is not known. |

* Zidovudine continuous infusion: 2 mg/kg zidovudine intravenously over 1 hour followed by continuous infusion of 1 mg/kg/hr until delivery.

(Adapted from Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Last accessed: October 22, 2006. Available at: http://AIDSInfo.nih.gov.)
Guidelines include an expanded section on preconception counseling, which refers to the CDC guidance on preconception counseling for all women and then addresses issues that are specific to HIV-infected women. In addition, the new guidelines summarize whatever pregnancy information is available for recently approved antiretrovirals, such as tipranavir and darunavir.

**Comment**

Throughout the HIV epidemic in the United States, the Public Health Service and its agencies such as the CDC and the National Institutes of Health have worked to translate rapidly the latest scientific findings into usable guidance for clinicians on the frontline who take care of HIV-infected patients. In the case of HIV screening of pregnant women, the autonomy of the woman must be balanced against the benefits of identifying HIV-infected pregnant women so that preventive measures may be offered. In addition, when prophylaxis and treatment are administered to HIV-infected pregnant women, the risks and benefits to the woman must be balanced with those of the infant. Although a great deal of research in this area has resulted in dramatic progress, the prophylactic and treatment regimens for HIV-infected pregnant women and their infants have become increasingly complex. Current Public Health Service guidance regarding HIV screening of pregnant women has been published recently and up-to-date recommendations regarding prophylaxis and treatment are posted on the internet and are updated regularly. A major revision to the prophylaxis and treatment guidelines is anticipated in 2008. These HIV screening and treatment guidelines are designed as a resource for clinicians and are recommendations only. Clinicians should be aware that they are subject to the laws and statutes in their states, which may differ somewhat from these federal guidelines.

**References**

Use of enhanced perinatal human immunodeficiency virus surveillance methods to assess antiretroviral use and perinatal human immunodeficiency virus transmission in the United States, 1999-2001

Norma S. Harris, PhD; Mary Glenn Fowler, MD; Stephanie L. Sansom, PhD; Nan Ruffo, BS; Margaret A. Lampe, RN, MPH

In 1994, the results of a randomized trial Pediatric AIDS Clinical Trial Group (PACTG) 076 demonstrated that an intensive regimen of maternal zidovudine from the second trimester through the intrapartum period that was followed by 6 weeks of infant zidovudine could reduce perinatal human immunodeficiency virus (HIV) transmission by almost 70%. In response to these striking results, the United States Public Health Service rapidly issued recommendations for the use of zidovudine for the reduction of perinatal HIV transmission in 1994. As a result of these findings, in 1995, the Centers for Disease Control and Prevention (CDC) issued recommendations for the universal counseling and voluntary testing of all pregnant women to ensure that all HIV-infected pregnant women and their newborn infants have access to this perinatal HIV-prevention regimen. Revised recommendations for HIV screening of pregnant women were issued in 2004 and in 2006 that reemphasized the importance of universal voluntary screening of all pregnant women, the need to reduce barriers to healthcare providers offering screening by the use of an opt-out approach, the importance of retesting in the third trimester of pregnancy in some jurisdictions, and rapid testing at labor and delivery for women whose HIV status was still unknown. Since the publication of the PACTG 076 study results, other observational studies in the United States have confirmed dramatic decreases in perinatal transmission. Perinatal cohort and clinical trial data from 1997 to the present time suggests that zidovudine, when combined with other antiretrovirals, and obstetric interventions such as scheduled cesarean section before labor onset and avoidance of breast feeding, can reduce perinatal HIV transmission to ≤2%.

In the United States, 91% of all reported pediatric acquired immunodeficiency syndrome (AIDS; required reporting in all states) cases and 85% of all pediatric HIV cases that were reported from the 35 states and 4 territories with HIV surveillance are attributed to perinatal transmission of HIV. Pediatric AIDS incidence has declined by 94% from 1992-2003; most of this decline is due to the reduction in the number of cases that were attributed to perinatal HIV transmission. Despite this decline, an estimated 280-370 perinatally infected infants were born in 2000. Additionally, more than one-half of perinatal HIV infections in children were attributed to missed opportunities for perinatal HIV prevention.

Data on the effect of antiretroviral use and its impact on perinatal HIV infant infection rates from a population-based national enhanced perinatal surveillance (EPS) system have not been described previously in the literature. Therefore, the objectives of this article were to describe recent surveillance trends in anti-
retroviral use for the prevention of perinatal HIV transmission in the United States and to assess the impact of antiretroviral prophylaxis on perinatal HIV transmission rates with the use of data from the EPS system from 19 states and territories and 5 US cities for HIV-exposed infants who were born in 1999, 2000, and 2001.

Materials and Methods
The EPS project constitutes an integrated surveillance system for HIV-infected mothers and their perinatally exposed infants and was designed as an extension of routine surveillance for HIV/AIDS.

State and local health departments that conducted surveillance of adult and pediatric HIV infection also conducted the EPS project, which consisted of enhanced case ascertainment of HIV-exposed infants and HIV-infected mothers. These enhanced surveillance methods consisted of (1) increased efforts to completely ascertain mothers-infant pairs by matching birth registries to HIV/AIDS surveillance registries and (2) the systematic collection of supplemental data from multiple sources for both the mother and infant from all available medical charts, which included the maternal HIV clinic; prenatal and labor/delivery medical records; the newborn infant and pediatric records; data from laboratory reports; and data from birth and death certificates.

State health departments and the 6 independently funded city health departments that received federal funds for HIV/AIDS surveillance that have reported ≥60 HIV-positive women who gave birth per year (as determined from the 1994 Survey of Childbearing Women [SCBW]) were eligible for funding for the EPS project. The study sites that were funded through the cooperative agreement mechanism for 2003 were Alabama, California, Chicago, Los Angeles, Connecticut, District of Colombia, Florida, Houston, Louisiana, Maryland, Michigan, Mississippi, North Carolina, New Jersey, New York State, New York City, Ohio, Pennsylvania, Philadelphia, Puerto Rico, South Carolina, Tennessee, Texas, and Virginia. These sites represented 89% of all perinatal AIDS cases that were reported in 2003.

The infants who were identified through enhanced surveillance were followed up by the health department every 6 months until their HIV infection status was determined. Data were collected on HIV-infected mothers and their HIV-exposed infants who were born in 1999, 2000, and 2001. Women who were known to be HIV-infected in pregnancy (tested before or at delivery) and women who were not known to be HIV-infected in pregnancy but whose child was reported to surveillance because of a positive laboratory test that was indicative of HIV were included. All infants who were born in or had received care in the specific project site (i.e., the state or city) were eligible for inclusion. For women who gave birth more than once during the time period, a separate confidential HIV/AIDS case report form and EPS abstraction form were completed. If a woman had twins or triplets, a separate confidential HIV/AIDS case report form and EPS abstraction form were completed for each infant.

Variables that were used in the analysis included year of birth, maternal age, race/ethnicity, prenatal care, maternal HIV testing, and receipt of prophylactic antiretroviral therapy (ART). Prenatal care was defined as a dichotomous variable with “yes” being coded as the receipt of any prenatal care visits. Maternal HIV testing was defined as the relationship between maternal testing for HIV and the birth of the exposed infant. Receipt of prophylactic ART was based on the 3 time periods when ART could have been received: prenatally, during delivery, or neonatally during the first 6 weeks of life. Zero (0) arms was defined as no ART received during any of the 3 time periods; 1 arm was defined as ART received at only 1 of the 3 time periods; 2 arms was defined as ART received 2 of the 3 time periods; and 3 arms was defined as ART received during all 3 time periods. For the outcomes in which we assessed receipt of ART, we used the number of HIV-infected women for whom data on antiretroviral use were available and defined it as known receipt or known nonreceipt of antiretroviral drugs. Prenatal ART regimens were categorized in the following manner: (1) zidovudine monotherapy; (2) zidovudine and other drugs with a protease inhibitor (PI; zidovudine in combination with other drugs at least 1 of which was a PI); (3) zidovudine and other drugs with no PI (zidovudine in combination with other drugs in which none were PIs); (4) other drugs with PI, no zidovudine (an ART combination that includes a PI but does not include zidovudine); (5) other drugs with no PI, no zidovudine (an ART combination that does not include a PI or zidovudine); and (6) monotherapy, no zidovudine (an ART regimen with 1 drug that was not zidovudine). For defining HIV infection in perinatally exposed infants, we used the revised CDC surveillance HIV case definition for adults and children to classify children as infected with HIV, not infected with HIV, or indeterminate.14

All analyses were conducted with SAS software (version 9.1; SAS Institute Inc, Cary, NC). There were 8530 singleton births reported through the EPS system for children who were born 1999-2001. Of the 8530 singleton births, 1186 birth records contained incomplete data on ART use, which resulted in a sample size of 7344 births. To accommodate the logistic regression analysis, an additional 347 records were excluded because of missing or unknown data on maternal age at delivery, maternal race/ethnicity, receipt of any prenatal care, maternal timing of HIV test, and type of delivery, which resulted in a sample size of 6997. Because of the small sample sizes and to accommodate the logistic regression model, we further excluded 23 records of women among whom 10 women received prenatal ART only, 3 women received intrapartum ART only, and 10 women received prenatal and intrapartum ART, which resulted in a sample size of 6974 records.

Chi-square test for trend was used to test for trends in infant HIV infection status from 1999-2001. Stratified analysis was used to examine the univariate relationship between demographic variables and infant HIV infection. Unadjusted odds ratios (OR) and 95% CIs
were used to assess the relationship between each variable and the outcome of infant HIV infection status. Unconditional logistic regression was used to produce ORs and 95% CIs for the relationship between covariates and infant HIV-infection status.

This project was deemed exempt from CDC Institutional Review Board review because it was determined that the project constitutes data collection for the purposes of disease surveillance and program evaluation and is not research. For this project, data were abstracted from existing medical and ancillary records. There was no contact with individual patients. Data were collected by trained health department personnel or their agents, and no names of individuals were reported to CDC.

**Results**

There were 8530 singleton births reported through EPS for children who were born 1999-2001. The overall infant infection rate for the 3 years was 4.7% (95% CI, 4.2,5.1). The infant infection rates for 1999, 2000, and 2001 were 6.0% (95% CI, 5.1, 6.9), 4.2% (95% CI, 3.5, 4.9), and 3.9% (95% CI, 3.2, 4.6), respectively. The infant infection rates declined by year, but the trend over time was not statistically significant (P = .0680).

Of the 8530 singleton births, 1186 records (13.9%) contained incomplete data on ART use, which resulted in a sample size of 7344 births. Receipt of arms of ART by infection status is presented in Table 1. Eighty-two percent of the mother-infant pairs (n = 6029) received arms of ART. The infant infection rate among infants who received 3 arms of ART was 2.5% (95% CI, 2.1, 2.8). Of the 7344 mother-infant pairs, 638 pairs (8.7%) received 2 arms of ART; 359 pairs (4.9%) received 1 arm of ART, and 292 pairs (4.0%) received 0 arms of ART. The infant infection rates among the pairs who received intrapartum and neonatal ART and neonatal-only ART were 4.7% (95% CI, 2.4, 7.0%) and 11.1% (95% CI, 7.9, 14.3%), respectively. Among mother-infant pairs who received no ART at any time (0 arms of ART), the infant infection rate was 25.7% (95% CI, 20.7%, 30.7%).

Demographic characteristics by infant infection status are shown in Table 2. Mothers 13-19 years of age were more likely to have an infected infant (OR, 1.7; 95% CI, 1.1-2.6), but there were no differences in infant infection status by race/ethnicity. Ninety-four percent of mothers received some prenatal care; however, mothers with no prenatal care were more likely than mothers with prenatal care to have an infected infant (OR, 2.4; 95% CI, 1.7-3.5). Most of the mothers (92%) were tested before or during the pregnancy. Women who were tested for HIV at delivery or after birth were more likely than women who were tested for HIV before and during pregnancy to have an infected infant (OR, 3.1; 95% CI-1.9, 4.9; OR, 8.1; 95% CI, 5.8, 11.3).

The logistic model that examined the relationship of arms of ART that was received and infection status of infants is presented in Table 3. When we controlled for maternal age at delivery, maternal race/ethnicity, receipt of prenatal care, timing of maternal HIV test, and delivery type, the receipt of ART by arms remained statistically significant. In addition, study site (not shown) was an independent risk factor for infants who became infected and maternal age of ≥40 was a significant protective factor for infants not becoming infected.

Compared with mother-infant pairs who received 3 arms of ART, the odds for becoming infected were 10.7 (95% CI, 6.1, 18.9), 6.2 (95% CI, 3.6, 10.6), and 2.0 (95% CI, 1.1, 3.7), respectively, for those who received 0 arms of ART, 1 arm (neonatal only), and 2 arms only (intrapartum and neonatal arms). Among mother-infant pairs who received only the neonatal arm of ART and for whom we have data on the time of the administration of ART after birth (n = 100), approximately one-third of the pairs (32%) received ART ≤12 hours after birth; 20% of the pairs received ART between 13 and 24 hours after birth; 23% of the pairs received ART between 25 and 48 hours after birth. The transmission rates for each group relative to the timing of the administration of the ART was 6.3%, 10%, 13%, and 16%, respectively; however, the sample sizes were small, and the precision of these estimates is limited.

Among the 5522 mother-infant pairs who received 3 arms of ART, we examined the ART regimens by infant infec-
## TABLE 2
Demographic and clinical characteristics of singleton births to HIV-infected mothers, 24 sites, United States, 1999-2001 (n = 6997)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infected</th>
<th></th>
<th>Total</th>
<th></th>
<th>Unadjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>259</td>
<td>3.7</td>
<td>6997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>98</td>
<td>4.4</td>
<td>2240</td>
<td>1.3</td>
<td>1.0-1.8</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>86</td>
<td>3.4</td>
<td>2540</td>
<td>1.0</td>
<td>0.7-1.4</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>75</td>
<td>3.4</td>
<td>2217</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Maternal age at delivery (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-19</td>
<td>26</td>
<td>5.1</td>
<td>509</td>
<td>1.7</td>
<td>1.1-2.6</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>114</td>
<td>1.6</td>
<td>3641</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>110</td>
<td>4.2</td>
<td>2652</td>
<td>1.3</td>
<td>1.0-1.7</td>
<td></td>
</tr>
<tr>
<td>≥40</td>
<td>9</td>
<td>4.6</td>
<td>195</td>
<td>1.5</td>
<td>0.7-3.0</td>
<td></td>
</tr>
<tr>
<td>Maternal race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>27</td>
<td>3.3</td>
<td>826</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
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<tr>
<td>Black</td>
<td>178</td>
<td>3.6</td>
<td>4887</td>
<td>1.1</td>
<td>0.7-1.7</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>53</td>
<td>4.3</td>
<td>1224</td>
<td>1.3</td>
<td>0.8-2.1</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1.7</td>
<td>60</td>
<td>0.5</td>
<td>0.1-3.8</td>
<td></td>
</tr>
<tr>
<td>Receipt of any prenatal care</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>7.9</td>
<td>431</td>
<td>2.4</td>
<td>1.7-3.5</td>
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<tr>
<td>Yes</td>
<td>225</td>
<td>3.4</td>
<td>6566</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Maternal timing of HIV test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refused test</td>
<td>1</td>
<td>33.0</td>
<td>3</td>
<td>17.1</td>
<td>1.5-189.7</td>
<td></td>
</tr>
<tr>
<td>Tested HIV+ before or during pregnancy</td>
<td>183</td>
<td>2.8</td>
<td>6450</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Tested HIV+ at delivery</td>
<td>22</td>
<td>8.3</td>
<td>266</td>
<td>3.1</td>
<td>1.9-4.9</td>
<td></td>
</tr>
<tr>
<td>Tested HIV+ after birth</td>
<td>53</td>
<td>19.1</td>
<td>278</td>
<td>8.1</td>
<td>5.8-11.3</td>
<td></td>
</tr>
<tr>
<td>Type of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>113</td>
<td>3.1</td>
<td>3678</td>
<td>0.7</td>
<td>0.5-0.9</td>
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</tr>
<tr>
<td>Vaginal</td>
<td>146</td>
<td>4.4</td>
<td>3319</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Arms received</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 arms</td>
<td>59</td>
<td>22.3</td>
<td>265</td>
<td>11.6</td>
<td>8.3-16.2</td>
<td></td>
</tr>
<tr>
<td>1 arm: neonatal ART only</td>
<td>38</td>
<td>11.0</td>
<td>344</td>
<td>5.0</td>
<td>3.4-7.3</td>
<td></td>
</tr>
<tr>
<td>1 arm: intrapartum ART only</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>5.7</td>
<td>0.3-111.9</td>
<td></td>
</tr>
<tr>
<td>1 arm: prenatal ART only</td>
<td>1</td>
<td>1.0</td>
<td>10</td>
<td>4.5</td>
<td>0.6-35.7</td>
<td></td>
</tr>
<tr>
<td>2 arms: prenatal ART &amp; intrapartum ART</td>
<td>0</td>
<td>0.0</td>
<td>10</td>
<td>1.9</td>
<td>0.1-32.9</td>
<td></td>
</tr>
<tr>
<td>2 arms: prenatal ART &amp; neonatal ART</td>
<td>8</td>
<td>2.7</td>
<td>302</td>
<td>1.1</td>
<td>0.5-2.3</td>
<td></td>
</tr>
<tr>
<td>2 arms: intrapartum ART &amp; neonatal ART</td>
<td>14</td>
<td>4.6</td>
<td>306</td>
<td>1.9</td>
<td>1.1-3.4</td>
<td></td>
</tr>
<tr>
<td>3 arms: prenatal ART &amp; intrapartum ART &amp; neonatal ART</td>
<td>139</td>
<td>2.4</td>
<td>5757</td>
<td>1.0</td>
<td>Referent</td>
<td></td>
</tr>
</tbody>
</table>
tion status. Ninety percent of the pairs who received 3 arms of ART received zidovudine each of the 3 time periods. Of the 4976 pairs who received zidovudine each of the 3 time periods and who received 3 arms of ART, 15% of the pairs received zidovudine monotherapy; 42% of the pairs received zidovudine in combination with other drugs that included a PI; and 42% of the pairs received zidovudine in combination with other drugs that did not include a PI (data not shown).

Among the pairs who received zidovudine monotherapy during the intrapartum and neonatal periods, receipt of the type of ART during the prenatal period varied. The receipt of zidovudine monotherapy during all 3 time periods occurred in 710 mother-infant pairs (12.9%). Of the mothers (62%) who received prenatal zidovudine in combination with other drugs, 31% received combinations with PIs, and 31% received combinations without PIs (data not shown).

The receipt of prenatal zidovudine in combination with other drugs that included a PI, with intrapartum zidovudine monotherapy and neonatal zidovudine monotherapy, occurred in 1,696 cases of the study population (31%). We also examined prenatal ART regimens and infection status among mother-infant pairs who received 3 arms of treatment (Table 4). When we controlled for maternal age, race, prenatal care, delivery type, and timing of HIV test, the prenatal ART regimens remained an independent predictor of infant infection status. The odds of a mother having an infected infant were less for those mothers who received either a prenatal regimen that contained zidovudine in combination with other drugs that included at least 1 PI or a prenatal regimen that contained zidovudine in combination with other drugs without any PIs, compared with mothers whose prenatal regimen consisted of zidovudine monotherapy (OR, 0.40; 95% CI, 0.3-0.7; OR, 0.50; 95% CI, 0.3-0.8, respectively). Other non–zidovudine-containing prenatal regimens demonstrated a similar effect on infant status; however, none of them was statistically significant. Two hundred thirty-seven women were prescribed combination ART that contained a PI but no zidovudine; 135 women were prescribed combination ART regimen that contained no PI and no zidovudine.

**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-19</td>
<td>1.1</td>
<td>0.7-1.8</td>
</tr>
<tr>
<td>20-29</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>30-39</td>
<td>1.1</td>
<td>0.5-2.3</td>
</tr>
<tr>
<td>40+</td>
<td>0.7</td>
<td>0.5-0.9</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Black</td>
<td>1.0</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.3</td>
<td>0.8-2.2</td>
</tr>
<tr>
<td>Other</td>
<td>0.4</td>
<td>0.1-3.2</td>
</tr>
<tr>
<td>Prenatal care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0</td>
<td>0.6-1.6</td>
</tr>
<tr>
<td>Yes</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Timing of maternal HIV test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refused test</td>
<td>3.2</td>
<td>0.2-41.5</td>
</tr>
<tr>
<td>Before/during pregnancy</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>At delivery</td>
<td>1.5</td>
<td>0.9-2.6</td>
</tr>
<tr>
<td>After birth</td>
<td>0.8</td>
<td>0.4-1.5</td>
</tr>
<tr>
<td>Delivery type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>1.1</td>
<td>0.8-1.4</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Arms received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 arms</td>
<td>10.7</td>
<td>6.1-18.9</td>
</tr>
<tr>
<td>1 arm: neonatal ART only</td>
<td>6.2</td>
<td>3.6-10.6</td>
</tr>
<tr>
<td>2 arms: intrapartum ART &amp; neonatal ART</td>
<td>2.0</td>
<td>1.1-3.7</td>
</tr>
<tr>
<td>2 arms: prenatal ART &amp; neonatal ART</td>
<td>1.1</td>
<td>0.5-2.4</td>
</tr>
<tr>
<td>3 arms: prenatal ART &amp; intrapartum ART &amp; neonatal ART</td>
<td>1.0</td>
<td>Referent</td>
</tr>
</tbody>
</table>

* Controlled for all variables in the model and site. Model excludes 23 observations: 10 patients who received prenatal ART only; 3 patients who received intrapartum ART only, and 10 patients who received prenatal ART and intrapartum ART.

**COMMENT**

We examined the impact of ART on the perinatal infant infection rates in 24 sites across the United States from 1999-2001. These 24 sites represent 89% of the cumulative perinatal AIDS cases that were reported through 2003 in the United States. The proportion of infants who became infected is associated with the use and timing of the ART. Mother-infant pairs who receive all 3 arms (prenatal, intrapartum, and neonatal) have the lowest proportion of infants who are infected (2.5%; 95% CI, 2.1%, 2.8%). Those mothers who receive no treatment...
TABLE 4
Final Logistic Regression Model* examining prenatal ART regimens and infant infection status among mother-child pairs who received 3 arms of treatment (n = 5602)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>2000</td>
<td>0.7</td>
<td>0.5, 1.1</td>
</tr>
<tr>
<td>2001</td>
<td>0.7</td>
<td>0.4-1.1</td>
</tr>
<tr>
<td>Maternal age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-19</td>
<td>1.2</td>
<td>0.7-2.1</td>
</tr>
<tr>
<td>20-29</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>30-39</td>
<td>0.8</td>
<td>0.3-2.7</td>
</tr>
<tr>
<td>40+</td>
<td>0.7</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Black</td>
<td>1.0</td>
<td>0.6-1.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.1</td>
<td>0.6-2.2</td>
</tr>
<tr>
<td>Other</td>
<td>0.0</td>
<td>0.0-999.9</td>
</tr>
<tr>
<td>Delivery type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>1.1</td>
<td>0.8-1.5</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Prenatal regimens received</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine monotherapy</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Zidovudine &amp; other drugs with PI</td>
<td>0.4</td>
<td>0.3-0.7</td>
</tr>
<tr>
<td>Zidovudine &amp; other drugs no PI</td>
<td>0.5</td>
<td>0.3-0.8</td>
</tr>
<tr>
<td>Other drugs with PI, no zidovudine</td>
<td>0.6</td>
<td>0.2-1.4</td>
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<tr>
<td>Other drugs no PI, no zidovudine</td>
<td>0.3</td>
<td>0.1-1.5</td>
</tr>
</tbody>
</table>

* Controlled for all variables in the model and site. Model excludes 155 observations; 14 patients who received monotherapy that was not zidovudine; 141 patients for whom the type of ART that was received was unspecified.

at all (eg, 0 arms) have 25.7% infant infection rate (95% CI, 20.7%-30.7%), which is similar to the results that were obtained by Connor et al1 in the early 1990s. We also found that women and infants who received antiretroviral treatment during the intrapartum and neonatal periods, but not the antenatal period, received only some benefit from prophylaxis (4.7%; 95% CI, 2.4%-7.0%).

Our results among mother-infant pairs who received all 3 arms (antenatal, intrapartum, and neonatal) of ART are similar (2.5%; 95% CI, 2.1-2.8) to those reported by Wade et al16 (3.3%) and Peters et al19 (3%). Additionally, we found infant infection rates for mother-infant pairs who receive neonatal-only ART (11.0%; 95% CI, 7.7%-14.4%) to be comparable with that found by Wade et al (11.9%). When we further examined those pairs who received neonatal-only ART (n = 100, with dose timing data), 6.3% (95% CI, 2.1-14.6) of infants who received ART ≤12 hours were found to be infected (data not shown); this rate was approximately one-half that found by Wade et al (11.9%) and Peters et al (14%). Additionally, the EPS infant infection rate for mother-infant pairs who received intrapartum and neonatal ART (4.6%; 95% CI, 2.2%-6.9%) was approximately one-half that reported by Wade et al (9.4%) and Peters et al (8.0%).

The availability of ART became widespread by early 1997; combination ART that consists of 2 nucleoside reverse transcriptase inhibitors and either a PI or a non–nucleoside/nucleotide reverse transcriptase is the recommended standard treatment for HIV-1–infected adults who are not pregnant.17 Current antiretroviral drug recommendations for pregnant women now include offering the 3-part zidovudine regimen with additional antiretroviral drugs to women whose HIV-1 RNA levels are >1000 copies/mL, regardless of their clinical or immunologic status.18 The decision to treat pregnant women with combination antiretroviral drugs is a complex one, and clinicians are advised to discuss the benefits and potential negative consequences with pregnant women. However, in many instances, the benefits outweigh the potential negative consequences; 87% of the women in this study who gave birth from 1999-2001 received prenatal combination ART. Clinical studies have demonstrated decreasing perinatal HIV infant infection rates since the publication of the results of the PACTG 076.8,19-21 The PACTG 185 study confirmed the efficacy of the zidovudine regimen that was observed in PACTG 076 and extended the results to HIV-infected women who had advanced disease.22 More recent studies, which have also examined the relationship between perinatal infant infection rates and combination maternal ART, have found perinatal infant infection rates of approximately 2%.5,10,16,23-26 In a randomized trial that assessed single-dose nevirapine at delivery compared with placebo, and in the background of primarily combination antiretrovirals during pregnancy followed by infant zidovudine for 6 weeks, the infant infection rate was 1.6%.23 In 2004 in a trial from Thailand, Lallemant et al25 reported that the use of zidovudine from 28 weeks of gestation plus single-dose nevirapine to the mother at labor followed by single-dose nevirapine to the infant and 1 week of zidovudine was associated with an infant infection rate of 2%. Observational perinatal cohort
studies from the United States and Europe have also documented very low infant infection rates with the use of combination antiretrovirals for perinatal HIV prevention. A nonrandomized study in France demonstrated an infant infection rate as low as 1.6% among women who received lamivudine in addition to the zidovudine regimen. In this study, the treatment regimen for the pregnant women consisted of lamivudine that was started at 32 weeks gestation in addition to zidovudine and to the infant for 6 weeks after birth in addition to zidovudine.11 Another observational study by Cooper et al10 demonstrated perinatal infant infection rates to be 1.2% among women who received combination therapy with a PI and 3.8% among women who received combination therapy without a PI. A study by Wade et al16 also demonstrated low perinatal infection rates among women who received prenatal combination therapy with and without PIs, compared with women who received no prenatal ART (relative risk, 0.15 [95% CI, 0.10-0.24]; relative risk, 0.14 [95% CI, 0.08-0.22], respectively). In our analysis, when we examined prenatal ART regimens among those who received all 3 arms of ART, women who received combination prenatal ART that contained zidovudine and a PI or a combination prenatal ART that contained zidovudine and no PI had low infant infection rates (1.9% [95% CI, 1.3-2.4]; 2.4% [95% CI, 1.8-3.0], respectively; data not shown). Other transmission rates by prenatal ART regimen among mother-infant pairs who received 3 arms of ART, women who received combination prenatal ART that contained zidovudine and a PI or a combination prenatal ART that contained zidovudine and no PI had low infant infection rates (1.9% [95% CI, 1.3-2.4]; 2.4% [95% CI, 1.8-3.0], respectively; data not shown). In many instances, clinicians may be testing exposed children earlier than the 4-month time period stated in the pediatric HIV surveillance case definition and then discharging them so that their final HIV status is not known for surveillance purposes. Because we assumed that most of the indeterminate cases were uninfected, we may have underestimated perinatal HIV infant infection rates. However, that is unlikely to have occurred, because our results are comparable with other clinical studies that used a more stringent case definition of HIV infection in children who were born exposed to HIV infected mothers than the current surveillance pediatric HIV case definition.14 Third, sites conducted the project as population-based (n = 16) or facility-based (n = 8). In population-based sites, all HIV-exposed infants who were born to HIV-infected mothers within the geographic site defined by the project (eg, state or city) were eligible for medical chart abstraction. In facility-based sites, medical chart abstraction was conducted in selected facilities (eg, delivery hospitals, high-risk prenatal clinics, specialty pediatric clinics, or pediatric HIV clinics) within the geographic site defined by the project site. In conducting the project in these 2 ways, we could have over- or underestimated perinatal infant infection rates; however, when we examined the
infant infection rates by project type (population-based compared with facility-based), we found no statistically significant difference ($P = .07$). Fourth, we did not assess adherence to antiretroviral medications; we were able to record only whether antiretroviral medications were prescribed. Fifth, the date and time of the onset of labor were not included in this analysis because of the high proportion of missing data (60% and 67%, respectively); consequently, we were unable to examine the impact of cesarean section on infant infection status.

The CDC, in partnerships with other Department of Health and Human Services agencies, state health departments, and national organizations, aims to further reduce and potentially eliminate perinatal HIV transmission. Current strategies include (1) supporting universal HIV screening for all pregnant women by making HIV screening part of the routine panel of tests during the prenatal period, unless the woman declines testing (the “opt out” approach); (2) supporting rapid testing at labor and delivery for women whose status is still unknown and to the newborn infant if the testing cannot be done intrapartum; and (3) social marketing to increase the awareness of women and clinicians of the importance and benefits of testing for HIV during pregnancy.

The CDC is also assisting states to monitor and evaluate their perinatal HIV prevention efforts by (1) assessing prenatal HIV testing rates in select states around the country, (2) evaluating perinatal prevention programs that use EPS data in 15 states, and (3) continuing to monitor perinatal infection rates by conducting EPS in states that are also conducting perinatal prevention programs.

These EPS data document the striking success in lowering perinatal infant infection rates in the United States in recent years. However, the CDC estimates that there are still $>130$ HIV-infected infants each year. To maximally reduce perinatal HIV transmission in the United States, we must make sure that all pregnant women are receiving prenatal care and that HIV screening is part of the routine panel of prenatal screening, unless a woman declines testing. In addition, rapid testing should be available widely and used at labor and delivery if a woman’s HIV status is still unknown; treatment should be offered to women during labor/delivery and to the infants within 12 hours of birth to reduce the risk of HIV transmission.

Given that AIDS cases among female patients increased 15% from 1999 through 2003, it is also imperative that public health efforts address and test innovative strategies to reduce the risk of acquiring HIV among adolescent girls and women of childbearing age.

REFERENCES


International recommendations on antiretroviral drugs for treatment of HIV-infected women and prevention of mother-to-child HIV transmission in resource-limited settings: 2006 update

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The primary mode of acquisition of the human immunodeficiency virus (HIV) in children worldwide is through mother-to-child transmission (MTCT), which can occur during pregnancy, labor and delivery, or breastfeeding. Without interventions to reduce MTCT, the estimated risk of transmission ranges from 15%-25% in non-breastfeeding populations and 25%-40% in breastfeeding populations.1

In the last decade, there has been impressive success in the United States, Europe, and several other resource-rich countries in the reduction of MTCT. In 1994, the Pediatric AIDS Clinical Trials group (PACTG) protocol 076 showed that the administration of zidovudine (AZT) to the woman who is infected with HIV starting at approximately 14 weeks of gestation during pregnancy and labor and to her newborn infant decreased the risk of perinatal HIV transmission from 25.5% in the placebo arm to 8.3% in the AZT arm at 18 months, which is a relative risk reduction of nearly 70%.2 With the implementation of recommendations for universal prenatal HIV testing and counseling, antiretroviral treatment (ART) and combination prophylaxis, elective cesarean delivery, and avoidance of breastfeeding, MTCT of HIV has decreased to <2% in resource-rich countries.3 Many antiretroviral drug regimens that are used in highly active antiretroviral therapy (HAART) have been shown to reduce the MTCT of HIV.

The World Health Organization recommends that countries adopt more effective antiretroviral regimens to increase the effectiveness of the prevention of mother-to-child human immunodeficiency virus (HIV) transmission programs. The 2006 guidelines recommend a tiered approach for the delivery of antiretroviral to pregnant women who are infected with HIV and include triple-drug antiretroviral treatment for those women who are eligible. Those women who are not eligible for antiretroviral treatment should receive a combination prophylaxis antiretroviral regimen, preferably zidovudine from 28 weeks of gestation; zidovudine, lamivudine, and a single dose of nevirapine during delivery; and zidovudine and lamivudine for 7 days after delivery to reduce the development of nevirapine resistance. Newborn infants should receive a single dose of nevirapine and 1-4 weeks of zidovudine, depending on the duration of the regimen received by the mother. Although steps are being taken to provide more effective regimens, the use of single-dose nevirapine alone should still be used in situations in which more effective regimens are not yet feasible or available. HIV transmission through breastfeeding remains a problem, and several interventions are under evaluation that include maternal and/or infant antiretroviral prophylaxis during breastfeeding.

Key words: antiretroviral, HIV, prevention of mother-to-child transmission

Received Dec. 14, 2006; accepted Mar. 1, 2007.

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0002-9378/$32.00 © 2007 Mosby, Inc. All rights reserved. doi: 10.1016/j.ajog.2007.03.001
that have been learned in antiretroviral prophylaxis for MTCT and the new 2006 World Health Organization (WHO) public health guidelines for the treatment of pregnant women and the prevention of HIV infection in infants in resource-limited settings.4 Based on new evidence and programmatic experiences that have become available, the 2006 guidelines go beyond delivery of SD-NVP for PMTCT to the mother and the neonate to include more effective antiretroviral prophylaxis and treatment regimens. The new guidelines recommend a tiered approach for PMTCT antiretroviral interventions that supports the best interventions where feasible but at least some effective interventions at all levels of the health system. The guidelines recommend a public health approach that aims to support the development of PMTCT and treatment programs that can reach as many people as possible.5 This approach is built around evidence-based standardized regimens and simplification to facilitate the implementation at country level, balancing feasibility with impact, and flexibility to allow for changing circumstances. The guidelines complement and are harmonized fully with the WHO 2006 Adult6 and Pediatric HIV7 treatment guidelines.

The new guidelines differ from those in resource-rich settings primarily in recommendations for women who do not require antiretroviral therapy for their own health. In resource-rich settings, HAART is recommended for PMTCT in all pregnant women with HIV RNA levels of >1000 copies/mL and is often used in women with lower RNA levels.8 However, resource-limited settings have constraints that are related to cost, laboratory capacity, limited antiretroviral drugs that require the reserve of certain antiretrovirals for second-line and salvage therapy, and safety. With the public health approach to treatment, the first-line ART regimen for infected individuals in resource-limited settings, which includes women for whom contraception cannot be guaranteed, is a non–nucleoside reverse transcriptase inhibitor (NNRTI)–based regimen;9 in women, the NNRTI of choice is NVP, protease inhibitors are reserved preferentially for second-line ART. However, there is the potential for life-threatening hepatic toxicity with chronic NVP therapy in women with higher CD4 cell counts. Thus, a new key point is that WHO recommends a 2-part approach for PMTCT in resource-limited settings: NVP-based ART for women whose condition requires therapy for their own health and short-course combination antiretroviral regimens plus single-dose intrapartum/neonatal SD-NVP for women who do not require therapy for their own health. Lessons learned from clinical trials and current WHO guidelines will be discussed later.

**Clinical Trials of Antiretroviral Prophylaxis of MTCT: Lessons Learned**

When first shown to be effective in 1994, the complexity and cost of the 3-part PACTG 076 AZT regimen limited its applicability and implementation in resource-limited settings, which led researchers to evaluate the efficacy of shorter, less expensive prophylactic regimens (Table 1). These studies demonstrate that a number of different regimens have efficacy in preventing in utero and intrapartum transmission, but that efficacy is diminished in breastfeeding populations because of postnatal HIV acquisition through breast milk.

Table 1 summarizes the results of the major clinical studies of antiretroviral interventions for PMTCT. Direct comparison between trials is difficult, because they enrolled patient populations from different geographic areas who were infected with different viral subtypes with different infant feeding practices and different infant age of diagnosis and outcome. However, some general conclusions can be drawn.

**Combination antiretroviral regimens are more effective than single-drug antiretroviral regimens**

Efficacy has been demonstrated for regimens with AZT alone, AZT plus 3TC, SD-NVP, and more recently, SD-NVP plus either short-course AZT or AZT/3TC (Table 1).9-20 Combination regimens, such as short-course AZT plus SD-NVP, are more effective than single-drug regimens in reducing MTCT; when feasible and affordable, a longer 3-part antepartum/intrapartum/postpartum regimen is superior for PMTCT than a shorter 2-part antepartum/intrapartum or intrapartum/postpartum regimen.

**Longer duration of antiretroviral prophylaxis is more effective**

Almost all studies in developing countries include an oral intrapartum antiretroviral prophylaxis component, with varying durations of maternal antiretroviral drug administration antepartum and postpartum and/or infant antiretroviral postpartum prophylaxis. Regimens with antepartum components that start as late as 36 weeks of gestation with no infant prophylaxis component can reduce the risk of transmission9,11; however, longer duration of antepartum therapy (starting at 28 weeks of gestation) is more effective than shorter duration regimens (starting at 36 weeks of gestation).10 Additionally, if the duration of the maternal antepartum regimen is short (<4 weeks), longer infant prophylaxis (4-6 weeks) appears more effective than shorter infant prophylaxis (3 days-1 week).11

Regimens that include no antepartum prophylaxis but include intrapartum and postpartum drug administration are also effective, although less than those with an antepartum component.14-16 The WHO/UNAIDS multicenter trial to Prevent Mother to Child Transmission of HIV1 by short course ARV treatment (PETRA study) demonstrated that intrapartum prophylaxis with AZT/3TC alone, without postexposure prophylaxis of the infant, is not effective.14 The South African Nevirapine Trial (SAINT) demonstrated that the 2 proven effective intrapartum/postpartum regimens (AZT/3TC or SD-NVP) are similar in efficacy and safety.16

**Efficacy of antiretroviral regimens is diminished over time in breastfeeding populations**

Although the short-course regimens that were identified as effective in nonbreastfeeding populations are also effective in
TABLE 1
Results of major studies on antiretroviral prophylaxis to prevent mother-to-child HIV transmission

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Antenatal and intrapartum period</th>
<th>Postpartum period</th>
<th>Mode of infant feeding</th>
<th>Mother-to-child transmission rate and efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACTG 076/ANRS 024 trial (USA and France)²</td>
<td>AZT vs placebo</td>
<td>Long (from 14 wk); intravenous intrapartum</td>
<td>Long (6 wk), infant only</td>
<td>Replacement feeding</td>
<td>8.3% in AZT arm vs 25.5% in placebo arm at 18 mo (68% efficacy)</td>
</tr>
<tr>
<td>CDC short-course AZT trial (Thailand)⁹</td>
<td>AZT vs placebo</td>
<td>Short (from 36 wk); oral intrapartum</td>
<td>None</td>
<td>Replacement feeding</td>
<td>9.4% in AZT arm vs 18.9% in placebo arm at 6 mo (50% efficacy)</td>
</tr>
<tr>
<td>DITRAME (ANRS 049a) trial (Côte d’Ivoire and Burkina Faso)¹²,¹³,¹⁸</td>
<td>AZT vs placebo</td>
<td>Short (from 36 wk); oral intrapartum</td>
<td>Short (1 wk), mother only</td>
<td>Breastfeeding (96%)</td>
<td>18.0% in AZT arm, 27.5% in placebo arm at 6 mo (38% efficacy); 21.5% vs 30.6% (30% efficacy) at 15 mo</td>
</tr>
<tr>
<td>CDC short-course AZT trial (Côte d’Ivoire)¹¹,¹³</td>
<td>AZT vs placebo</td>
<td>Short (from 36 wk); oral intrapartum</td>
<td>None</td>
<td>Breastfeeding (100%)</td>
<td>16.5% in AZT arm vs 26.1% in placebo arm at 3 mo (37% efficacy)</td>
</tr>
<tr>
<td>PETRA trial (South Africa, Tanzania, and Uganda)¹⁴</td>
<td>Antenatal, intrapartum/postpartum AZT + 3TC vs intrapartum/postpartum AZT + 3TC vs intrapartum-only AZT + 3TC vs placebo</td>
<td>Short (from 36 wk); oral intrapartum</td>
<td>Short (1 wk), mother and infant</td>
<td>Breastfeeding (74%; median duration, 26 wk) and replacement feeding</td>
<td>5.7% at 6 wk for antepartum/intrapartum/postpartum AZT + 3TC, 8.9% for intrapartum/postpartum AZT + 3TC, 14.2% for intrapartum-only AZT + 3TC, and 15.3% for placebo (efficacy compared with placebo: 63%, 42% and 0%, respectively)</td>
</tr>
<tr>
<td>HIVNET 012 trial (Uganda)¹⁵</td>
<td>SD-NVP vs AZT</td>
<td>No antepartum antiretroviral; oral intrapartum: SD-NVP vs oral AZT</td>
<td>SD-NVP within 72 hr of birth (infant only) vs AZT (1 wk), infant only</td>
<td>Breastfeeding (99%; median duration, 9 mo)</td>
<td>11.8% in NVP arm vs 20.0% in AZT arm (42% efficacy) at 6-8 wk; 15.7% in NVP arm vs 25.8% in AZT arm (41% efficacy) at 18 mo</td>
</tr>
<tr>
<td>SAINT trial (South Africa)¹⁶</td>
<td>SD-NVP vs AZT + 3TC</td>
<td>No antepartum antiretroviral; oral intrapartum: SD-NVP vs AZT + 3TC</td>
<td>SD-NVP within 48 hours of birth (mother and infant) vs AZT + 3TC (1 wk), mother and infant</td>
<td>Breastfeeding (42%) and replacement feeding</td>
<td>12.3% in SD-NVP arm vs 9.3% in AZT + 3TC arm at 8 wk (difference not statistically significant, P = .11)</td>
</tr>
<tr>
<td>Perinatal HIV Prevention Trial (PHPT-1; Thailand)¹⁰</td>
<td>Four AZT regimens with different durations of antepartum and infant postpartum administration, no placebo</td>
<td>Long (from 28 wk), short (from 36 wk); oral intrapartum</td>
<td>Long (for 6 wk), short (for 3 d), infant only</td>
<td>Replacement feeding</td>
<td>Short-short arm stopped at interim analysis (10.5%); MTCF 6.5% in long-long arm vs 4.7% in long-short arm and 8.6% in the short-long arm at 6 mo (no statistical difference); in utero transmission significantly higher with short vs long maternal therapy regimens (5.1% vs 1.6%)</td>
</tr>
</tbody>
</table>

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TABLE 1
Results of major studies on antiretroviral prophylaxis to prevent mother-to-child HIV transmission

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Antenatal and intrapartum period</th>
<th>Postpartum period</th>
<th>Mode of infant feeding</th>
<th>Mother-to-child transmission rate and efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACTG 316 trial (Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, UK, and USA)²⁷</td>
<td>SD-NVP vs placebo among women already receiving AZT alone (23%) or AZT + other antiretroviral drugs (77% combination therapy)</td>
<td>Nonstudy antiretroviral regimen; oral intrapartum: placebo vs SD-NVP, + intravenous AZT</td>
<td>Placebo vs SD-NVP within 72 hr of birth + nonstudy antiretroviral drugs (AZT), infant only</td>
<td>Replacement feeding</td>
<td>77% of women received dual or triple-combination antiretroviral regimens during pregnancy</td>
</tr>
<tr>
<td>Perinatal HIV Prevention Trial (PHPT-2; Thailand)¹⁷</td>
<td>AZT alone vs AZT + maternal and infant SD-NVP vs AZT + maternal SD-NVP</td>
<td>AZT from 28 wk; oral intrapartum: AZT alone or AZT + SD-NVP</td>
<td>AZT for 1 wk with or without SD-NVP, infant only</td>
<td>Replacement feeding</td>
<td>AZT-alone arm was stopped because of higher MTCT than the NVP–NVP arm (6.3% vs 1.1%); in arms in which the mother received SD-NVP, MTCT rate did not differ significantly between the infant receiving or not receiving SD-NVP (2.0% vs 2.8%)</td>
</tr>
<tr>
<td>DITRAME Plus (ANRS 1201.0) trial (Abidjan, Côte d’Ivoire)¹⁸</td>
<td>Open label, AZT + SD-NVP</td>
<td>AZT from 36 wk; oral intrapartum: AZT + SD-NVP</td>
<td>SD-NVP + AZT for 1 wk, infant only</td>
<td>Breastfeeding (54%) and replacement feeding</td>
<td>6.5% (95% CI, 3.9%-9.1%) at 6 wk; historic control group receiving short AZT only had MTCT 12.8% (98% breastfed in historic control group)</td>
</tr>
<tr>
<td>DITRAME Plus (ANRS 1201.1) trial (Abidjan, Côte d’Ivoire)¹⁸</td>
<td>Open label, AZT + 3TC + SD-NVP</td>
<td>AZT + 3TC from 32 wk (stopped at 3 d postpartum); oral intrapartum: AZT + 3TC + SD-NVP</td>
<td>SD-NVP + AZT for 1 wk, infant only</td>
<td>Breastfeeding (66%) and replacement feeding</td>
<td>4.7% (95% CI, 2.4%-7.0%) at 6 wk; historic control group receiving short AZT only had MTCT 12.8% (98% breastfed in historic control group)</td>
</tr>
<tr>
<td>NVAZ trial (Malawi)¹⁹</td>
<td>Neonatal SD-NVP vs SD-NVP + AZT</td>
<td>No antepartum or intrapartum antiretroviral (lactocomers)</td>
<td>SD-NVP with or without AZT for 1 wk, infant only</td>
<td>Breastfeeding (100%)</td>
<td>15.3% in SD-NVP + AZT arm and 20.9% in SD-NVP only arm at 6-8 wk; MTCT rate at 6-8 wk among infants who were HIV-uninfected at birth, 7.7% and 12.1%, respectively (36% efficacy)</td>
</tr>
<tr>
<td>Postnatal NVP + AZT trial (Malawi)²⁰</td>
<td>Neonatal SD-NVP vs SD-NVP + AZT</td>
<td>No antepartum antiretroviral; oral intrapartum: SD-NVP</td>
<td>SD-NVP with or without AZT for 1 wk, infant only</td>
<td>Breastfeeding (100%)</td>
<td>16.3% in NVP + AZT arm and 14.1% in SD-NVP only arm at 6-8 wk (difference not statistically significant); MTCT rate at 6-8 wk among infants who were HIV-uninfected at birth, 6.5% and 16.9%, respectively</td>
</tr>
</tbody>
</table>

breastfeeding populations, their efficacy in reducing antepartum and intrapartum transmission is overcome by subsequent risk from breastfeeding transmission.⁴⁻⁶ Efficacy was diminished subsequently (after 6 weeks) with AZT or AZT/3TC short-course regimens in 2 trials that followed infants to 18 months but was much less with SD-NVP in 1 trial. These differences may be explained partially by the prolonged half-life of NVP; detectable drug levels can persist for ≥2 weeks in women after SD-NVP, thereby providing a much longer period of prophylaxis than AZT and 3TC, which

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**TABLE 1**  
Results of major studies on antiretroviral prophylaxis to prevent mother-to-child HIV transmission

Continued from page S45.

<table>
<thead>
<tr>
<th>Study</th>
<th>Drugs</th>
<th>Antenatal and intrapartum period</th>
<th>Postpartum period</th>
<th>Mode of infant feeding</th>
<th>Mother-to-child transmission rate and efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MASHI (Botswana)</td>
<td>Initial: short-course AZT with/without maternal and infant SD-NVP and with/without breastfeeding</td>
<td>First randomization: AZT from 34 wk; oral intrapartum: AZT + either SD-NVP vs placebo</td>
<td>Second randomization: Breastfeeding + AZT (infant) 6 mo + SD-NVP, infant only vs formula feeding + AZT (infant) 4 wk + SD-NVP, infant only</td>
<td>Randomization: 50% breastfeeding (median duration, 5.8 mo), 50% formula feeding</td>
<td>Initial design: in formula-feeding arm. MTCT at 1 mo 2.4% in maternal &amp; infant SD-NVP arm and 8.3% in placebo arm (P = .05); in breastfeeding + infant AZT arm, MTCT at 1 mo 8.4% in SD-NVP arm and 4.1% in placebo arm (difference not statistically significant)</td>
</tr>
<tr>
<td></td>
<td>Revised: Short-course AZT + infant SD-NVP with/without maternal SD-NVP and with/without breastfeeding; women with CD4 &lt;200 receive HAART</td>
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<tr>
<td></td>
<td>Revised design: MTCT at 1 mo 4.3% in maternal + infant SD-NVP arm and 3.7% in maternal placebo + infant SD-NVP arm (no significant difference; no interaction with mode of infant feeding)</td>
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<tr>
<td>Côte d’Ivoire</td>
<td>Open label, NVP-HAART for women who meet WHO criteria for therapy, short AZT + 3TC + SD-NVP for women who do not require therapy</td>
<td>Women who need therapy: AZT + 3TC + NVP during pregnancy; oral intrapartum: continue regimen</td>
<td>Women who need therapy: continue AZT + 3TC + NVP; SD-NVP + AZT for 1 wk, infant only</td>
<td>Primarily replacement feeding</td>
<td>Women who needed therapy: MTCT 2.4% (95% CI, 0.3%-8.5%) at 4-6 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women who do not need therapy: AZT + 3TC from 32 wk; oral intrapartum: AZT + 3TC + SD-NVP</td>
<td>Women who do not need therapy: 3 days AZT + 3TC; SD-NVP + AZT for 1 wk, infant only</td>
<td>Primarily replacement feeding</td>
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<tr>
<td>DREAM cohort (Mozambique)</td>
<td>Open label NVP-HAART</td>
<td>D4T or AZT + 3TC + NVP from 24 wk; oral intrapartum: continued regimen</td>
<td>Mother, if breastfeeding, continue d4T or AZT + 3TC + NVP regimen until weans, then stop antiretroviral; SD-NVP + AZT for 1 wk, infant only</td>
<td>Primarily replacement feeding</td>
<td>2.7% at 6 mo</td>
</tr>
</tbody>
</table>

have significantly shorter half-lives. SD-NVP may protect uniquely against early breast milk HIV transmission, which is likely the highest risk time for breast milk transmission.22 In a study that compared the effect of SD-NVP to short-course AZT on breast milk HIV RNA levels, the SD-NVP regimen significantly reduced breast milk virus for approximately 2-3 weeks, but no reduction was seen with AZT.23 Protection was also observed in a study in South Africa that compared SD-NVP with 6 weeks of AZT infant prophylaxis; AZT was significantly less effective in reducing MTCT in breast-
feeding than formula-fed infants, whereas NVP was equally effective in reducing MTCT, regardless of infant feeding mode.\textsuperscript{24}

**Addition of SD-NVP improves the efficacy of other short-course antiretroviral regimens**

To improve the efficacy of short-course regimens but to retain a simple low-cost approach, researchers have evaluated whether the addition of a potent intrapartum/postpartum intervention (the SD-NVP regimen) to short-course regimens might increase efficacy. The Perinatal HIV Prevention Trial (PHPT)-2 study in non-breastfeeding women in Thailand and the “Diminution de la Transmission Mére-Enfant” (DITRAME) studies in a partly breastfeeding population in Côte d’Ivoire demonstrated that the addition of SD-NVP to short-course AZT alone or to short-course AZT/3TC significantly increases efficacy (Table 1).\textsuperscript{17,18,25,26} Data from Côte d’Ivoire indicate that short-course AZT plus SD-NVP has equivalent efficacy to short-course AZT/3TC plus SD-NVP.\textsuperscript{18} A clinical trial conducted in resource-rich countries, PACTG 316, demonstrated that the addition of SD-NVP did not appear to offer significant benefit in the setting of potent combination antiretroviral therapy throughout pregnancy and very low viral load at the time of delivery.\textsuperscript{27}

**Relative importance of maternal vs infant SD-NVP is unclear**

The relative importance of maternal vs infant SD-NVP in the context of short-course AZT regimens remains unclear. The Thailand PHPT-2 study suggests that the infant SD-NVP dose at age 48 hours may not add significant efficacy to the maternal NVP dose alone.\textsuperscript{17,25,26} Additionally, the Botswana Mashi study showed no difference in transmission rates between women who were given SD-NVP vs placebo in a setting in which women and infants received short-course AZT and infants received SD-NVP.\textsuperscript{17,25,26}

In some countries, a significant proportion of women may lack antenatal care and first appear in the healthcare system in late labor, which is too late to allow the initiation of intrapartum prophylaxis. A Malawi trial in a breastfeeding population evaluated infant prophylaxis when no antepartum or intrapartum maternal ART was received. The addition of 1 week of AZT to infant SD-NVP reduced the risk of transmission by 36% in infants who were HIV-negative at birth, compared with infant SD-NVP alone, from 12.1% at 6-8 weeks in children with SD-NVP alone to 7.7% in infants with SD-NVP plus AZT.\textsuperscript{19} However, when maternal intrapartum NVP was received, which provided preexposure prophylaxis in addition to postexposure prophylaxis, transmission rates at 6-8 weeks that excluded infections at birth were similar for infants who received SD-NVP only (6.5%) and for infants who received the combined NVP/AIDS infant postexposure prophylaxis regimen (6.9%).\textsuperscript{20} which suggests that NVP may have a unique impact on early postpartum transmission through breastfeeding.

**Short-course combination antiretroviral regimens are as effective as HAART for the reduction of MTCT in pregnant women who do not require treatment for their own health**

A study in Côte d’Ivoire evaluated a 2-part PMTCT strategy of NVP-based HAART for women whose condition required therapy for their own health (eligible for treatment) and short-course AZT/3TC plus SD-NVP for women who were not eligible. Transmission in the women who received HAART was 2.4% (95% CI, 0.3%-8.5%), compared with 3.8% (95% CI, 1.0%-9.5%) in women who received the short-course combination regimen \( (P = .7)\).\textsuperscript{28} Additionally, in a study in Mozambique where all women received NVP-based HAART regardless of indication, overall transmission was 2.7%, which was similar to that observed with the 2-part WHO-recommended approach in Côte d’Ivoire.\textsuperscript{29}

**SD-NVP and NVP resistance**

NVP-prolonged half-life is beneficial in that NVP likely prevents postnatal MTCT during the first few weeks of life and intrapartum, but the prolonged presence of the single drug in the mother’s body also promotes the development of drug resistance. NVP drug resistance is well-known to develop in some women who receive either a single-dose or chronic therapy. The risk of NVP resistance after SD-NVP exposure is most strongly related to higher maternal plasma RNA levels and lower CD4 count at the time of exposure.\textsuperscript{30} Other factors that are associated with the development of NVP resistance after MTCT prophylaxis include viral subtype (more common with subtype C and D than with subtype A), compartment (such as archived virus in breast milk or other organs), the number of NVP doses the woman receives during labor (repeat dosing induces more resistance), and the time since SD-NVP was received (resistance more likely closer to the time of exposure).\textsuperscript{31,32}

NNRTI resistance can be detected within the first 6 months after SD-NVP with the use of standard genotyping in approximately 25%-50% of women who receive SD-NVP; however, more sensitive techniques have shown that NVP resistance may occur in as many as 60%-89% of women early after exposure.\textsuperscript{33-36} The proportion of viral variants with NVP resistance declines over time, but low levels of resistant viral populations can be detected in some women for \( \geq 1 \) year after exposure. The clinical significance of such low level resistance is unclear. NVP-resistant viral strains are also selected for women who received NVP in addition to other antiretroviral drugs for the prevention of MTCT, although rates may be lower than in for women who are exposed to SD-NVP alone.\textsuperscript{37}

The women who are most at risk of the development of NVP resistance with exposure to SD-NVP are those women with more advanced HIV disease. Therefore, 1 of the best ways to prevent the development of NVP resistance is likely to be the assessment of all pregnant women for their need for ART by clinical stage and CD4 count during pregnancy, if possible, and the initiation of HAART for those women who require therapy.\textsuperscript{38}

Some data suggest that the incidence of resistance may be decreased if a “tail” of other antiretroviral drugs is given during
ART may be important. A lower rate of sure and the initiation of NNRTI-based NNRTI-based HAART, although clinical and immunologic responses did not differ from those without SD-NVP exposure.43 The time between SD-NVP exposure and the initiation of NNRTI-based ART may be important. A lower rate of maximal viral suppression appears more likely if HAART is started at <6 months after SD-NVP exposure,45 but recent studies from Botswana, South Africa, Côte d’Ivoire, and Zimbabwe suggest that virologic and immunologic response to therapy is the same as in women without SD-NVP exposure if HAART is started 6–18 months after exposure.44–47 Studies are in progress to determine more definitively whether SD-NVP prophylaxis compromises subsequent HAART with NNRTI-based regimens.

WHO Recommendations for the Use of ART for Maternal Treatment and Prevention of MTCT

The new WHO recommendations aim to maximize access to high-quality services at the population level. Tables 2–5 give recommendations for various clinical situations; Table 6 provides dosing information for the regimens.

HIV-infected women who require ART for their own health

A key principle of the new recommendations is that the condition of pregnant HIV-infected women should be evaluated for treatment eligibility and that women who are eligible for treatment should receive ART during pregnancy and should then continue on chronic treatment thereafter. A woman’s clinical stage and, where available, her CD4 cell count should be assessed to determine her eligibility for ART. CD4 cell counts are most important for asymptomatic women. To ensure that pregnant women who require ART are identified, efforts should be made to include CD4 cell count measurement in PMTCT programs or through efficient links between antenatal care and ART services. The choice of antiretroviral regimen in HIV-infected pregnant women must include consideration of fetal drug exposure, while assuring optimal treatment to preserve maternal health. The choice of ART in women with the potential to become pregnant must also include the consideration of the possibility of inadvertent fetal drug exposure during the primary period of fetal organ development.18 The antiretroviral of most concern is efavirenz, because significant central nervous defects have been observed in infant monkeys with in utero efavirenz exposure at drug levels that are similar to those that are seen with human

### Table 2: Recommended antiretroviral regimens for prevention of MTCT in resource-limited countries in different scenarios

<table>
<thead>
<tr>
<th>Variable</th>
<th>Maternal HAART indicated*</th>
<th>Maternal HAART not indicated*</th>
<th>No maternal antepartum antiretrovirals</th>
<th>No maternal antepartum or intrapartum antiretrovirals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum period</td>
<td>HAART*</td>
<td>AZT twice a day at ≥28 wk</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intrapartum period</td>
<td>HAART</td>
<td>SD-NVP† + AZT/3TC</td>
<td>SD-NVP</td>
<td>—</td>
</tr>
<tr>
<td>Postpartum period</td>
<td>HAART</td>
<td>AZT/3TC twice a day × 7 d</td>
<td>AZT/3TC twice a day × 7 d</td>
<td>—</td>
</tr>
<tr>
<td>Infant</td>
<td>AZT × 7 d²</td>
<td>SD-NVP + AZT twice a day × 1 wk²</td>
<td>SD-NVP + AZT twice a day × 4 wk⁶</td>
<td>SD-NVP + AZT twice a day × 4 wk⁶</td>
</tr>
</tbody>
</table>

* Recommended for all HIV-infected pregnant women with WHO clinical stage 4, WHO clinical stage 3 and CD4 <350 cells/mm³, WHO clinical stage 1 or 2 and CD4 <200 cells/mm³. Some experts suggest that ART also be considered for pregnant women with WHO clinical stage 1 or 2 and CD4 <350 cells/mm³, particularly if the CD4 values are near the threshold of 200 cells/mm³.

† Recommended regimen: AZT + 3TC + NVP.

‡ If the woman receives at least 4 weeks of AZT during pregnancy, the omission of the maternal intrapartum NVP dose may be considered; in this case, the infant NVP dose must be given immediately at birth and received for 4 weeks, instead of 1 week of infant AZT; and the mother will not require 3TC during labor and AZT/3TC “tail” postpartum.

§ Data on the added efficacy of 4 compared to 1 week of infant AZT in this situation is limited.

**Table 2:** Recommended antiretroviral regimens for prevention of MTCT in resource-limited countries in different scenarios

**Recommended antiretroviral regimens for prevention of MTCT in resource-limited countries in different scenarios**

- **Maternal HAART indicated:**
  - AZT twice a day at ≥28 wk
- **Maternal HAART not indicated:**
  - SD-NVP + AZT/3TC
- **No maternal antepartum antiretrovirals:**
  - SD-NVP + AZT twice a day × 4 wk⁶
- **No maternal antepartum or intrapartum antiretrovirals:**
  - SD-NVP + AZT twice a day × 4 wk⁶

**Who recommendations for the use of ART for maternal treatment and prevention of MTCT**

To ensure that pregnant women who require ART are identified, efforts should be made to include CD4 cell count measurement in PMTCT programs or through efficient links between antenatal care and ART services. The choice of antiretroviral regimen in HIV-infected pregnant women must include consideration of fetal drug exposure, while assuring optimal treatment to preserve maternal health. The choice of ART in women with the potential to become pregnant must also include the consideration of the possibility of inadvertent fetal drug exposure during the primary period of fetal organ development. The antiretroviral of most concern is efavirenz, because significant central nervous defects have been observed in infant monkeys with in utero efavirenz exposure at drug levels that are similar to those that are seen with human.
### TABLE 3
Advantages and disadvantages of recommended and alternative antiretroviral prophylaxis regimens in resource-limited countries for pregnant women whose condition does not require therapy for their own health*

<table>
<thead>
<tr>
<th>Rank</th>
<th>Time of administration</th>
<th>Advantages</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td>AZT (&gt;28 wks gestation)</td>
<td>SD-NVP* + AZT/3TC Maternal: AZT/3TC $\times$ 7 d; Infant: SD-NVP + AZT $\times$ 7 d†</td>
<td>Highly effective regimen More complex to deliver than other regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Substantially reduces in utero transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal AZT/3TC “tail” may reduce development of maternal NVP resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infant AZT reduces risk of NVP resistance in infants who become infected</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>AZT (&gt;28 wks gestation)</td>
<td>SD-NVP Infant: SD-NVP + AZT $\times$ 7 d†</td>
<td>Highly effective regimen Higher risk of NVP resistance, with possible less than optimal viral response if NNRTI-HAART needed within 6 mo postpartum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Substantially reduces in utero transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infant AZT reduces risk of NVP resistance in infants who become infected</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>—</td>
<td>SD-NVP + AZT/3TC Maternal: AZT/3TC $\times$ 7 d; Infant: SD-NVP</td>
<td>Effective in reducing MTCT Less effective than preferred regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal AZT/3TC “tail” reduces development of maternal NVP resistance Does not reduce in utero transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More complex to deliver than SD-NVP alone</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>SD-NVP Infant: SD-NVP</td>
<td>Effective in reducing MTCT Less effective than preferred regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simplest regimen to administer Does not reduce in utero transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High risk of NVP resistance, with possible less than optimal viral response, if NNRTI-HAART needed within 6 mo postpartum</td>
</tr>
</tbody>
</table>

*If the woman receives at least 4 weeks of AZT during pregnancy, the omission of the maternal NVP dose may be considered; in this case, the infant NVP dose must be given immediately at birth and be received for 4 weeks instead of 1 week of infant AZT; and the mother will not require 3TC during labor and AZT/3TC “tail” after delivery.
†If the mother receives <4 weeks of AZT during pregnancy, 4 weeks instead of 1 week of infant AZT is recommended.

exposure at standard therapeutic doses and in 4 human infants with first-trimester exposure to efavirenz-containing regimens.49-51 Efavirenz should thus be avoided in women of childbearing potential who are not receiving adequate contraception and women in the first trimester of pregnancy. However, for women in whom effective contraception can be assured or women in the second or third trimester (in whom postpartum contraception can be assured), efavirenz is thought to be safe; this may be particularly important for women who are coinfected with tuberculosis, where efavirenz should be considered.

**When to start HAART.** ART should be initiated in pregnant women with...
WHO clinical stage 4,52 WHO clinical stage 3 and CD4 count <350 cells/mm$^3$, or WHO clinical stage 1 or 2 and CD4 count of <200 cells/mm$^3$.6 The optimal time to initiate ART with a CD4 count between 200 and 350 cells/mm$^3$ is unknown for asymptomatic women. Available data suggest that, if NNRTI-based ART is initiated <6 months after exposure to SD-NVP, viral suppression may be compromised$^{43,44}$; some women with CD4 counts between 200 and 350 cells/mm$^3$ may require the initiation of therapy within the first year after delivery. Thus, some experts suggest that ART be considered for pregnant women with stage 1 or 2 and CD4 count of <350 cells/mm$^3$, particularly for women with CD4 cell count nearing the threshold of 200 cells/mm$^3$.

**First-line regimen.** The recommended first-line regimen for pregnant women who are eligible for treatment is AZT + 3TC + NVP.6 These are the antiretroviral drugs with the greatest clinical experience with use in pregnant women and are known to reduce MTCT. However, toxicity, which includes hepatitis, is more common in women who begin receiving NVP-containing ART and who have a CD4 cell count of >250 cells/mm$^3$.33-36 There are concerns about the initiation of NVP-containing ART in women with a CD4 cell count between 250 and 350 cells/mm$^3$. This situation may arise because ART is recommended for pregnant women who have a CD4 cell count of <350 cells/mm$^3$ and WHO clinical stage 3 disease. In general, women have lower CD4 cell counts during pregnancy compared with after delivery, partly because of pregnancy-related hemodilution; the impact of this on the use of the CD4 350 cells/mm$^3$ threshold in pregnant women, especially in women in clinical stage 1 or 2, is not known. Approaches to this issue include the initiation of a NVP-con-

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Time of administration</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended</strong></td>
<td>SD-NVP + AZT/3TC</td>
<td>Maternal: AZT/3TC x 7 d; Infant: SD-NVP + AZT for 4 wks</td>
<td>SD-NVP is effective in reducing MTCT by &gt;40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal AZT/3TC “tail” reduces development of maternal NVP resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In breastfeeding population, NVP-based regimen may be advantageous</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infant AZT reduces risk of NVP resistance in infants who become infected$^{29}$</td>
</tr>
<tr>
<td><strong>Alternative</strong></td>
<td>AZT/3TC</td>
<td>Maternal: AZT/3TC x 7 d; Infant: SD-NVP</td>
<td>Equal efficacy to intrapartum/postpartum SD-NVP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No risk of NVP resistance in women or infants should they become infected</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>SD-NVP + AZT/3TC</td>
<td>Maternal: AZT/3TC × 7 d; Infant: SD-NVP</td>
<td>SD-NVP is effective in reducing MTCT by &gt;40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maternal AZT/3TC infant: SD-NVP “tail” reduces development of maternal NVP resistance</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>SD-NVP</td>
<td></td>
<td>SD-NVP is effective in reducing MTCT by &gt;40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Simplest regimen to administer</td>
</tr>
</tbody>
</table>
maintaining regimen with close monitoring in the first 12 weeks of therapy, the initiation of an efavirenz-containing regimen (if after 12 weeks of gestation and effective contraception can be assured after delivery), or the administration of a triple NRTI or a protease inhibitor (PI) based regimen. Each approach has advantages and disadvantages, and there are currently no data to favor 1 approach over the other.

**HIV-infected pregnant women whose condition does not require ART or where ART is not available: antiretroviral prophylaxis for PMTCT**

HIV-infected women who are seen during pregnancy (Tables 2 and 3). The recommended regimen for antiretroviral prophylaxis of MTCT is AZT that is started at 28 weeks of gestation or as soon as feasible thereafter, intrapartum SD-NVP, and single-dose infant NVP combined with 1 week of AZT. In addition, intrapartum AZT/3TC followed by 7 days of maternal postpartum AZT/3TC is recommended to reduce the development of NVP resistance. In situations in which infrastructure or availability of antiretrovirals is limited, at least the SD-NVP regimen should be given, ideally coupled with the intrapartum/postpartum AZT/3TC “tail”, if possible.

If the mother has received <4 weeks of AZT, the duration of infant AZT prophylaxis should be increased from 1-4 weeks. The recommendation for longer infant dosing when the mother has received only a short-course of antepartum AZT is based on the Thailand PHPT-1 study (Table 1), in which AZT that was started at 36 weeks of gestation and given to the infant for 4-6 weeks was superior to AZT that was started at 36 weeks of gestation and given to the infant for 3 days.

Repeat dosing of maternal SD-NVP during labor in women who received a dose during “false labor” generally is not recommended because the risk of NVP resistance is higher after 2 NVP doses. Consideration can be given to the omission of the maternal intrapartum NVP dose if the mother has received >4 weeks of antepartum AZT, based on the Mashi data (Table 1). Additionally, because transplacental NVP passage to the infant requires 1-2 hours, if delivery is imminent, maternal intrapartum NVP dosing may be omitted. When the maternal NVP dose is not received, the infant should receive SD-NVP immediately after birth and should receive 4 weeks rather than 1 week of AZT. No AZT/3TC tail is required if no maternal NVP is given.

**HIV-infected women who are in labor and who have not received antiretroviral prophylaxis** (Tables 2 and 4). The recommended regimen for women in labor who have not received antepartum antiretroviral prophylaxis (eg, women with a diagnosis of HIV late in pregnancy) is intrapartum SD-NVP combined with the intrapartum and 7-day postpartum AZT/3TC tail. The infant should receive SD-NVP combined with AZT for 4 weeks.

Alternative regimens include intrapartum AZT/3TC plus 1 week of infant and maternal AZT/3TC. This intrapartum/postpartum regimen had equivalent early efficacy to SD-NVP in the South African Nevirapine Trial (SAINT). In settings with very limited infrastructure, the minimum intervention of SD-NVP to mother and/or infant should be administered.

### TABLE 5

<table>
<thead>
<tr>
<th>Ranking</th>
<th>Postpartum period</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended</td>
<td>Infant: SD-NVP (at birth) + AZT × 4 wk</td>
<td>Infant SD-NVP plus AZT is more effective in reducing MTCT than SD-NVP alone</td>
<td>More complex to deliver than SD-NVP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consistent with recommended PMTCT regimen when mother receives antepartum or intrapartum prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Alternative</td>
<td>Infant: SD-NVP (at birth) + AZT × 1 wk</td>
<td>Clinical trial data demonstrate that infant SD-NVP plus 1 wk of AZT is more effective in reducing MTCT than SD-NVP alone</td>
<td>More complex to deliver than SD-NVP alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infant AZT reduces the risk of NVP resistance</td>
<td>Data on added efficacy of 4 wk of infant AZT in this situation limited</td>
</tr>
<tr>
<td>Minimum</td>
<td>Infant: SD-NVP (at birth)</td>
<td>Infant prophylaxis with SD-NVP was equivalent to infant prophylaxis with 6 wk of AZT</td>
<td>Risk of NVP resistance in infants who become infected despite NVP prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simplest regimen to administer</td>
<td></td>
</tr>
</tbody>
</table>
The 7-day tail includes AZT that is given during labor in addition to 3TC. If the mother receives pediatric formulations exist for the main drugs that is used in current prophylactic regimens to prevent transmission (AZT, NVP and 3TC). If the mother requires antiretroviral drugs for the treatment of HIV infection, standard adult treatment doses are used for the mother during the antepartum, intrapartum and postpartum periods.

<table>
<thead>
<tr>
<th>Regimen with ante-, intra-, and postpartum components</th>
<th>Antenatal period</th>
<th>Intrapartum period</th>
<th>Postpartum period</th>
<th>Postnatal period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother requires therapy for maternal health (recommended first-line therapy)</td>
<td>Mother: AZT 300 mg twice a day + 3TC 150 mg twice a day + NVP 200 mg twice a day</td>
<td>Mother: AZT 300 mg twice a day + 3TC 150 mg twice a day + NVP 200 mg twice a day</td>
<td>Mother: AZT 300 mg twice a day + 3TC 150 mg twice a day + NVP 200 mg twice a day</td>
<td>Infant: AZT 4 mg/kg twice a day for 7 d</td>
</tr>
<tr>
<td>AZT + SD-NVP</td>
<td>Mother: AZT 300 mg twice a day starting at 28 wk or as soon as possible thereafter</td>
<td>Mother: AZT 600 mg at onset of labor + SD-NVP 200 mg at onset of labor OR AZT 300 mg at onset of labor and every 3 hr until delivery + SD-NVP 200 mg at onset of labor</td>
<td>None</td>
<td>Infant: NVP 2 mg/kg oral suspension or 6 mg at once immediately after birth OR NVP 2 mg/kg oral suspension immediately after birth</td>
</tr>
<tr>
<td>Seven-day tail of AZT plus 3TC</td>
<td>None</td>
<td>Mother: 3TC 150 mg at onset of labor and every 12 hours until delivery</td>
<td>AZT 300 mg twice a day for 7 d + 3TC 150 mg twice a day for 7 d</td>
<td></td>
</tr>
<tr>
<td>Regimen with intrapartum and postpartum components</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Infant: NVP 2 mg/kg oral suspension immediately after birth + AZT 4 mg/kg twice a day for 4 wk</td>
</tr>
<tr>
<td>AZT + SD-NVP</td>
<td>None</td>
<td>Mother: AZT 600 mg at onset of labor + SD-NVP 200 mg at onset of labor OR AZT 300 mg at onset of labor and every 3 hrs until delivery + SD-NVP 200 mg at onset of labor</td>
<td>None</td>
<td>Infant: NVP 2 mg/kg oral suspension immediately after birth + AZT 4 mg/kg twice a day for 4 wk</td>
</tr>
<tr>
<td>AZT + 3TC</td>
<td>None</td>
<td>Mother: AZT 600 mg at onset of labor + 3TC 150 mg at onset of labor, followed by 3TC 150 mg every 12 hr until delivery OR AZT 300 mg at onset of labor and every 3 hrs until delivery + 3TC 150 mg at onset of labor, followed by 3TC 150 mg every 12 hr until delivery</td>
<td>Mother: AZT 300 mg twice a day + 3TC 150 mg twice a day for 7 d</td>
<td>Infant: AZT 4 mg/kg twice a day + 3TC 2 mg/kg twice a day for 7 d</td>
</tr>
<tr>
<td>SD-NVP</td>
<td>None</td>
<td>NVP 200 mg at onset of labor</td>
<td>None</td>
<td>Infant: NVP 2 mg/kg oral suspension immediately after birth</td>
</tr>
<tr>
<td>Regimen with only the infant component</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Infant: NVP 2 mg/kg oral suspension immediately after birth + AZT 4 mg/kg twice a day for 4 wk</td>
</tr>
</tbody>
</table>

* All regimens are administered by mouth. Pediatric formulations exist for the main drugs that is used in current prophylactic regimens to prevent transmission (AZT, NVP and 3TC). If the mother requires antiretroviral drugs for the treatment of HIV infection, standard adult treatment doses are used for the mother during the antepartum, intrapartum and postpartum periods. Infants who are prescribed SD-NVP can receive the dose immediately after delivery or within 72 hours. Giving the infant the NVP dose as soon as possible after childbirth and before discharge from the health facility is preferable, and many programs to prevent MTCT have found this to be more practical than the administration of the dose at 48 or 72 hours after delivery. If the mother receives <4 weeks of AZT during pregnancy, 4 weeks instead of 1 week of AZT is recommended for the infant. The 7-day tail includes AZT that is given during labor in addition to 3TC.
Infants who are born to HIV-infected women who have not received antiretroviral drugs during pregnancy or labor (Tables 2 and 5)

The recommended regimen for infants whose mothers have been unable to receive any antiretroviral prophylaxis is SD-NVP plus 4 weeks of AZT. Based on results from a randomized 4-group clinical trial in a non-breastfeeding population in Thailand that investigated the efficacy of AZT prophylaxis that was given for varying durations to pregnant women and infants, the regimen that consists of SD-NVP and AZT for 4 weeks for the infant is likely to be more effective than SD-NVP and 1 week of AZT. However, as noted earlier, the duration of recommended infant AZT is based on limited data, and 1 week is a potential alternative. Although infant-only SD-NVP was found to have equivalent efficacy to 6 weeks of AZT in a trial in South Africa, the Nevirapine and Zidovudine (NVAZ) in Malawi demonstrated that, when the mother has not received any antiretroviral drugs, SD-NVP combined with 1 week of AZT is more efficacious than SD-NVP alone.

HIV-infected women who are breastfeeding

The WHO recommends exclusive breastfeeding for HIV-infected women for the first 6 months of life, unless replacement feeding is acceptable, feasible, affordable, sustainable, and safe for them and their infants before that time. When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breastfeeding by HIV-infected women is recommended. For breastfeeding women who meet the WHO criteria for the initiation of therapy for their own health, ART is recommended, because the benefit to the health of the woman outweighs potential risks to the infant. This symptomatic group of infected women, who have high viral loads and suppressed immune systems, is also likely the highest risk group to transmit HIV to their infant through breastfeeding.

The safety and efficacy of ART for the prevention of breast milk transmission in women who do not require ART for their own health remains a research question. The use of NVP in women with CD4 of >250 cells/mm³ carries a significant risk of hepatic toxicity; thus, alternative regimens are needed. There are very limited data about penetration of antiretrovirals into breast milk; if there is differential penetration, some drugs may have high levels, and others may have low or undetectable levels, which leads to the potential for the induction of drug-resistant HIV in milk and the potential for toxicity in the infant. Data from Botswana indicate that levels of NVP in breast milk of women who receive NVP-based ART were lower than in maternal plasma, although levels of 3TC and AZT in breast milk were 3-fold higher. Data from Zimbabwe in women who were exposed to SD-NVP indicate that NVP resistance was found more frequently in breast milk than maternal plasma and that there were divergent resistance mutations found between breast milk and plasma. Whether HIV RNA or DNA is more important in breast milk transmission is not known; some data suggest that cell-associated virus is more important in the early months of breastfeeding. Thus, the risks and benefits of ART solely for the prevention of breast milk transmission must be elucidated more fully before this can be recommended. Several studies are currently ongoing to address this issue. Several studies are also assessing the efficacy of antiretroviral prophylaxis to the breastfeeding infant to prevent MTCT. Observational studies have suggested this may be effective, but safety and efficacy must be validated in clinical trials before this can be recommended.

Comment

The WHO recommends a tiered approach for the delivery of antiretroviral drugs for treatment of HIV-infected pregnant women and for PMTCT of HIV in resource-limited settings that includes (1) ART for pregnant women who are eligible for treatment, (2) a combination PMTCT prophylaxis regimen for pregnant women who are not eligible for ART or where ART is not available, and (3) the maintenance of a minimum SD-NVP where more effective regimens are not yet available, although steps are taken to provide more effective regimens. To ensure that pregnant women who require ART are identified, efforts should be made to include CD4 cell count measurement in PMTCT programs or through active links between antenatal care and ART services. These interventions must also become part of routine maternal and child health and maternity activities at different levels of the healthcare system to address the HIV epidemic adequately.

Acknowledgment

We thank the WHO and the group of experts who participated in several WHO technical consultations that led to the development of these guidelines.

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Use of single-dose nevirapine for the prevention of mother-to-child transmission of HIV-1: does development of resistance matter?

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The World Health Organization (WHO) estimated that, in 2005, 40.3 million people were living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) worldwide, with most of these people in sub-Saharan Africa. With current standards for HIV treatment in the United States, Canada, and Western Europe, approximately 9 million of those individuals meet the criteria for antiretroviral treatment. With increasing availability of antiretroviral drugs in resource-poor settings, an increasing number of HIV-infected people are now being placed on treatment.

Despite increased attention to the global AIDS epidemic, HIV-1 mother-to-child transmission (MTCT) continues to be a problem, with >600,000 children infected every year. In resource-rich countries, potent antiretroviral drug regimens are available for the prevention of MTCT (PMTCT); guidelines for pregnant HIV-infected women include zidovudine (ZDV) from 28 weeks of gestation, through delivery, and after delivery to the infant. Combination treatment is provided to women with viral loads of >1000 copies/mL and may also be considered for women with viral loads of <1000 copies/mL. Nonpregnant HIV-infected patients in developed countries qualify for antiretroviral treatment if they are symptomatic or have a CD4 count of <200 cells/mm$^3$, and consideration is given to the initiation of treatment in patients with CD4 counts of 201-350 cells/mm$^3$. However, in resource-limited settings, many women are unaware of their HIV status, and access to antiretrovirals is often limited. Even if antiretrovirals are available for HIV treatment, only 10%-20% of pregnant HIV-positive women in Africa are expected to be eligible for highly active antiretroviral therapy (HAART) for their own health. Therefore, 80%-90% of women will continue to rely on simpler regimens for PMTCT, which include single-dose nevirapine (SD-NVP) or combination regimens that include SD-NVP.

In 1999, the HIV Network for Prevention Trials (HIVNET) 012 trial in Uganda demonstrated that the provision of a single 200 mg dose of NVP to women in labor and a single 2 mg/kg dose of NVP to their infants within 72 hours of birth could reduce the risk of MTCT by nearly one-half. This is the simplest PMTCT regimen to implement; at least 7 clinical trials that included >4000 mother-infant pairs have documented its safety and efficacy. SD-NVP is also the least expensive regimen available for PMTCT. Although greater efficacy has been demonstrated using more complex antiretroviral regimens, SD-NVP is often the most deliverable and sustainable option for PMTCT in settings with limited resources. Currently, the WHO recommends that women who...
are not eligible for HAART for their own health receive ZDV, starting at 28 weeks of gestation or as soon as possible thereafter, with SD-NVP and lamivudine (3TC) at the onset of labor and ZDV/3TC for 7 days after delivery. The administration of ZDV/3TC after delivery is recommended to reduce the development of NVP resistance. Infants should receive SD-NVP after birth plus ZDV for 7 days. In areas that do not have the capacity to deliver this regimen, SD-NVP alone is recommended.15,16

Despite the programmatic advantages and efficacy of SD-NVP, several studies have demonstrated the selection of NVP-resistant HIV-1 variants after SD-NVP exposure.17,18 Other studies have demonstrated the emergence of NVP resistance after SD-NVP in combination with other antiretrovirals.19-21 This is in contrast to ZDV, which is also given for PMTCT prophylaxis, in which resistance requires multiple mutations and generally develops after months of drug exposure.22

The high prevalence of NVP resistance after SD-NVP prophylaxis raises 2 concerns: (1) that SD-NVP may not be as effective for PMTCT in repeat pregnancies and (2) that persistence of NVP-resistant strains may compromise the future treatment of women with nonnucleoside reverse transcriptase inhibitor (NNRTI)–containing regimens. This is a major concern, because the first-line treatment regimen for women who require HAART for their own health in most resource-limited settings is an NNRTI-based regimen.23 With the growing availability of antiretrovirals in resource-limited countries, an increasing number of SD-NVP–exposed women are expected to initiate treatment with an NNRTI-based HAART regimen in the years to come. This article reviews data on NVP resistance after SD-NVP prophylaxis, on what is known currently about the effectiveness of NNRTI-based HAART after SD-NVP, and on the effectiveness of SD-NVP in repeat pregnancies. It also highlights areas for additional research.

**NVP Resistance in Women After SD-NVP**

Antiretroviral resistance is detected most commonly through the use of genotypic assays. Genotyping assays detect viral resistance-associated mutations in the relevant viral genes. Most commonly used genotyping assays can detect drug-resistant viruses that represent at least 10%-20% of the circulating virus population. More sensitive assays can detect specific resistance-associated mutations at lower levels.

NVP resistance frequently emerges after SD-NVP exposure and has been detected in 19%-76% of women 2-8 weeks after the administration of SD-NVP.17,19,24-26 HIV-1 variants with NVP resistance mutations also may exist at low levels in some HIV-1–infected individuals even before antiretroviral drug exposure.27,28 NVP can often be detected in maternal serum for 2-3 weeks after delivery29-31 in women who are exposed to a single 200 mg oral dose at delivery. This provides time for the selection of NVP-resistant strains. Different rates of NVP resistance are seen in women with different HIV-1 subtypes after SD-NVP (eg, 19% in subtype A, 36% in subtype D, and 69% in subtype C).24,32 It is particularly concerning that subtype C is associated with high rates of NVP resistance, because most HIV infections in southern Africa are subtype C and because this is precisely where SD-NVP is used most commonly. The emergence of NVP resistance after SD-NVP is also associated with higher viral loads and lower CD4 cell counts at the time of exposure17 and with increased pharmacokinetic exposure to NVP after a single dose (longer median NVP elimination half-life and decreased median oral clearance).33,34 NVP resistance is detected after SD-NVP in an even greater portion of women with the use of more sensitive resistance assays, such as mutation-specific polymerase chain reaction and LigAmp assay.18,35-37

The most common NVP mutation that is seen in women after SD-NVP exposure is the lysine (K) to asparagine (N) mutation at codon 103 (K103N). In some patients who are infected with K103N-containing strains, these variants may persist for years, even with no further antiretroviral drug exposure.38 K103N-containing variants can also persist for extended periods in patients after the discontinuation of NNRTI-containing treatment regimens.39 Testing of SD-NVP–exposed women with the use of sensitive resistance assays has shown that NVP-resistant variants fade to undetectable levels in most women within a year of SD-NVP exposure but that these variants can persist at low levels in some women for ≥1 year after SD-NVP exposure.18,35,40,41 Persistence of K103N-containing variants in cellular DNA after SD-NVP exposure appears to be uncommon.40 However, further studies are needed both to confirm these findings and to evaluate the persistence of NVP-resistant strains in other cellular compartments after the administration of SD-NVP. Studies are also needed to determine whether repeated use of SD-NVP influences emergence or persistence of NVP-resistant strains.

**NVP Resistance in Infants After SD-NVP**

NVP resistance is also seen in infants who become HIV-infected, despite SD-NVP prophylaxis. At 6-8 weeks of age, NVP resistance was detected in 46% of infected Ugandan infants17 and 87% of Malawian infants42 and at 4-12 weeks in 45% of South African infants.43 The most common NVP-resistance mutation that has been detected in infants after SD-NVP exposure is tyrosine to cysteine at HIV reverse transcriptase codon 181.17,25 Routine genotyping assays suggest that most NVP-resistant strains fade from detection in infants by 12 months of age.17 However, more sensitive assays show that NVP-resistant strains can persist in infants above baseline levels for at least 1 year after SD-NVP.25 Further studies are needed to evaluate the impact of previous SD-NVP exposure on future treatment of HIV-infected children with NNRTI-containing regimens.

NVP is also transferred to breast milk after women receive SD-NVP. NVP concentrations in breast milk and the half-life of NVP in breast milk are slightly less than or similar to the levels in maternal serum.44 The presence of NVP in breast
milk may help to reduce the risk of MTCT during breastfeeding by suppressing breast milk viral load, but this also allows for the selection of NVP-resistant strains in breast milk, which may be transmitted to breastfeeding infants. In 1 study, 65% of women had at least 1 NVP resistance mutation detected in breast milk 8 weeks after receiving SD-NVP. There are little data available on the long-term persistence of NVP-resistant strains in breast milk, despite the fact that many women breastfeed for ≥1 year in resource-limited settings. Further studies are needed to identify factors that influence the emergence and persistence of NVP resistance in breast milk after SD-NVP and to assess the impact of NVP resistance on MTCT and transmission of NVP-resistant strains to breastfeeding infants.

**Response to Treatment After SD-NVP**

Several studies suggest that NNRTI-containing treatment regimens may still be effective as first-line therapy in women with previous SD-NVP exposure, particularly if, as 1 study suggests, there is sufficient time between SD-NVP dosing and treatment initiation. (Table 1).

The Thai Perinatal HIV Prevention Trials (PHPT)-2 study assessed the efficacy of an NNRTI-based treatment regimen in SD-NVP–exposed vs unexposed women. The analysis included 269 women who had previously received short- or long-course ZDV (from 35 or 28 weeks of gestation, respectively), 221 of whom (85%) also received SD-NVP in labor for PMTCT. Baseline characteristics, such as viral load and CD4 cell count, were comparable among NVP-exposed and unexposed women. However, the time between delivery and treatment initiation differed in the 2 groups (median, 6.1 months in the NVP-exposed group and 14.9 months in the unexposed group). A lower rate of virologic response was seen in NVP-exposed women compared with unexposed women; 49% and 68% of women, respectively, had a viral load of <50 copies/mL after 6 months of treatment \( (P<.03) \). However, this difference was not seen when the analysis was restricted to a subset of unexposed women with a median time between delivery and treatment initiation similar to that of the SD-NVP–exposed group of women. The authors also reported that, among SD-NVP–exposed women, there were no differences in virologic response between those who started HAART within 6 months of exposure to SD-NVP and those who started HAART >6 months after exposure to SD-NVP, although the specific response rates in these 2 groups were not reported.

The Mashi study in Botswana randomly assigned women during pregnancy to receive SD-NVP or placebo at delivery in addition to short-course ZDV from 34 weeks of gestation to prevent MTCT. After delivery, women who had either a CD4 cell count of <200 cells/mm³ or an AIDS-defining illness were offered HAART. NVP-based HAART was initiated in 218 women after SD-NVP exposure. More than 90% of women had follow-up virologic measurements available at 6 months, and 87%-89% of NVP-exposed and unexposed women, respectively, had follow-up at 12 months after treatment initiation. In 60 of those women (28%), HAART was initiated within 6 months of

<table>
<thead>
<tr>
<th>Study</th>
<th>PMTCT regimen for exposed women</th>
<th>Patients (n)</th>
<th>Viral load threshold for treatment response</th>
<th>Time since nevirapine-based HAART was started until assessment of virologic response</th>
<th>SD-NVP–exposed women who responded to treatment (%)</th>
<th>Un-exposed women who responded to treatment (%)</th>
<th>( P ) value for difference in treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>ZDV + SD-NVP</td>
<td>269*</td>
<td>&lt;50</td>
<td>6 mo</td>
<td>49</td>
<td>68</td>
<td>.03</td>
</tr>
<tr>
<td>Botswana</td>
<td>ZDV ± SD-NVP</td>
<td>158† (&gt;6 mo since exposure)</td>
<td>&lt;400</td>
<td>6 mo</td>
<td>88</td>
<td>92</td>
<td>.39</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>12 mo</td>
<td>88</td>
<td>86</td>
<td>.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60† (&lt;=6 mo since exposure)</td>
<td>6 mo</td>
<td>86</td>
<td>100                  (&lt;.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 mo</td>
<td>54</td>
<td>97</td>
<td>(&lt;.0001)</td>
</tr>
<tr>
<td>South Africa</td>
<td>SD-NVP</td>
<td>90‡</td>
<td>&lt;50</td>
<td>6 mo</td>
<td>100</td>
<td>76</td>
<td>Not reported</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>ZDV or SD-NVP</td>
<td>41§</td>
<td>&lt;500</td>
<td>12 mo</td>
<td>71</td>
<td>70</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 mo</td>
<td>50</td>
<td>56</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

* Thailand: 269 women (48 SD-NVP–exposed; 221 unexposed).
† Botswana: 218 women (112 SD-NVP–exposed; 106 unexposed).
‡ South Africa: 90 women (60 SD-NVP–exposed; 30 unexposed); results are an interim analysis of first 55 women (38 SD-NVP–exposed; 17 unexposed) who had viral load data completed at 6 months.
§ Zimbabwe: 41 women (27 SD-NVP–exposed; 14 unexposed).
NVP exposure. When treatment was initiated at least 6 months after SD-NVP exposure, there was no difference in virologic response (viral load <400 copies/mL) between SD-NVP–exposed vs unexposed women. In contrast, when HAART was initiated <6 months after SD-NVP exposure, a poorer virologic response was seen in NVP-exposed women compared with unexposed women, with 42% and 0% of women, respectively, failing to respond after 6 months of treatment ($P < .0001$). Similarly, results were obtained at 12 and 24 months after treatment initiation. Among 30 infants who received either SD-NVP or placebo within 72 hours of birth and who had data available after a later start of NVP-based antiretroviral therapy, there was a higher rate of virologic failure among the SD-NVP–exposed infants than the unexposed infants. At 6 months, 77% of SD-NVP–exposed vs 9% of unexposed infants had virologic failure ($P < .0001$).

Similarly, in a South African study, 90 women with previous deliveries were followed for treatment outcomes after the initiation of an NNRTI-based regimen; 60 of the women (67%) were SD-NVP–exposed. The median time between delivery and treatment initiation was 18 months in NVP-exposed women and 36 months in unexposed women. There were no significant differences in virologic response among the SD-NVP–exposed vs unexposed women. Among 53 SD-NVP–exposed women who had 24-week outcome data, all had viral loads <50 copies/mL.

A smaller study in Zimbabwe that assessed treatment response at 48 weeks in 41 women and 28 men included 27 women who previously had received ZDV and 14 women who previously had received SD-NVP for PMTCT. There were no significant differences in virologic suppression between SD-NVP–exposed and unexposed women. However, the virologic response was better in men than women overall (viral loads of <500 copies/mL were achieved in 93% of men and 71% of women; viral loads of <50 copies/mL were achieved in 79% of men and 53% of women; $P < .025$).

A study from Cote d’Ivoire evaluated immunologic response to an NNRTI-containing regimen among 115 SD-NVP–exposed and 94 unexposed women. The median time between delivery and treatment initiation was 19 months. At 6 months after treatment initiation, there were no significant differences in immunologic response, which was measured by a change in CD4 cell count between SD-NVP–exposed and unexposed women (median increase, 189 CD4 cells/mm$^3$ vs 222 CD4 cells/mm$^3$, respectively; $P = .53$). Previous SD-NVP also did not appear to influence immunologic response to treatment in the other studies that were described earlier.

In Zambia, an analysis of maternal immunologic response and clinical outcomes on NNRTI-based HAART after self-reported exposure to SD-NVP compared NVP-exposed women to unexposed women. Increases in CD4 count from baseline among SD-NVP–exposed vs unexposed women were similar at 6 months (mean increase, 202 vs 182 cells/mm$^3$; $P = .20$) and 12 months (mean increase, 201 vs 211 cells/mm$^3$; $P = .94$). However, among women who initiated treatment within 6 months of SD-NVP exposure vs women who initiated treatment >6 months after SD-NVP exposure, there was a trend towards a less favorable CD4+ cell response at 6 months (mean increase, 150 vs 219 cells/mm$^3$; $P = .06$) and at 12 months (mean increase, 149 vs 215 cells/mm$^3$; $P = .39$).

Further research is needed to confirm the findings of available studies and to determine the optimal time to initiate treatment for HIV infection in SD-NVP–exposed women with different HIV subtypes and different stages of HIV disease. Additional studies are also needed to examine the risk of the reemergence of NVP resistance in NVP-unexposed vs -exposed women who start treatment with NNRTI-containing regimens.

Similar studies are needed in children who are infected with HIV, despite prophylaxis with SD-NVP or other NVP-containing regimens. HIV-1 disease often progresses quickly in infants, and the mortality rate of HIV-1–infected infants is high in the first 2 years of life. Antiretroviral treatment is often indicated in very young infants, when NVP-resistant virus may still be circulating.

**Effectiveness of SD-NVP in Subsequent Pregnancies**

Two studies have evaluated the effectiveness of SD-NVP prophylaxis in women who received the same regimen in a previous pregnancy. A follow-up study of 207 women from the HIVNET 012 cohort and a PMTCT program in Uganda found no difference in transmission risk among NVP-exposed women compared with unexposed women (20.6% vs 18.7%, respectively; $P = .81$). In that study, the median time between delivery and previous SD-NVP exposure was 32 months. Similar results were seen in a study that was conducted in South Africa and Cote d’Ivoire. In both first and subsequent pregnancies, women in South Africa received SD-NVP and women in Cote d’Ivoire received SD-NVP plus a short-course of other antiretrovirals for PMTCT. The median time between delivery and previous SD-NVP exposure was 22 months in South Africa and 23 months in Cote d’Ivoire. Among 108 women in both studies, HIV transmission risk was equal in first and second pregnancies (10.5% in both first and second pregnancies in South Africa and 8.6% in both pregnancies in Cote d’Ivoire).

**Addition of Antiretrovirals After Delivery to Reduce the Risk of NVP Resistance After SD-NVP**

Two studies have investigated whether the risk of NVP resistance after SD-NVP can be reduced by the addition of ZDV/3TC for 3-7 days after delivery. This “tail” provides additional antiretroviral coverage while NVP levels in plasma are declining. A study from South Africa compared NVP resistance among 226 women who received a short antenatal course of ZDV plus either SD-NVP alone or SD-NVP plus a 4- or 7-day ZDV/3TC tail. The risk of NVP resistance was 60%
in women and 78% in infants with SD-NVP alone at 6 weeks after exposure. In contrast, when the mother received a 4-day ZDV/3TC tail, the risk of NVP resistance was 13% in both women and infants; when the mother received a 7-day ZDV/3TC tail, the risk was 9% in women and 0% in infants. Similarly, a study in Cote d’Ivoire compared NVP resistance in women who received ZDV from 36 weeks of gestation plus either SD-NVP alone or SD-NVP plus a 3-day postpartum course of ZDV/3TC. NVP resistance was detected at 4 weeks after delivery in 33% of women in the SD-NVP alone arm and in 1% of women who received the 3-day ZDV/3TC tail.

Additional studies are needed to determine whether a postpartum course of 7 days of ZDV/3TC after SD-NVP is optimal for reduction of the risk of NVP resistance. Studies are also needed to determine whether the addition of a ZDV/3TC tail influences the subsequent response of women to an NNRTI-containing treatment regimen. And finally, in resource-limited settings, one must consider whether it is logistically feasible to provide a ZDV/3TC tail after SD-NVP exposure.

**Ongoing and Planned Studies**

At least 4 ongoing studies are evaluating interventions to complement NVP-containing PMTCT regimens and to reduce the development of NNRTI resistance mutations. These include (1) a US Centers for Disease Control and Prevention–sponsored study of 200 mother-infant pairs in Lilongwe, Malawi, where women and newborn infants received SD-NVP plus a 7-day tail of ZDV/3TC or SD-NVP alone; (2) a study in Lusaka, Zambia, where 400 women who accessed SD-NVP in addition to ZDV in antenatal care are randomly assigned at delivery to receive a single dose of tenofovir/emtricitabine or no additional intervention; (3) a US National Institutes of Health–sponsored study by the AIDS Clinical Trials Group in India, Haiti, and possibly other countries where 420 mother-infant pairs will be provided 1 of 3 antiretroviral regimens (ZDV/3TC, tenofovir/emtricitabine, and ritonavir-boosted lopinavir) for either 7 or 21 days after SD-NVP exposure; and (4) a 3-arm Pediatric AIDS Clinical Trials Group study that compares 7 days of ZDV + didanosine + ritonavir-boosted lopinavir vs 30 days of ZDV + didanosine + ritonavir-boosted lopinavir vs 30 days of ZDV + didanosine.

Three ongoing studies are assessing maternal response to NNRTI-containing HAART after SD-NVP exposure for PMTCT. These include (1) a US Centers for Disease Control and Prevention–sponsored study in Thailand, Kenya, and Zambia that is prospectively enrolling SD-NVP–exposed and unexposed women who are matched for CD4 count and clinical disease stage and commencing NNRTI-containing HAART (women with varying time periods between exposure and treatment initiation are enrolled and rates of viral suppression [defined as <400 copies/mL]) are being compared; (2) a US National Institutes of Health–sponsored AIDS Clinical Trials Group study at several sites in Africa that is randomly assigning SD-NVP–exposed and unexposed women to NNRTI vs protease inhibitor–containing HAART in 2 parallel randomized trials; all participants have >6 months since exposure; and (3) a study in South Africa that is also assessing the response of SD-NVP–exposed and unexposed women to NNRTI-based treatment; all participants in this study have at least 18 months between SD-NVP exposure and the start of therapy. This is an important entry criterion, because it likely will be the most common scenario in real practice as women who require HAART for their own health increasingly initiate treatment during pregnancy (Table 2).

**Comment**

Although preliminary, currently available data indicate that SD-NVP is effective for PMTCT in repeat pregnancies and that SD-NVP exposure does not compromise future treatment with an NNRTI-regimen, so long as treatment is initiated at least 6 months after SD-NVP exposure. The 1 study that assessed virologic response rates among women who initiated treatment within 6 months of SD-NVP exposure found a suboptimal response rate in these women, compared with women who began treatment >6

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**Table 2**

**Summary of ongoing evaluations to determine virologic consequences of previous SD-NVP exposure among women who start NNRTI-containing HAART**

<table>
<thead>
<tr>
<th>Name</th>
<th>Sponsor</th>
<th>Countries</th>
<th>Design</th>
<th>N</th>
<th>Exposure Interval</th>
<th>Primary Outcome</th>
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<tbody>
<tr>
<td>NNRTI Response Study</td>
<td>US Centers for Disease Control and Prevention</td>
<td>Zambia, Thailand, Kenya</td>
<td>Prospective cohort; SD-NVP–exposed and unexposed</td>
<td>900 (ratio of 1 SD-NVP–exposed: 1.5 unexposed)</td>
<td>Any</td>
<td>Percentage with viral load &lt;400 copies/mL at 12 mo</td>
</tr>
<tr>
<td>AIDS Clinical Trial Group 5208 (OCTANE)</td>
<td>US National Institutes of Health</td>
<td>Botswana, South Africa, Malawi, Kenya, Zambia, Zimbabwe</td>
<td>Parallel randomized clinical trials of NNRTI vs protease inhibitor–based antiretroviral therapy in SD-NVP–exposed and unexposed women</td>
<td>640 (240 SD-NVP–exposed; 400 unexposed)</td>
<td>&gt;6 mo</td>
<td>Percentage with viral load &lt;400 copies/mL at 6 mo or (2) viral load &lt;1 log10 below baseline at 3 mo</td>
</tr>
<tr>
<td>Nevirapine Resistance Study (NEVEREST)</td>
<td>US National Institutes of Health</td>
<td>South Africa</td>
<td>Prospective cohort; SD-NVP–exposed and unexposed</td>
<td>&gt;18 mo</td>
<td>Percentage with viral load &lt;50 copies/mL at 12 mo</td>
<td></td>
</tr>
</tbody>
</table>
months after exposure to SD-NVP. Currently, only 10%-20% of women being seen for pregnancy care in resource-poor settings are expected to meet criteria for HAART for their own health. Antiretroviral treatment is becoming more widely available in resource-poor settings, and pregnant women who require treatment for their own care increasingly are able to access it. Therefore, in most women, sufficient time should elapse between SD-NVP exposure and treatment initiation to allow for the fading of NVP-resistant strains. However, additional studies are needed to confirm these findings, to evaluate treatment response in women who initiate HAART close to the time of SD-NVP exposure, to evaluate the time to fading of NVP-resistant variants in women with different HIV subtypes and its impact on treatment outcome, and to evaluate the impact of SD-NVP exposure on subsequent treatment response in infants.

Many of the world’s poorest countries with the greatest HIV burden face significant obstacles to the implementation of PMTCT programs. Current estimates indicate that >90% of HIV-infected women in many resource-poor settings still do not have access to any antiretroviral prophylaxis, including SD-NVP. Even when SD-NVP is available, uptake into many PMTCT programs has been limited because of infrequent offering of rapid HIV testing in many antenatal settings that rely on an opt-in strategy, refusal of women to be tested for HIV, inconsistent supply of NVP and HIV test kits, inadequate numbers of counselors, lack of space for counseling, poor delivery of NVP to mothers, evaluation of women at delivery without previous HIV testing, and reluctance of women to disclose their HIV status to caregivers at delivery. As a result, only approximately one half of eligible women receive even the simplest and most deliverable regimen, SD-NVP, in settings where PMTCT programs are in place. To maximally reduce mother-to-child HIV transmission, additional efforts are needed to scale-up PMTCT programs, but in many settings, SD-NVP will continue as the most feasible option for prophylaxis.

To address growing concerns of NVP resistance, some resource-limited countries have proposed changes to their national guidelines, recommending HAART for all pregnant HIV-infected women, regardless of immunologic criteria. Although HAART should be offered when indicated and feasible, these efforts should not detract from routine PMTCT implementation efforts. The implementation of PMTCT programs has been slow in resource-limited countries, even with a regimen as simple as SD-NVP, and the implementation of HAART for PMTCT is expected to be a far greater challenge. In addition, the provision of NVP-based HAART during pregnancy for PMTCT may add additional risk to pregnant women and their infants. The extended use of NVP in pregnancy is associated with toxicity in some women, especially those women with higher CD4+ lymphocyte counts. Efavirenz should be avoided in pregnancy because of its teratogenic potential. The use of protease inhibitors may be problematic in resource-limited settings because of cost, a requirement for refrigeration for some, and the need for more intensive toxicity monitoring. Importantly, clinical trials have not shown any appreciable increase in the efficacy of HAART for PMTCT over combination prophylaxis regimens such as long-course ZDV plus SD-NVP. Furthermore, even when NVP-based HAART is used for PMTCT, NVP resistance can still be observed. In the Drug Resource and Enhancement Against AIDS and Malnutrition (DREAM) cohort in Mozambique, NVP resistance was seen in 5 of 42 women (12%) who did not require HAART for their own health but who received NVP-based HAART for PMTCT. NVP resistance was also seen in 5 of 29 women (17%) in Ireland who received HAART for PMTCT, even though the dual NNRTI component of the regimen was continued for 3-5 days after NVP was stopped.

In summary, it is likely that NNRTI-based HAART regimens will continue to be offered for some time as first-line treatment for HIV-infected patients in resource-limited settings and that SD-NVP will continue as an option for PMTCT. In these settings, public health decision makers must consider the concerns that are associated with the use of SD-NVP for PMTCT and balance them against the low cost, safety, and simplicity of this regimen. Current studies suggest that the consequences of NVP resistance after SD-NVP may be less than previously feared. On the other hand, given the challenges that are recognized in the implementation of even SD-NVP for PMTCT, the exclusion of SD-NVP as an option for PMTCT would further reduce the effectiveness of the existing PMTCT programs and likely result in an increase in the already staggering number of HIV-infected infants worldwide.


27. Church JD, Hudelson SE, Guay LA, et al. HIV-1 variants with nevirapine resistance mutations are rarely detected in antiretroviral drug naive African women with subtypes A, C, and D. AIDS Res Hum Retroviruses [In press].


Infant human immunodeficiency virus diagnosis in resource-limited settings: issues, technologies, and country experiences

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In the absence of intervention, 30-40% of infants of human immunodeficiency virus (HIV)-positive mothers may acquire HIV during pregnancy, delivery, or 2 years of breastfeeding. Antiretroviral drugs, safer infant feeding practices, and obstetrical interventions for prevention of mother-to-child HIV transmission (PMTCT) can reduce the transmission rate to less than 1-20%, depending on the interventions provided. Globally, more than 700,000 infants each year are infected with HIV, and without treatment, about half will die before they reach the age of 2 years. Early treatment of HIV-infected children is critical to their survival; however, following up HIV-exposed infants and identifying those infected with HIV is 1 of the most challenging tasks for PMTCT programs in resource-limited settings in which most pediatric HIV infections occur. Clinical findings often accurately identify infants with acquired immunodeficiency syndrome (AIDS), but their absence cannot rule out HIV infection in children who are asymptomatic. Inexpensive, accurate HIV enzyme-linked immunosorbent assay (ELISA) and rapid antibody (serologic) tests are increasingly available worldwide and used to detect HIV infection, but because infants of HIV-positive mothers acquire HIV antibody transplacentally, young infants test antibody positive regardless of their HIV infection status. Maternal antibodies disappear over time, with most uninfected infants becoming antibody negative by age 12 months; all are negative by age 18 months. Before 18 months, HIV infection can usually be ruled out by a negative antibody test, but only a virologic test such as a polymerase chain reaction (PCR) can diagnose HIV infection by directly detecting virus. PCR in the first weeks of life is the standard method of diagnosing HIV in infants in resource-rich countries. HIV testing, including PCR, is becoming more available for infants and children in resource-limited settings, but there are many barriers and policy decisions that need to be addressed before universal early testing can become standard. This paper reviews challenges and progress in the field and suggests ways to facilitate early infant testing in resource-limited settings.

Key words: infant human immunodeficiency virus testing and diagnosis, mother-to-child transmission, pediatric antiretroviral treatment, polymerase chain reaction, rapid human immunodeficiency virus tests

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Received December 15, 2006; revised February 16, 2007; accepted March 1, 2007.

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The findings and views expressed herein are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

0002-9378/$32.00 © 2007 Mosby, Inc. All rights reserved. doi: 10.1016/j.ajog.2007.03.002

Diagnostic human immunodeficiency virus (HIV) infection in infants is difficult because maternal HIV antibodies cross the placenta, causing positive serologic tests in HIV-exposed infants for the first several months of life. Early definitive diagnosis of HIV requires virologic testing such as polymerase chain reaction (PCR), which is the diagnostic standard in resource-rich settings but has been too complex and expensive for widespread use in most countries with high HIV prevalence. Early PCR testing can help HIV-infected infants access treatment, provide psychosocial benefits for families of uninfected infants, and help programs for prevention of mother-to-child transmission of HIV monitor their effectiveness. HIV testing, including PCR, is increasingly available for infants in resource-limited settings, but there are many barriers and complex policy decisions that need to be addressed before universal early testing can become standard. This paper reviews challenges and progress in the field and suggests ways to facilitate early infant testing in resource-limited settings.

Key words: infant human immunodeficiency virus testing and diagnosis, mother-to-child transmission, pediatric antiretroviral treatment, polymerase chain reaction, rapid human immunodeficiency virus tests

Why test young infants?

Early HIV testing can help HIV-infected infants access treatment, provide reassurance for families of uninfected infants, and help PMTCT programs monitor their effectiveness. In settings with high HIV prevalence, a substantial proportion of infants who are ill may have HIV, and diagnosing symptomatic HIV cases on inpatient wards and in outpatient clinics is a critical priority for HIV treatment programs. Testing infants of known HIV-infected mothers through
routine screening before they become symptomatic is another essential pathway for identification of infants who require therapy. Untreated HIV-infected infants have high mortality, with up to 20% dying before the age of 6 months, 35-40% by the age of 1 year, and 50-60% by 2 years. Mothers who know their infant is HIV infected may be more alert to minor illnesses and seek medical care without delay. Early diagnosis and treatment of HIV infection can improve outcomes for infected children and reduce early mortality. Health encounters during follow-up for HIV-exposed infants also provide an opportunity to link mothers and other infected family members to HIV care and treatment. Advanced maternal HIV and maternal death have been associated with mortality among infected and uninfected children, and improved maternal health may improve child survival.

Even without prophylactic interventions, most infants of HIV-positive mothers are uninfected. Many families and even health care providers in resource-limited settings do not know this, and children of HIV-positive mothers are often assumed to be infected. Pessimism about the child’s survival may affect a family’s ability to care for the child, especially if the child’s mother is ill or dies. It has been shown that extended families bond to infants more easily if the infant is known to be HIV negative. Routine infant testing may also improve morale for health workers; seeing first-hand that PMTCT leads to HIV-negative infants may improve their willingness to advocate for and provide PMTCT services.

In addition to benefits for infants and their families, infant testing can provide useful data on the field effectiveness of PMTCT programs and allows programs to use locally collected data to make policy decisions. Programs that find higher-than-expected transmission rates can identify program weaknesses and alter PMTCT service delivery systems or drug regimens to improve their effectiveness.

Barriers to testing infants
Early infant testing is becoming more available, but significant barriers still exist. Many clinicians believe that antibody tests have no value in infants; virologic tests are expensive and require sophisticated laboratory facilities. The expense of creating a laboratory with appropriate quality control and assurance to perform virologic testing is substantial, as are ongoing costs of test reagents. Laboratory technicians are in short supply in many resource-limited countries, and highly trained technicians may have high turnover because they are often sought by researchers and other countries seeking to expand their capabilities.

Even in countries with adequate laboratory infrastructure, other barriers may complicate infant testing efforts. Venipuncture of infants requires training and supplies that are often unavailable outside large cities. Transport difficulties and distances may prohibit whole blood samples from reaching high-level laboratories in adequate time and condition for testing. Difficulties in returning results quickly to clinical sites may reduce acceptability of testing and cause results to go unclaimed.

In addition to the logistical barriers, programs may have difficulty deciding on a testing algorithm. Determining the optimal age for infant HIV testing depends on several factors, including availability of HIV treatment; whether infants have ongoing postnatal exposure to HIV through breastfeeding; and the potential impact of early weaning on the survival of HIV-uninfected infants. Possible algorithms for testing in 2 different sets of circumstances are shown in Figures 1 and 2.

The World Health Organization (WHO) and the United Nations Children’s Fund have advocated for increased attention to pediatric HIV treatment in resource-limited settings, and diagnosing HIV in infants is a critical final step for PMTCT programs, which cannot prevent all infections. Effective infant diagnosis programs require a combination of clinical, serologic, and virologic approaches to the question of infant HIV status.

Determining the HIV status of infants
Identifying infants for testing. The most obvious and accessible population requiring HIV testing is hospitalized and ill outpatient infants, who will have a high prevalence of HIV in any highly HIV-affected country. When available, PCR testing should be applied in hospital settings to confirm the HIV status of infants and direct their long-term medical management. In hospital settings in high-prevalence areas, routine HIV screening for all people with symptoms suggestive of HIV, quick access to HIV test results, and/or policies to begin prophylaxis for opportunistic infections and HIV treatment before definitive diagnoses are made can save many lives. Immediate HIV diagnosis for children older than 18 months can be provided through routine rapid HIV testing of all ill children. Rapid antibody tests can also play a significant role in testing of infants younger than 18 months old. Many can be determined to be HIV negative through the use of an antibody test. Those who test antibody positive and have signs and symptoms compatible with HIV may need to initiate highly active antiretroviral therapy (ART) therapy without a definitive diagnosis if PCR is not available. Wherever possible, virologic tests should be used to make the definitive diagnosis, but children who access ART therapy without virologic testing can have their HIV status confirmed by an antibody test at 18 months.

All infants known to have HIV-positive mothers, whether ill or well, should also receive diagnostic HIV testing. Successful testing of HIV-exposed infants requires a system for record keeping that facilitates their identification in settings in which children receive care. Follow-up care and HIV testing for exposed infants should take place within existing child health systems, such as immunization and growth-monitoring clinics, which are well attended in many countries and provide an excellent opportunity for provision of prophylactic cotrimoxazole, HIV testing, and referral for other services. Ensuring that each child’s HIV exposure status is documented on

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Supplement to SEPTEMBER 2007 American Journal of Obstetrics & Gynecology S65
A possible testing algorithm for HIV-exposed infants in a setting in which infant antiretroviral treatment is readily available, PCR can be performed, and resources permit either replacement feeding or 2 tests per infant.

**HIV-exposed infant**

- **Less than 9 months old**
  - Collect and send dried blood spot for PCR
  - If PCR positive, refer to HIV clinic
  - If PCR negative, collect blood on rapid HIV test and dried blood spot card at the same time

- **9 months old or older**
  - Collect blood on rapid HIV test and dried blood spot card at the same time

**PCR positive**

- Infant is HIV infected
- Refer to HIV clinic
- Continue cotrimoxazole
- If breastfed, continue breastfeeding as long as possible
- Where possible, confirm result with second PCR, quantitative RNA, or confirm with antibody test at 18 months
- Start ARV treatment if indicated

**PCR negative**

- **Not breastfed in the last 6 weeks**
  - Infant is not HIV infected
  - Stop cotrimoxazole
  - Avoid putting baby to breast
  - All: provide cotrimoxazole prophylaxis, routine immunizations, assess nutritional status, provide safe infant feeding counseling

- **Breastfed in the last 6 weeks**
  - Infant is probably not HIV infected, but is still at risk
  - Continue cotrimoxazole
  - Repeat test 6 weeks after last breastmilk
  - Provide infant feeding counseling – infant should only be weaned if acceptable, feasible, affordable, sustainable, and safe to provide replacement feeding

**Rapid test positive**

- Infant may be HIV infected, or may still have maternal antibody
- Continue cotrimoxazole while awaiting PCR result
- Infant is HIV infected
- Stop cotrimoxazole
- Avoid putting baby to breast

**Rapid test negative**

- Infant is probably not HIV infected, but is still at risk
- Continue cotrimoxazole
- Repeat test 6 weeks after last breastmilk
- Provide infant feeding counseling – infant should only be weaned if acceptable, feasible, affordable, sustainable, and safe to provide replacement feeding

**Infant is not HIV infected**

- Stop cotrimoxazole
- Avoid putting baby to breast
- Infant is probably not HIV infected, but is still at risk
- Continue cotrimoxazole
- Repeat test 6 weeks after last breastmilk
- Provide infant feeding counseling – infant should only be weaned if acceptable, feasible, affordable, sustainable, and safe to provide replacement feeding

**Infant is HIV infected**

- Refer to HIV clinic
- Continue cotrimoxazole
- All: provide cotrimoxazole prophylaxis, routine immunizations, assess nutritional status, provide safe infant feeding counseling

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*ARV,* highly active antiretroviral therapy.


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his or her immunization and growth records is an essential step for countries seeking to expand access to infant HIV testing. Several suggested methods of improving the care of HIV-affected children through modifications to routine maternal-child health services are provided in Table 1.

Child health clinics can also be used to identify infants with unknown exposure status. HIV testing for mothers can be offered in these settings, and either mothers or infants can be tested to determine the need for ongoing HIV care. In settings with high HIV incidence, repeat HIV testing for women who were HIV negative during pregnancy may also be offered during routine child health care because women who acquire HIV during breastfeeding are at high risk of transmitting HIV to their infants.

**The role of physical examination in HIV diagnosis.** Physical examination of infants may reveal signs of AIDS, including failure to thrive, lymphadenopathy, hepatosplenomegaly, chronic dermatitis, oral candidiasis, and recurrent pneumonia or diarrhea. If the infant is known to be HIV exposed by either maternal history or a positive antibody test, these findings are highly specific (89% in 1 study in South Africa) in identifying infants with AIDS. However, many infants do not manifest any sign of a failing immune system until a serious infection occurs. A clinical examination by an experienced doctor had 53% sensitivity at 6 weeks and 93% sensitivity at 12 months for detecting HIV infection in the same study. Other clinical case definitions have been evaluated; 1 algorithm from Kenya had 80% sensitivity in children younger than 24 months of age. Criteria used by the Integrated Management of Young Child Illness system allowed identification of only 19% of HIV-infected children at 6 weeks and 53% at 12 months. Based on these data, clinical assessment has a limited but essential role in HIV diagnosis. Even in the presence of advanced testing technologies, both clerical and technological errors may cause incor-
rect test results to be delivered to clinicians, and clinical evaluations must not be overlooked.

**HIV antibody testing.** Despite its limitations, HIV antibody testing is a vital part of pediatric HIV testing programs, and antibody tests are inexpensive ($1-2 for ELISA or rapid tests). Even in a very young infant, an antibody test may have an important role if the mother’s HIV status is unknown because the infant’s test result can indicate whether or not he or she was exposed to HIV. Because infants lose maternal antibodies at different rates, the use of antibody tests to identify infants who have lost maternal antibody (seroreverted) is a reasonable and low-cost approach to ruling out HIV infection in children younger than 18 months old. Most published data on time to seroreversion are relatively old, and studies using new rapid tests to redefine the time to seroreversion are ongoing. Preliminary results indicate that a large proportion of uninfected infants are antibody negative by 9 months of age using rapid tests and that seroreversion sometimes occurs as early as age 4 months.20 Errors have been found with some rapid test kits producing false-negative results in extremely ill infants, possibly because of hypogammaglobulinemia accompanying severe illness (Gayle Sherman, personal communication, May 2006). This reinforces the need for clinical judgment and physical examination in HIV diagnosis but does not negate the usefulness of negative antibody tests.

The testing of saliva for HIV antibody may be particularly useful in infants because oral fluid contains lower concentrations of all antibodies in comparison with blood. Waning maternal HIV antibodies in HIV-exposed but uninfected infants likely become undetectable earlier in oral fluids than in blood. Laboratory-based or rapid HIV tests performed on oral fluid can potentially exclude HIV infection earlier in life, and sample collection is less traumatic for infant and caregiver. Further validation of oral fluid assays is needed to establish the youngest age at which seroreversion can be detected and to determine the sensitivity and specificity of the test at different ages.21

**Virologic testing**

**HIV deoxyribonucleic acid (DNA) PCR.** HIV DNA PCR is the standard method for virologic diagnosis of HIV in infants in the developed world. It has been used for many years, is the diagnostic test of choice recommended by the American Academy of Pediatrics and the WHO, and has excellent sensitivity and specificity.22-24 HIV infection can often be detected at birth, and essentially all perinatal infections are detectable by 4 weeks of age.25 Infected infants acquire postpartum (ie, through breast-feeding) can be detected by 4-6 weeks after the last exposure.

A variety of commercial and in-house processing methods for DNA PCR testing exist worldwide, and not all tests are equally accurate with all HIV subtypes. One commercially available PCR test, Amplicor HIV-1 DNA PCR (version 1.5, Roche Molecular Systems, Branchburg, NJ), is highly accurate in detecting the multiple HIV-1 subtypes circulating in Africa, is standardized and supported for use in Africa, and has been used by researchers and pilot infant diagnosis programs in several countries.26-28 The cost for each PCR test in developing countries currently varies between $8 and $18. An earlier version of this assay, the Roche Amplicor version 1.0, is slightly less sensitive in detecting non-B subtypes. The choice of assay should be dictated by the prevailing subtypes in the country.

**Ribonucleic acid (RNA) PCR.** An HIV RNA PCR, quantitative or qualitative, is also an accurate method of diagnosing HIV in young infants, with sensitivity and specificity comparable with DNA PCR testing.9,29 However, this test is more expensive and requires the use of plasma, which is difficult to obtain from...
infants and transport intact, and for these reasons it has not yet had a role in large-scale infant diagnostics.

**Real-time PCR.** Real-time PCR allows the technician to view the increase in the amount of DNA or RNA because it is amplified. Real-time PCR as a new approach is gaining acceptability because of its improved rapidity, sensitivity, reproducibility, and the reduced risk of carry-over contamination, and it may reduce the cost of nucleic acid testing. This method is in use in numerous research settings and performs very well. However, at present the only commercial kits available are for quantitative and not qualitative detection of HIV, and large-scale use of these assays for public health programs has not been attempted.

**Ultrasensitive (US) p24 antigen assay.** The US p24 antigen assay is slightly less sensitive than HIV PCR in identifying HIV infection in infants across various subtypes and has a specificity similar to that of HIV PCR. This quantitative viral protein detection assay utilizes simpler technology than is required for detection of viral nucleic acids, but it is still relatively complex with multiple processing steps. US p24 is not in general use because studies validating it for infant diagnosis are recent, and achieving valid results in field settings has been challenging. US p24 may provide a useful alternative where PCR is not available.

**Dried blood spots (DBS).** The collection of infant blood on DBS is expanding opportunities for infant diagnosis in settings around the world. Because infant blood for testing can be taken by simply pricking a heel, toe, or finger and dried cards are stable for relatively long periods without refrigeration, many logistical barriers to infant testing can be overcome using this simple technique. PCR performed on DBS is as accurate as PCR performed on whole blood but has higher reagent cost and some increase in processing time. DNA and RNA PCR, both standard and real time, have been successfully performed on DBS in a wide variety of settings and HIV subtypes with no loss of accuracy. US p24 assays have been performed successfully on DBS; however, further validation is required before DBS can be recommended for routine use with this assay. Routine collection of DBS for early infant diagnosis is being implemented in many settings, including some described in Table 2.

**WHO infant HIV diagnosis guidelines.** The most recent WHO infant testing guidelines recommend using DNA PCR on dried blood spots for routine screening of exposed infants as early as 6 weeks old. Confirmation of a positive test result is recommended where possible, but because of the high accuracy of the DNA PCR test, it is recommended that antiretroviral therapy be initiated before confirmation based on a single positive PCR if therapy is indicated. In settings in which in-

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**TABLE 1**

**Suggested additions to standard maternal-child health systems to improve care, tracking, and testing of HIV-exposed infants in settings with high HIV prevalence**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Suggested additions to standard practices</th>
<th>Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal care</td>
<td>Include routine HIV testing, screening for antiretroviral therapy, and interventions to prevent mother-to-child transmission of HIV in package of routine antenatal services.</td>
<td>Modify clinic log books and patient antenatal cards to include space for HIV counseling received, HIV test results, clinical status of mother (by CD4 or exam), referrals for or provision of prophylactic or therapeutic ARV drugs, and infant feeding counseling.</td>
</tr>
<tr>
<td>Delivery care</td>
<td>Include routine HIV testing for women in labor, and single-dose nevirapine for HIV-infected women, in package of routine delivery services.</td>
<td>Modify delivery log books and antenatal cards to include HIV test results, provision of antiretroviral drugs during labor and to infants, and infant feeding counseling.</td>
</tr>
<tr>
<td>Well-child or immunization clinics</td>
<td>Include follow-up of HIV-exposed children in routine well-child or immunization visits. Follow-up includes routine physical examinations, nutritional status evaluations, cotrimoxazole prophylaxis, HIV testing, and referral for antiretroviral therapy if needed.</td>
<td>Ensure that maternal HIV status is transferred to child health cards either at delivery or through sending antenatal care cards with mothers to child health visits. Modify child health cards and logs to include space for maternal HIV status, PMTCT interventions received by mother and infant, feeding method and nutrition counseling, infant HIV test method and results, and referrals to ARV therapy if needed.</td>
</tr>
<tr>
<td>Ill-child care or hospital settings</td>
<td>Include screening for HIV exposure and HIV infection in standard intake procedures for ill children.</td>
<td>Modify hospital logs and charts to include space for maternal and infant HIV status, clinical status of mother and infant, and provision of or referral for ARV therapy for both.</td>
</tr>
</tbody>
</table>
TABLE 2

Current infant HIV diagnosis practices in resource-limited settings

<table>
<thead>
<tr>
<th>Country</th>
<th>HIV prevalence in pregnant women</th>
<th>Number of HIV-exposed infants born each year</th>
<th>PMTCT interventions provided by national program</th>
<th>HIV testing schedule for HIV-exposed infants</th>
<th>Infant testing technology, cost, number of laboratories</th>
<th>Progress toward scale-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>33.4% (2005 surveillance)</td>
<td>15,000</td>
<td>Mothers: CD4 &lt; 200: ARV therapy; CD4 &gt; 200: 12 weeks AZT, SD NVP</td>
<td>PCR at 6-week immunization visit, repeat 6 weeks after weaning if breast-fed</td>
<td>Roche Amplicor 1.5 DNA PCR on DBS (manual extraction) and whole blood in 1 national reference laboratory, cost $18/test.*</td>
<td>Approximately one third of HIV-exposed children tested nationwide in 2005-2006, rollout of DBS testing to all clinics providing care for infants completed in 2007</td>
</tr>
<tr>
<td>South Africa</td>
<td>30.2% (2005 surveillance)</td>
<td>300,000</td>
<td>Mothers: SD NVP Limited access to ARV if CD4 &lt; 200</td>
<td>PCR at 6-week immunization visit, repeat 6 weeks after weaning if breast-fed</td>
<td>Roche Amplicor 1.5 DNA PCR on DBS and whole blood in 6 national laboratories, charged at ~$50/test</td>
<td>Approximately one third of required lab capacity available, ~32% of HIV-exposed children tested in September 2006</td>
</tr>
<tr>
<td>Uganda</td>
<td>6.5% (2004-2005 surveillance)</td>
<td>78,000</td>
<td>Mothers: 8-12 weeks AZT or ZDV/3TC 6-8 weeks, SD NVP</td>
<td>PCR at 6 weeks and when clinically indicated, serology at 18 months</td>
<td>Roche Amplicor 15 DNA PCR on DBS. Cost varies by lab from $8 to $25. Currently at least 12 labs do PCR, although not all do on DBS</td>
<td>PMTCT services delivered to ~10% of HIV+ pregnant women nationally in 2005, early infant testing available in capital. Serology available in rural areas.</td>
</tr>
<tr>
<td>Rwanda</td>
<td>4.9% (2005 surveillance)</td>
<td>12,000</td>
<td>Mothers: CD4 &lt; 350: ARV therapy; First ANC visit before 28 weeks: AZT 12 weeks, SD NVP, AZT/3TC 1 week after delivery; First ANC visit after 28 weeks: ARV if available, otherwise above regimen. Infants: SD NVP</td>
<td>In pilot sites: PCR at 6-week immunization visit, repeat 6 weeks after weaning if breast-fed in other sites: rapid test at 15 months</td>
<td>Roche Amplicor 1.5 DNA PCR on DBS (manual extraction) in 1 national reference lab (second lab is planned) Cost $12-15 (U.S.) per test</td>
<td>Pilot sites provide PCR to &gt;600 infants. Plan to roll out routine early infant testing at rural sites in 2007.</td>
</tr>
</tbody>
</table>

ARV, highly active antiretroviral therapy; AZT, zidovudine; SD NVP, single-dose nevirapine.
* Estimated price to purchase test kits and process test in laboratory.

Fants are tested later, screening with antibody tests is recommended before performing PCR on infants older than 9 months. These guidelines recommend HIV testing technologies but do not address the complex issues of test timing and leave country programs to determine an optimal algorithm based on the local context.

Timing of infant HIV testing. In countries in which pediatric ARV therapy is readily available, infants of HIV-positive mothers do not breast-feed, and resources permit multiple tests, infants of HIV-positive mothers are tested at birth, 1-2 months old, and 2-4 months old, with confirmation of seroreversion at 12-18 months. This approach is expensive, and each repeat test is less cost effective because fewer new infections are detected. In resource-limited settings, funding may dictate that an infant can have only 1 virologic test. For non-breast-fed infants, this test should probably be done at 4-6 weeks of age when perinatal infections are detectable and infants are entering the child health care system for immunizations (Figure 1).

In settings in which the use of infant formula is not acceptable, feasible, affordable, sustainable, and safe (AFASS), most HIV-positive women breast-feed, and some new infections occur throughout infancy, with slightly less than 1% of infants acquiring HIV for each month of breastfeeding after 2 months of age. In these settings, determining the optimal timing for infant HIV testing is more complex. Early testing at 4-6 weeks detects most infections: those acquired during pregnancy, birth, and early breastfeeding. This approach allows early treatment of the 20% of perinatally-infected infants who may die before 6 months of age without antiretroviral
therapy. Some programs have noted, however, that an HIV-negative infant test result may prompt HIV-infected mothers to stop breastfeeding very early. This may dramatically increase mortality of otherwise healthy infants in settings in which replacement feeding is not AFASS. Programmatic data from Uganda in 2006 revealed 19% mortality during 2 years of follow-up among HIV-infected infants of women receiving ARV therapy who were tested at 6 weeks, with short duration of breast-feeding (median 3 months) being the most significant predictor of mortality.

Programs with low perinatal HIV transmission may find that testing early compromises infant survival unless intensive patient education and infant feeding counseling can ensure that infants are not weaned too early. Testing early also necessitates a second test after weaning for infants who tested negative on their first test, thus increasing laboratory costs. In some settings in which infant formula use is not AFASS and risks of malnutrition and other morbidity are higher than the risk of HIV transmission, the WHO recommends that infants of HIV-infected mothers should breastfeed for 6 months or longer. If these infants are tested 6 weeks after their last breast milk, between 8 and 12 months of age, an HIV antibody test could be used for screening, reserving PCR for those infants who remain seropositive.

Testing breastfed infants only after weaning may promote a more appropriate length of breastfeeding and requires only 1 test per infant, but a number of infants, especially in programs with high HIV transmission rates, will become ill and die from AIDS without an opportunity for early treatment. Identification of HIV-exposed infants at routine follow-up visits and provision of high-quality basic medical care (including prophylactic cotrimoxazole) can play a significant role in reducing mortality in young infants. In areas in which pediatric ARV therapy is not available at all, testing at 6 weeks may confer little benefit, and a single test after weaning may be more appropriate. Individual programs must decide which approach promotes greater child survival in their context; ensure appropriate infant feeding practices are followed after testing; and be prepared to adapt their approach to changing circumstances, especially changing transmission rates, feeding practices, costs, and ARV treatment availability.

Examples of country approaches to infant diagnosis. Table 2 describes the current state of infant HIV diagnosis efforts in several resource-limited settings. An increasing number of programs are testing young infants, using increased resources available for PMTCT and pediatric HIV care. Small-scale projects have been successful in many settings, and expansion is ongoing. Programs initiating early HIV testing work closely with maternal and child health programs and are increasingly utilizing DBS for ease of sample collection and transport to referral laboratories performing PCR testing.

**Summary**

Advances in technology and increases in funding for pediatric HIV have made early infant diagnosis of HIV infection more accessible than ever before. Despite this, most HIV-exposed infants in resource-limited settings in 2007 will not be tested for HIV. Although definitive virologic testing is the gold standard for infant diagnosis of HIV, it is important for programs without immediate capacity for virologic testing to recognize that the judicious use of basic clinical assessment and antibody testing can both identify and rule out many, but not all, infant HIV infections. HIV programs with limited resources may find that the best use of resources is to focus on PMTCT, antibody testing of all sick children, and cotrimoxazole prophylaxis for HIV-exposed infants, leaving the establishment of routine infant virologic testing for second priority.

With the increasing availability of early infant HIV diagnostic testing as part of national programs, the uncertainty of families about their infant’s HIV status does not necessarily have to continue until 18 months or beyond. Decisions about when and how to test infants, based on the best available technology and information, should be made by ministries of health and partner organizations around the world, and allow quality HIV care for infants to become a reality.


A pproximately one quarter of human immunodeficiency virus (HIV)–infected persons in the United States are unaware that they are infected. It is particularly important that pregnant women know their HIV status, both for their own health and to prevent transmission to their infant. Because of the implementation of several effective strategies, including the use of combination antiretroviral prophylaxis, elective cesarean delivery, and avoidance of invasive obstetric procedures and breast-feeding, perinatal HIV transmission rates have dramatically decreased in the United States over the past decade.

The problem is that to implement these strategies successfully, a pregnant woman and her health care provider must be aware of her HIV status.

Since 1995, there have been guidelines in place in the United States recommending HIV testing for all pregnant women. These guidelines have evolved and now include routine opt-out testing, in which pregnant women are notified that HIV testing is included as a routine prenatal test to be performed unless they decline. However, women who do not obtain prenatal care are unlikely to be tested for HIV during pregnancy. Even women who receive prenatal care may not be offered or accept testing. Because most women in the United States deliver in hospitals, rapid HIV testing on labor and delivery units is the last opportunity to identify HIV-infected women before delivery and to provide antiretroviral prophylaxis to prevent perinatal transmission during labor and delivery.

The objective of the study was to evaluate the feasibility, acceptability, and accuracy of rapid human immunodeficiency virus (HIV) testing during labor. The Mother-Infant Rapid Intervention at Delivery (MIRIAD) study was a prospective, multicenter study that offered voluntary, rapid HIV testing to women with undocumented HIV status at 17 hospitals in 6 cities. Of 12,481 eligible women, 74% were approached for participation and 85.5% of those approached accepted rapid HIV testing. Among 7753 women tested, MIRIAD identified 52 (0.7%) HIV-infected women. The time between obtaining the blood sample for the rapid test and reporting the results to the health care provider was shorter for hospitals utilizing point-of-care testing than in hospitals utilizing laboratory-based testing (30 minutes vs 68 minutes; \( P < .0001 \)), and point-of-care testing strategies were 14 times more likely to have a short turnaround as laboratory testing strategies. Routine rapid testing during labor provides a feasible, acceptable, and accurate way to identify HIV-infected women before delivery.

Key words: rapid human immunodeficiency virus testing

The Mother-Infant Rapid Intervention at Delivery (MIRIAD) study was a large, prospective, multicenter project designed to evaluate the feasibility, acceptability, and accuracy of rapid HIV testing during labor. An earlier brief report included initial results from the study’s first 2 years. The present paper summarizes the final data from 17 hospitals during the entire 40-month study period. In addition, we present more extensive analyses by including variables and follow-up information not available when the earlier report was published.

The views expressed herein are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. Use of trade names is for identification purposes only and does not constitute endorsement by the Centers for Disease Control and Prevention or the Department of Health and Human Services. Preprints: Denise J. Jamieson, MD, MPH, Centers for Disease Control and Prevention, 4770 Buford Hwy, Mailstop K-34, Atlanta, GA 30341; djJ0@cdc.gov. 0002-9378/$32.00 © 2007 Mosby, Inc. All rights reserved. doi: 10.1016/j.ajog.2007.03.067

Rapid human immunodeficiency virus-1 testing on labor and delivery in 17 US hospitals: the MIRIAD experience

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This research was supported by the National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, under cooperative agreements U64/217724, 417719, 517715, 617734, and 479935.

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Reprints: Denise J. Jamieson, MD, MPH, Centers for Disease Control and Prevention, 4770 Buford Hwy, Mailstop K-34, Atlanta, GA 30341; djJ0@cdc.gov. 0002-9378/$32.00 © 2007 Mosby, Inc. All rights reserved. doi: 10.1016/j.ajog.2007.03.067
**Materials and Methods**

The MIRIAD study, which was a prospective, multicenter study funded by the Centers for Disease Control and Prevention (CDC), offered voluntary, rapid HIV testing to women with undocumented HIV status late in pregnancy. The MIRIAD protocol, which enrolled patients from November 2001 through February 2005, was successfully implemented in 17 hospitals in 6 cities (Atlanta, GA; Baton Rouge, LA; Chicago, IL; Miami, FL; New Orleans, LA; and New York, NY). One Atlanta hospital was unsuccessful in implementing the MIRIAD protocol because of problems in coordinating multiple obstetric providers and private practice groups. Because only 1% of the eligible women were tested, that hospital has been excluded from all analyses.

All women presenting to labor and delivery units were screened for eligibility for MIRIAD as either a “peripartum” or a “late presenter” participant. To be eligible, a woman had to have undocumented HIV status during her current pregnancy. Pregnant women with an estimated gestational age of 24 weeks or greater and in labor or with an indication for urgent delivery were eligible for the peripartum protocol. Labor was defined as ruptured membranes or cervical dilation of 4 cm or greater for pregnancies less than 34 weeks’ gestation and as regular, painful uterine contractions accompanied by cervical dilation for those at gestation of 34 weeks or longer. For the late-presenter protocol, eligible women had to have an estimated gestational age of 34 weeks or longer and not be in labor. The initial eligibility requirement that the late presenter group also had to have no prenatal care visits was dropped in early 2003.

Women determined to be eligible were approached and asked whether they were interested in MIRIAD. If a peripartum woman expressed interest, a flip-chart with pictures was used to present information about the study and to review the relevant parts of the informed consent process. Because the women eligible for the late-presenter protocol were not in labor, the flip-chart was not used for them and a standard consent process was followed. Toward the end of the study, the way women were approached for participation changed at 3 hospitals at which an opt-out approach for HIV testing during labor was evaluated as part of a substudy. Beginning in July 2004, all women eligible for MIRIAD at these 3 hospitals were consented for rapid testing using a standard institutional consent form, rather than the MIRIAD research consent form (opt-in approach). Then in October 2004, all women eligible for MIRIAD at the same 3 hospitals were given a 1-page information sheet listing the routine admission labor and delivery tests to be performed (eg, rapid plasma reagin, rapid HIV, complete blood count, blood type, and antibody screen) for all women. Those who did not want to be tested for HIV had to specifically decline the testing (opt-out approach). The findings from this substudy will be described more fully in a subsequent manuscript.

Information was collected on all eligible women, including the exact time (in minutes) when they arrived on the labor and delivery unit and when they were offered participation in MIRIAD, their reasons for declining participation (if applicable), and brief demographic and delivery information. One hospital, however, failed to collect the demographic and delivery information of eligible women who were not enrolled. All participants provided written informed consent, and the MIRIAD protocol was approved by the institutional review boards at the CDC and all participating hospitals.

Once a participant consented to join the study, blood was collected for both rapid and conventional HIV testing (in some cases residual blood routinely collected on the labor and delivery unit at admission could be used for HIV testing). OraQuick rapid HIV-1 antibody test (OraSure Technologies Inc, Bethlehem, PA) was used for the rapid testing.

For the MIRIAD study, the US Food and Drug Administration (FDA) allowed the use of the OraQuick test under an investigational device exemption before the test was formally licensed in November 2002. In some hospitals, the rapid testing was performed on the labor and delivery unit by trained staff (subsequently described as point-of-care testing), whereas in other hospitals it was performed in a laboratory. Two hospitals switched from laboratory testing to point-of-care testing during the course of the study.

All specimens were tested in parallel by conventional testing with enzyme immunoassay (EIA) and confirmatory Western blot. Seven institutions used the Abbott HIV-1/HIV-2 EIA (Abbott Laboratories, Abbott Park, IL), 7 institutions used the Genetic Systems HIV-1/HIV-2 peptide EIA (BioRad Laboratories, Hercules, CA), and 3 used the bioMerieux Vironostika HIV-1 ELISA kit (bioMerieux, Durham, NC). The bioMerieux EIA test is a second-generation test; the other EIA tests are third-generation tests. Initially, reactive rapid tests and EIAs were repeated in duplicate and a repeatedly reactive rapid test or EIA was confirmed using Western blot.

Most women were informed of the rapid test results as quickly as possible. Although there was an option on the informed consent form for peripartum women to indicate they did not want to be informed of the results until after delivery, only 136 women (2.3%) requested this option. When the rapid test result was positive, the woman was counseled that her test result was preliminarily positive and that the conventional testing results were still pending. These women were treated clinically as HIV infected and offered antiretroviral prophylaxis and other preventive obstetric care as appropriate, including avoiding invasive procedures during labor and delivery, such as the placement of fetal scalp electrodes.

An algorithm was designed to resolve discordant test results, when the results of rapid testing were not confirmed by conventional testing results. In these cases, the women and their infants were followed up at least 6 months to resolve the discrepancy. Infants born to HIV-infected women were tested using HIV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) at less than 48 hours, 2 weeks, 6 weeks, and 3 months,
and if they were still indeterminate, at 6 months.

To assess the duration of each step in the testing process from arrival on the labor and delivery unit until the woman received her results, the staff recorded the time of each event. In addition, the MIRIAD staff reviewed medical records and conducted face-to-face interviews with both MIRIAD-identified HIV-infected women and a sample of uninfected eligible women.

Statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC). Odds ratios with 95% confidence intervals were estimated using unconditional logistic regression, adjusting for study site and other covariates. The sensitivity, specificity, and predictive values of the rapid tests and the EIAs were calculated. For each of these measures, confidence intervals were estimated using exact binomial methods. The median turnaround times were compared using the Wilcoxon rank-sum test.

Results
During the 40-month study period, there were 153,014 labor and delivery visits at the 17 participating hospitals (Figure 1). Of these, 12,481 women (8.2% of all visits recorded) were eligible for either the late presenter or peripartum MIRIAD protocol. Approximately three quarters of eligible women were approached about enrollment in MIRIAD (and thus one quarter of the women were missed and never asked whether they wanted to participate).

Of the 9233 women who were approached for participation, approximately 15% declined, and the remaining 7898 women accepted. Among those who accepted, complete testing results were unavailable for 145 (1.8%) women. Conventional test results were missing largely because blood was inadvertently not sent for confirmatory testing or because specimens were lost. Among the 7753 women with available test results, 52 (0.7%) were HIV infected. In this group, 50 deliveries were recorded; 51 babies were born. Eight infants were lost to follow-up, and therefore, their HIV status remains unknown. Of the 43 infants with known HIV infection status, 5 (12%) were HIV infected.

Among women eligible for MIRIAD, the majority were younger than 25 years of age, almost two-thirds were black, and
most had 12 years or less of education (Table 1). Thirty-eight percent of the women had no prenatal care. In adjusted analyses, compared with women who were approached for participation in MIRIAD, the women who were “missed” (not offered participation) were more likely to be eligible for the late presenter protocol, to be younger than 20 years of age, to belong to a racial group other than black or white, to be admitted on a weekend, to be admitted during the evening shift (4:00 PM to 12:00 AM), and to have more advanced cervical dilation (8-10 cm) upon admission. Conversely, “missed” women were less likely to be Hispanic and to arrive 3-12 hours before delivery (Table 2).

The most common reason a woman was missed was that no staff member was available (33%) to approach her about participation. Although the participating hospitals were strongly encouraged to have 24-hour-a-day, 7-day-a-week coverage of labor and delivery, some of them had difficulty achieving continuous coverage. In addition, there were times at which some hospitals had to temporarily halt MIRIAD study activities, such as during hurricanes in New Orleans and Miami and during a temporary staffing shortage in Atlanta. During these times, all eligible women presenting to labor and delivery were not offered participation in MIRIAD and had to be classified as “missed.” When the periods when MIRIAD was not operating fully (eg, no night shift MIRIAD staff available or during hurricanes or staffing shortages) were excluded from the analysis, the risk factors for being missed were not appreciably changed. The only notable differences were that age younger than 20 years (adjusted odds ratio [AOR] 1.23; 95% confidence interval [CI] 0.95-1.60) and advanced cervical dilation (AOR 1.19; 95% CI 0.86-1.66) were no longer significant risk factors.

In adjusted analyses, factors significantly associated with having women decline participation in MIRIAD included older age (AOR 1.7; 95% CI 1.4-2.0 for age 25 years or older), nonblack race (AOR 1.8; 95% CI 1.4-2.4), non-Hispanic ethnicity (AOR 2.1; 95% CI 1.6-2.9), admission during the evening or

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TABLE 1
Characteristics of the 12,481 women presenting to labor and delivery who were eligible for the MIRIAD study, 2001-2005

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td>Participant group</td>
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<tr>
<td>Peripartum</td>
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<tr>
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</tr>
<tr>
<td>Age, y</td>
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<tr>
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<td>20-24</td>
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<tr>
<td>25-29</td>
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<tr>
<td>30 or older</td>
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</tr>
<tr>
<td>Missing</td>
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<td></td>
</tr>
<tr>
<td>Race</td>
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<td></td>
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<tr>
<td>White</td>
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<tr>
<td>Black</td>
<td>6969</td>
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<tr>
<td>Other</td>
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<tr>
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<td>Years of education</td>
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<td>12</td>
<td>2918</td>
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<td>12 or more</td>
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<td>New York, NY</td>
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Continued on page S76.
TABLE 1
Characteristics of the 12,481 women presenting to labor and delivery who were eligible for the MIRIAD study, 2001-2005

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
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<td>Admission on weekend*</td>
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<tr>
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<tr>
<td>Time of admission</td>
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<tr>
<td>12:00 AM to 8:00 AM</td>
<td>3600</td>
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<tr>
<td>8:00 AM to 4:00 PM</td>
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<tr>
<td>0-2</td>
<td>1813</td>
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<td>7-12</td>
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<td>“Laboratory-based” testing</td>
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</tr>
<tr>
<td>11/16/04 to 2/13/05</td>
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MIRIAD: Mother-Infant Rapid Intervention at Delivery.
* Weekend considered from Friday at 5 PM to Monday at 6 AM.

Night shifts (4:00 PM to 8:00 AM) (AOR 1.3; 95% CI 1.1-1.6), and having attended at least 1 prenatal care visit (AOR 1.8; 95% CI 1.4-2.2). Women eligible for the late-presenter protocol were more likely to decline than were those eligible for the peripartum protocol (AOR 3.5; 95% CI 2.8-4.3). The lowest rates of acceptance were on Friday evenings, when less than 80% of women accepted testing (Figure 2). The acceptance rate was higher in hospitals that used residual blood from a routine blood collection that did not require an extra needle stick to obtain a blood sample for the study (87.2% vs 73.9%; P < .0001). Staff members recorded women’s reasons for declining participation; more than 1 reason could be recorded. Among peripartum women, the most common reasons given included having already been tested for HIV during the current pregnancy (37%), refusing to participate in research (16%), not wanting to know their HIV status (12%), and a perception that they were not at risk for HIV (12%). Among late presenters, the most common reason was also already having been tested for HIV during the current pregnancy (65%); less common reasons were not wanting another blood draw (9%) and refusing to participate in research (8%).

Women who initially declined participation were asked whether they would agree to be approached for participation at a later time. Among the 374 women who said they would and were reapproached, 196 (52%) agreed to participate when asked a second time. Often the staff member reapproaching the woman was not the one who approached her initially. The median interval between the first and second approaches was 16.5 hours; in most cases the women were reapproached after delivery.

Among the peripartum participants, the median time from arrival on the labor and delivery unit until the woman was informed of her rapid test result was shorter for hospitals using point-of-care testing than for those using laboratory-based testing (242 minutes vs 295 minutes; P < 0.0001). More specifically, the time between obtaining the blood sample for the rapid test and the reporting of results to the health care provider was
TABLE 2
Odds of never being offered MIRIAD among women eligible for rapid HIV testing during labor, MIRIAD study, 2001-2005

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>MIRIAD never offered %</th>
<th>Odds ratio adjusted for study site (95% CI)</th>
<th>Odds ratio for full model* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripartum</td>
<td>8898</td>
<td>14.1</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Late presenter</td>
<td>3583</td>
<td>55.6</td>
<td>10.8 (9.74-12.0)</td>
<td>10.1 (8.13-12.5)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 20</td>
<td>2030</td>
<td>23.0</td>
<td>1.31 (1.13-1.51)</td>
<td>1.35 (1.07-1.70)</td>
</tr>
<tr>
<td>20-24</td>
<td>3621</td>
<td>22.1</td>
<td>1.12 (0.99-1.27)</td>
<td>1.00 (0.82-1.22)</td>
</tr>
<tr>
<td>25-29</td>
<td>2144</td>
<td>22.6</td>
<td>1.07 (0.94-1.23)</td>
<td>1.08 (0.87-1.33)</td>
</tr>
<tr>
<td>30 or older</td>
<td>2924</td>
<td>23.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Missing</td>
<td>1492</td>
<td>51.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3215</td>
<td>26.5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Black</td>
<td>6969</td>
<td>17.3</td>
<td>1.07 (0.95-1.19)</td>
<td>0.84 (0.64-1.09)</td>
</tr>
<tr>
<td>Other</td>
<td>595</td>
<td>14.5</td>
<td>1.65 (1.25-2.19)</td>
<td>2.20 (1.43-3.40)</td>
</tr>
<tr>
<td>Missing</td>
<td>1702</td>
<td>64.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>7372</td>
<td>18.3</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3740</td>
<td>29.1</td>
<td>1.11 (1.00-1.23)</td>
<td>0.71 (0.54-0.92)</td>
</tr>
<tr>
<td>Missing</td>
<td>1369</td>
<td>59.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission on weekend†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3860</td>
<td>28.3</td>
<td>1.25 (1.14-1.37)</td>
<td>1.82 (1.55-2.14)</td>
</tr>
<tr>
<td>No</td>
<td>8620</td>
<td>25.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:00 AM to 8:00 AM</td>
<td>3600</td>
<td>19.3</td>
<td>0.70 (0.63-0.78)</td>
<td>1.03 (0.85-1.25)</td>
</tr>
<tr>
<td>8:00 AM to 4:00 PM</td>
<td>5127</td>
<td>26.4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4:00 PM to 12:00 AM</td>
<td>3751</td>
<td>32.1</td>
<td>1.46 (1.32-1.61)</td>
<td>1.39 (1.16-1.66)</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>33.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of hours prior to delivery woman first arrived</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>1813</td>
<td>16.6</td>
<td>0.44 (0.38-0.52)</td>
<td>1.24 (0.95-1.63)</td>
</tr>
<tr>
<td>3-6</td>
<td>1859</td>
<td>11.0</td>
<td>0.28 (0.24-0.33)</td>
<td>0.73 (0.57-0.93)</td>
</tr>
<tr>
<td>7-12</td>
<td>1680</td>
<td>11.0</td>
<td>0.28 (0.23-0.33)</td>
<td>0.68 (0.53-0.87)</td>
</tr>
<tr>
<td>More than 12</td>
<td>3869</td>
<td>26.6</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Missing</td>
<td>3260</td>
<td>46.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 cm</td>
<td>6782</td>
<td>24.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>5-7 cm</td>
<td>1750</td>
<td>13.1</td>
<td>0.38 (0.32-0.44)</td>
<td>0.92 (0.73-1.14)</td>
</tr>
<tr>
<td>8-10 cm</td>
<td>1057</td>
<td>14.8</td>
<td>0.55 (0.45-0.66)</td>
<td>1.37 (1.02-1.82)</td>
</tr>
<tr>
<td>Missing</td>
<td>2892</td>
<td>42.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; MIRIAD, Mother-Infant Rapid Intervention at Delivery.
* Logistic regression model containing study site, study date, and all variables listed in the table.
† Weekend considered from Friday at 5:00 PM to Monday at 6:00 AM.
considerably shorter for hospitals using point-of-care testing than those employing laboratory-based testing (30 minutes vs 68 minutes; \( P < .0001 \); Figure 3). In addition, higher proportion of test results were reported back to the health care provider before delivery in point-of-care hospitals (65% vs 55%; \( P < .0001 \)).

In analyses adjusted only by study site, women arriving more than 2 hours before delivery were more likely to have a rapid turnaround time, defined as less than 60 minutes from drawing of blood until the health care provider received the results (Table 3). However, the strongest predictor of a rapid test turnaround was the hospital rapid testing process; point-of-care testing strategies were 14 times as likely to have a short turnaround as those with laboratory-based testing strategies.

In analyses adjusted for both study site and hospital testing process (point of care vs laboratory based), admission on the weekend or during the night shift (12 AM to 8 AM) was associated with a longer turnaround (Table 3). When we examined predictors of the receipt of test results after, as opposed to before, delivery, several factors were associated with such delayed receipt, including a short time (2 hours or less) between arrival and delivery (AOR 83.4; 95% CI 61.8-113.0), having more than 5 prenatal care visits (AOR 1.3; 95% CI 1.1-1.5), nondaytime admission (AOR 1.6; 95% CI 1.3-2.0 for night shift and AOR 2.5; 95% CI 2.1-3.1 for evening shift), and admission on the weekend (AOR 1.8; 95% CI 1.5-2.2).

Using rapid testing, MIRIAD identified 52 HIV-infected women on labor
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of prenatal care visits</th>
<th>No. of hours prior to delivery woman first arrived</th>
<th>MIRIAD study date</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of prenatal care visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1692 63.2</td>
<td>1.0 (0.86-1.19)</td>
<td>0.89 (0.74-1.07)</td>
</tr>
<tr>
<td>1-5</td>
<td>1186 62.3</td>
<td>0.95 (0.82-1.11)</td>
<td>0.97 (0.82-1.16)</td>
</tr>
<tr>
<td>More than 5</td>
<td>1853 63.9</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Missing</td>
<td>1988 65.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Gestational age, wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 32</td>
<td>623 64.5</td>
<td>1.01 (0.85-1.21)</td>
<td>0.95 (0.78-1.16)</td>
</tr>
<tr>
<td>32-36</td>
<td>1202 62.1</td>
<td>0.91 (0.80-1.04)</td>
<td>0.99 (0.85-1.15)</td>
</tr>
<tr>
<td>More than 36</td>
<td>4524 64.4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Missing</td>
<td>370 60.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Admission on weekend†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2089 62.1</td>
<td>0.91 (0.82-1.01)</td>
<td>0.85 (0.75-0.96)</td>
</tr>
<tr>
<td>No</td>
<td>4630 64.5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Time of admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:00 AM to 8:00 AM</td>
<td>2354 63.6</td>
<td>0.97 (0.87-1.09)</td>
<td>0.85 (0.75-0.97)</td>
</tr>
<tr>
<td>8:00 AM to 4:00 PM</td>
<td>2621 64.1</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>4:00 PM to 12:00 AM</td>
<td>1743 63.5</td>
<td>0.98 (0.86-1.11)</td>
<td>0.93 (0.80-1.07)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of hours prior to delivery woman first arrived</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>1321 61.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3-6</td>
<td>1472 64.6</td>
<td>1.19 (1.02-1.38)</td>
<td>1.11 (0.93-1.32)</td>
</tr>
<tr>
<td>7-12</td>
<td>1315 64.9</td>
<td>1.21 (1.04-1.42)</td>
<td>1.06 (0.89-1.27)</td>
</tr>
<tr>
<td>More than 12</td>
<td>1874 66.3</td>
<td>1.26 (1.09-1.46)</td>
<td>1.05 (0.89-1.24)</td>
</tr>
<tr>
<td>Missing</td>
<td>737 58.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital rapid testing process</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Point-of-care” testing</td>
<td>3914 81.0</td>
<td>14.3 (12.3-16.6)</td>
<td>—</td>
</tr>
<tr>
<td>“Laboratory-based” testing</td>
<td>2805 39.8</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>MIRIAD study date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/16/01 to 3/15/02</td>
<td>358 55.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3/16/02 to 7/15/02</td>
<td>546 54.4</td>
<td>0.97 (0.76-1.25)</td>
<td>0.87 (0.66-1.15)</td>
</tr>
<tr>
<td>7/16/02 to 11/15/02</td>
<td>769 50.6</td>
<td>0.79 (0.62-1.00)</td>
<td>0.73 (0.56-0.94)</td>
</tr>
<tr>
<td>11/16/02 to 3/15/03</td>
<td>894 55.9</td>
<td>0.99 (0.78-1.25)</td>
<td>0.83 (0.64-1.06)</td>
</tr>
<tr>
<td>3/16/03 to 7/15/03</td>
<td>746 56.6</td>
<td>0.99 (0.78-1.25)</td>
<td>0.83 (0.64-1.07)</td>
</tr>
<tr>
<td>7/16/03 to 11/15/03</td>
<td>854 69.1</td>
<td>1.75 (1.38-2.23)</td>
<td>1.03 (0.79-1.35)</td>
</tr>
<tr>
<td>11/16/03 to 3/15/04</td>
<td>831 70.4</td>
<td>1.95 (1.53-2.49)</td>
<td>0.79 (0.60-1.04)</td>
</tr>
<tr>
<td>3/16/04 to 7/15/04</td>
<td>791 77.1</td>
<td>2.88 (2.24-3.70)</td>
<td>1.18 (0.89-1.57)</td>
</tr>
<tr>
<td>7/16/04 to 11/15/04</td>
<td>656 76.2</td>
<td>2.99 (2.30-3.88)</td>
<td>1.23 (0.91-1.66)</td>
</tr>
<tr>
<td>11/16/04 to 2/13/05</td>
<td>274 71.2</td>
<td>2.13 (1.56-2.91)</td>
<td>0.89 (0.63-1.28)</td>
</tr>
</tbody>
</table>

CI: Confidence interval; MIRIAD, Mother-Infant Rapid Intervention at Delivery.

* Twenty peripartum women were missing turnaround times and were therefore not included.

† Weekend considered from Friday at 5:00 PM to Monday at 6:00 AM.
and delivery units. Neither OraQuick nor EIA produced false-negative results (Table 4). However, there were 6 false-positive OraQuick results and 18 false-positive EIA results. Sensitivity was 100% for OraQuick and EIA, and specificity was 99.92% and 99.77% for OraQuick and EIA, respectively.

Among 49 women identified as HIV infected who had their exact delivery time recorded (3 of the 52 women had missing delivery times), 32 (65%) were identified before delivery. Among the 43 women for whom data on delivery and intrapartum prophylaxis were available, 30 (69.8%) received intrapartum zidovudine (AZT) prophylaxis and 12 (27.9%) received nevirapine intrapartum prophylaxis in addition to AZT. Of the 42 HIV-exposed infants with information on prophylaxis available in the newborn’s hospital record, 41 (97.6%) received AZT, and of these, 21 (50%) also received nevirapine. On further investigation, 25 of the 52 HIV-infected women (48%) were found to have a previous positive HIV test, but this earlier testing was not documented in their medical records and was not known to the labor and delivery staff at presentation. None of these women had received antiretroviral prophylaxis during the current pregnancy. For women who presented in labor, the time from presentation to time of delivery was similar for HIV-infected and HIV-uninfected women (10 hours vs 7.8 hours; P = .1).

**COMMENT**

A variety of intrapartum antiretroviral regimens, when combined with neonatal antiretroviral prophylaxis, substantially reduce perinatal HIV transmission. Because the vast majority of deliveries in the United States occur in hospitals, presentation to labor and delivery represents a critical opportunity to test women with undocumented HIV status and to provide antiretroviral prophylaxis for those women identified as HIV infected.

MIRIAD demonstrates that routine rapid intrapartum HIV testing for women whose HIV status is unknown can be implemented in a variety of labor and delivery settings using different models of implementation. MIRIAD hospitals ranged from large teaching facilities to smaller community hospitals. In some cases, dedicated MIRIAD staff were responsible for carrying out the different aspects of the counseling and testing, but in most settings preexisting staff, including nurses, midwives, obstetrics and gynecology residents, and attending physicians were responsible for carrying out the different aspects of the counseling and testing. In some settings, labor and delivery nurses, midwives, or obstetrics and gynecology residents were trained to perform rapid testing on the labor and delivery unit.

The MIRIAD model of rapid HIV testing was well accepted by the women, with approximately 85% of women ac-

---

**TABLE 4**

<table>
<thead>
<tr>
<th>HIV infection status</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid test results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>52 (100.0)</td>
<td>6 (0.08)</td>
<td>58 (0.75)</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0.00)</td>
<td>7695 (99.92)</td>
<td>7695 (99.25)</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>7701</td>
<td>7753</td>
</tr>
<tr>
<td><strong>EIA results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>52 (100.0)</td>
<td>18 (0.23)</td>
<td>70 (0.90)</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0.00)</td>
<td>7683 (99.77)</td>
<td>7683 (99.10)</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>7701</td>
<td>7753</td>
</tr>
</tbody>
</table>

**Performance of rapid tests (95% CI)**

- Sensitivity: 100% (93.15-100%) (positive OraQuick results and 18 false-negative EIA results).
- Specificity: 99.92% (99.83-99.97%)
- Positive predictive value: 89.66% (78.83-96.11%)
- Negative predictive value: 100% (99.95-100%)

**Performance of EIA (95% CI)**

- Sensitivity: 100% (93.15-100%)
- Specificity: 99.77% (99.63-99.86%)
- Positive predictive value: 74.29% (62.44-83.99%)
- Negative predictive value: 100% (99.95-100%)

_EIA, Enzyme immunoassay; MIRIAD, Mother-Infant Rapid Intervention at Delivery._
cepting testing when offered. We note, however, that the MIRIAD study also found that acceptance rates for HIV testing were not uniform across different time periods during the day, most likely because of variability in staffing and other logistic factors at certain time periods. Acceptance rates were considerably lower during the evening and night shifts, with the lowest participation rate on Friday evenings. Rates of being approached about the study also varied by time of day and day of week, with admission on the weekend and admission during the evening shift associated with higher odds of being “missed” and thus not offered participation. Although labor and delivery units function 24 hours a day, 7 days a week, patterns of care may vary by day and time of week. A challenge for the widespread implementation of rapid testing will be to ensure that such testing is uniformly offered and available, regardless of the time of day, day of the week, or staff availability. In addition, women presenting with advanced cervical dilation were more likely to be “missed,” perhaps because the staff was too busy preparing for the imminent delivery. Ideally, these women should be approached before delivery, but if this is not feasible, they should be approached immediately after giving birth.

The MIRIAD study also demonstrated that rapid testing on labor and delivery can provide accurate and timely results. In this study, OraQuick performed better than the EIA, with higher specificity and positive predictive value. Although some hospitals have used an expedited EIA as a preliminary testing strategy to provide prophylaxis to women in labor before the results of the Western blot, this test still takes longer than does the rapid test and does not perform as well. Furthermore, EIAs cannot be used as a point-of-care test. MIRIAD demonstrated that use of a rapid test may be a better strategy than an expedited EIA testing strategy in terms of getting timely, accurate HIV results and intervening during the intrapartum period. With OraQuick, the majority of women received their test results before delivery, with point-of-care testing providing more rapid results than with laboratory-based testing.

In the United States, rapid HIV testing on labor and delivery is increasingly being recommended and implemented. Expeditied or rapid testing was initially recommended by the CDC for women on labor and delivery with unknown status in the 2001 recommendations, which was strengthened in a “Dear Colleague” letter (www.cdc.gov/HIV/projects/perinatal/2003/letter.htm, accessed July 11, 2006) 2 years later. In addition, professional organizations are increasingly recommending rapid HIV testing on labor and delivery; the American College of Obstetricians and Gynecologists includes rapid testing on labor and delivery in their most recent guidelines for HIV testing.

The CDC established a working group of experts, which developed a practical guide and model implementation protocol (www.cdc.gov/hiv/rapid_testing; accessed May 20, 2006) for HIV screening of women in labor. This guide, which was largely based on the MIRIAD experience, provides guidance and practical tips to clinicians, laboratorians, hospital administrators, and policymakers who are planning to implement a program for rapid HIV testing during labor. The guide, which is posted on the CDC website, is regularly reviewed and updated as additional experience and information become available.

Of the 17 MIRIAD hospitals, 13 have continued a rapid HIV testing program since completing the MIRIAD research study. Some hospitals found the transition to making rapid testing a standard practice to be challenging without the staff and resources provided by the MIRIAD study. MIRIAD investigators and project personnel played pivotal roles in expanding rapid HIV testing in hospitals in their regions. In Illinois, for example, the Chicago MIRIAD team partnered with the Illinois Department of Public Health to facilitate the development and adoption of a state law requiring that rapid HIV testing be offered to all women presenting in labor with undocumented HIV status. They also facilitated compliance with the law by providing resources and training to all birth hospitals in Illinois.

In Florida, 44 of the 124 hospitals that provide obstetric services have implemented rapid testing, and in July 2005 the governor signed an HIV testing bill that includes an opt-out approach to be implemented in all labor and delivery settings. New York has updated its regulations, requiring that women be offered testing and that results be available within 12 hours of admission to labor and delivery. In addition, MIRIAD investigators and project directors have been key technical experts during CDC-sponsored regional workshops to implement rapid testing in labor and delivery in US hospitals.

The findings from MIRIAD are also relevant for international settings. In these settings, in which the majority of HIV-infected pregnant women deliver worldwide, many pregnant women either do not access regular prenatal care or are not routinely offered HIV testing during prenatal care. As a result, many arrive at hospitals in labor with undocumented HIV status. A number of large hospitals including those in Kampala, Uganda (personal communication, M.G. Fowler) and St. Petersburg, Russia, are now offering rapid HIV testing at labor and delivery based on the results from the MIRIAD study.

In terms of implementing a rapid HIV testing program, several lessons can be learned from the MIRIAD experience. First, point-of-care testing provides more timely results than does laboratory-based testing. Initially, some hospital laboratories were reluctant to use a point-of-care model, but MIRIAD demonstrated that it can work quite well. For a test to be used on the labor and delivery unit, it must be specifically “waived” by the Clinical Laboratory Improvement Act (CLIA) (Public Health 42 C.F.R. § 493, http://www.access.gpo.gov/nara/cfr/waisidx_04/42cfr493_04.html, accessed May 20, 2006), indicating that it is not too complex to be used in this way. Currently there are 6 HIV rapid tests approved for use in the United States, and 4 of them are CLIA waived.

Second, almost half of women identified in MIRIAD as HIV infected had a previous
positive HIV test. Unfortunately, this information was not available to the labor and delivery staff at the time of presentation, suggesting that women may be reluctant or fearful of disclosing such a result when they come to a hospital for obstetric services. In addition, it suggests that results of prenatal testing and other medical records may not always be readily accessible on labor and delivery. Because medical records are increasingly stored and transmitted electronically, there may be opportunities for improving how and when prenatal and other medical records are communicated to labor and delivery staff.

Third, the MIRIAD study suggests that a routine opt-out approach to rapid HIV testing may increase testing rates. The considerable proportion of women (26%) who were “missed” by MIRIAD and thus never offered HIV rapid testing may represent the group of women who would most benefit by an opt-out approach, because these women were never given the opportunity to be tested.

Fourth, barriers to acceptance of HIV testing by women on labor and delivery should be eliminated. For example, some women reported not wanting another blood draw as a reason for declining testing, and acceptance rates were indeed lower when an additional blood draw was required. Making rapid HIV testing a routine part of intrapartum care and collecting blood at the time of other routine blood collection may improve testing rates.

As the number of women living with HIV in the United States continues to increase, rapid HIV testing on labor and delivery for women with undocumented HIV status is an important last opportunity to identify HIV-infected women to not only provide preventive interventions for their infants but to also encourage women to seek the care needed for their own health.

Ideally, all infected women would be identified before pregnancy. Preconception care should include HIV testing and should assure that future pregnancies are desired. For infected women, early antiretroviral prophylaxis with a regimen appropriate for pregnancy is recommended. If HIV-infected women are not identified before pregnancy, then prenatal care provides another, albeit later, opportunity to assess their status. If those who are infected are still not identified prenatally, then routine rapid testing at labor and delivery may provide the last good opportunity to identify them and may serve as a safety net to identify HIV-infected women and to institute measures to decrease the risk of perinatal HIV transmission. The MIRIAD study demonstrates that this last approach is feasible and acceptable and provides timely and accurate results.

ACKNOWLEDGMENT
We thank Siva Rangarajan, Shawn Wei, and Krystal Hodge for superb assistance at the CDC. Dr Alan Greenberg (CDC) provided guidance and support throughout the duration of the study and critically reviewed this manuscript. At the study sites, we especially thank Renata Dennis (Atlanta, GA), Yolanda Olszewski (Chicago, IL), and Angela Bradley-Byers (New Orleans, LA). Dr Pat Garcia (Northwestern University) provided critical input into protocol development, and Carol Fridlund (CDC) provided training on rapid testing at each of the participating sites.

REFERENCES
Approaches for scaling up human immunodeficiency virus testing and counseling in prevention of mother-to-child human immunodeficiency virus transmission settings in resource-limited countries

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The Joint United Nations Program on HIV/AIDS (UNAIDS) estimates that 1800 children acquire human immunodeficiency virus (HIV) infection daily. More than 85% of HIV-infected children live in sub-Saharan Africa, and the vast majority of infections occur from mother-to-child transmission (MTCT). Without intervention, there is a 15-45% chance of HIV transmission from mother to infant during pregnancy, delivery, and breast-feeding. International studies have demonstrated that the risk of MTCT in resource-limited settings can be reduced substantially, depending on the interventions provided. Prevention of mother-to-child human immunodeficiency virus (HIV) transmission (PMTCT) programs have nearly eliminated mother-to-child transmission of HIV in developed countries, but progress in resource-limited countries has been slow. A key factor limiting the scale-up of PMTCT programs is lack of knowledge of HIV serostatus. Increasing the availability and acceptability of HIV testing and counseling services will encourage more women to learn their status, providing a gateway to PMTCT interventions. Key factors contributing to the scale-up of testing and counseling include a policy of provider-initiated testing and counseling with right to refuse (opt-out); group pretest counseling; rapid HIV testing; innovative staffing strategies; and community and male involvement. Integration of testing and counseling within the community and all maternal and child health settings are critical for scaling-up and for linking women and their families to care and treatment services. This paper will review best practices needed for expansion of testing and counseling in PMTCT settings in resource-limited countries.

Key words: counseling, human immunodeficiency virus, mother-to-child human immunodeficiency virus transmission, testing
• Male partner involvement and couples counseling.29-31
• Community involvement.32
• Extension of testing and counseling into all maternal and child health (MCH) services.10,21

This paper reviews data supporting the approaches used to expand testing and counseling for PMTCT programs and discusses the priorities and best practices needed for ongoing expansion of testing and counseling for PMTCT in resource-limited settings.

**Provider-Initiated Testing and Counseling**

Current global recommendations from the World Health Organization (WHO) and UNAIDS advocate for provider-initiated testing and counseling with the right to refuse (opt-out) within PMTCT settings (antenatal, labor and delivery, and postdelivery settings).14,15 With provider-initiated testing and counseling, health care workers or providers recommend HIV testing as part of the standard package of services provided routinely to all clients. The client must specifically opt-out or refuse the test if she does not want to know her HIV status.14,15 There is no need for a separate written consent for HIV testing; consent is almost always verbal. This is a shift from the historical practice of client-initiated (opt-in) testing, or voluntary counseling and testing, in which the client specifically requests an HIV test and usually provides written consent. The rationale for provider-initiated testing and counseling is that it normalizes HIV testing in medical settings, increases the number of people who know their HIV status, and improves PMTCT program impact.14,33

International and national policies increasingly endorse provider-initiated testing and counseling within the context of pregnancy. Various articles in the past have referred to the provider-initiated testing and counseling with right to refuse as an opt-out strategy and client-initiated testing and counseling as an opt-in strategy, but for the purpose of this paper, we will use provider- and client-initiated testing and counseling when referring to these strategies. New WHO guidelines, to be released in early 2007, will further advocate for provider-initiated testing and counseling within various medical settings including PMTCT, sexually transmitted infection and tuberculosis clinics. As shown in the Table, data from both developed countries16,34-36 and resource-limited countries17,18 have shown an increase in the uptake of testing and counseling when the provider-initiated testing and counseling approach is implemented.

**Country Experiences Implementing Provider-Initiated Testing and Counseling**

Data from developed countries such as the United States and Canada show that HIV testing rates were generally higher in states or provinces that used provider-initiated testing and counseling than in those that used client-initiated testing—71-98%, compared with 25-83%.16 These findings resulted in a change in U.S. policy to provider-initiated testing for women in prenatal care.57,58 In 2006, the U.S. government released new guidelines that recommend HIV screening for all patients in all health care settings after the patient is notified that testing will be performed, unless the patient declines (referred to as opt-out screening).39 Universal screening in health care settings was recommended despite the low national prevalence of HIV infection in the United States (less than 1%) because strategies that incorporated universal screening such as those among pregnant women and blood donors had resulted in increased testing and near elimination of perinatal transmission and transfusion-associated HIV infection. In addition, providers in busy health care settings often lack the time necessary to conduct risk assessments and might perceive counseling requirements as a barrier to testing. Furthermore, earlier diagnosis could lead to earlier treatment of HIV infection and potential reduction of risk behaviors by HIV-infected individuals.39

The lessons learned from developed countries in implementing provider-initiated testing and counseling have been adapted and used in resource-poor settings. Increases in HIV testing uptake have been reported in several African settings in which provider-initiated testing and counseling has been implemented. For example, Botswana implemented provider-initiated testing and counseling in 2004,17 following a declaration by the President for universal testing in medical settings. An evaluation of the early impact of routinely recommended testing on HIV-test acceptance and the rates of return for care in prenatal settings in Botswana’s second largest city showed that acceptance of testing increased from 75.3% to 90.5% (Table); there was no difference in the percentage of tested women who did not receive results (29.4% client initiated vs 33.0% provider initiated, P = .29), and there was no change in the number of women seeking prenatal care. National data show that uptake of testing and counseling in prenatal settings in Botswana has similarly increased to more than 90%.17 Although the experience in other settings has shown that not all women will return for test results,40 the increased emphasis on rapid HIV testing with same-day results will increase the number of women who know their HIV status.14,15

Despite the evidence, a number of resource-limited countries with generalized HIV epidemics (HIV prevalence greater than 1%) have either not adopted or fully implemented this approach. Even where it is the policy, field experience in Africa indicates that testing still needs to be greatly expanded to increase coverage and ensure wide provision of appropriate interventions.41 There are also concerns that women may feel coerced into accepting testing and may not return for their test results and other PMTCT interventions if they accept testing in a provider-initiated program.40,42 Despite these concerns, the provider-initiated testing and counseling approach has been found to be acceptable21,32 and does not appear to deter women from returning for their results.17
**Group Pretest Education**

Many PMTCT programs now provide HIV pretest information to groups of clients (rather than individually) and incorporate the information into general health talks. The group pretest session helps to reduce the burden on providers and allows more time for the individual posttest counseling session during which the client is provided with the result and, if HIV positive, information about PMTCT interventions and HIV-related treatment and care. During the group pretest session, provider-initiated testing and counseling can be easily offered as part of routine services while ensuring that confidentiality, consent (with a choice to opt out), and counseling (provided during individual posttest sessions) are maintained. The same basic information provided in individual sessions is offered during the group session, although the individual session does offer an opportunity to discuss more in-depth personal issues.

**Using Rapid HIV Testing with Same-Day Results**

Use of rapid HIV testing is recommended by the WHO to increase uptake of HIV testing and counseling and is now widely available, and the testing method of choice in many African countries. Rapid HIV testing has several advantages: It is simple to perform, is highly sensitive and specific, cost effective, simplifies logistics, minimizes recording errors, and offers the opportunity for same-day results.

Rapid HIV testing takes 10-20 minutes to perform so that clients can be given their results on the same day. This is extremely important because many women in resource-limited countries may make only 1 prenatal visit or may present late in pregnancy for their first visit. Same-day results on the first prenatal visit ensures that clients have the opportunity to know their HIV status as part of prenatal care and to receive PMTCT interventions and referrals.

A study in Uganda found that rapid testing with same-day results increased notification rates, compared with standard enzyme-linked immunosorbent assay (ELISA) testing among pregnant HIV-positive women (96% vs 65%). Rapid tests also play an important role in labor and delivery settings in which eligibility for PMTCT interventions may depend on the quick return of test results.

Because whole blood or oral fluids are used for rapid testing, nonlaboratory personnel can be trained to collect and test specimens. Specialized laboratory facilities are not required, and testing can be conducted in front of clients, increasing confidence in results and reducing clerical errors. The sensitivity and specificity of rapid HIV testing are similar to ELISA. Rapid testing has also been shown to be cost effective when compared with ELISA and Western blot. However, support is needed to establish and maintain the quality of rapid testing through the establishment of both internal and external quality assurance systems, including regular training and supervision of health care staff.

**Testing and Counseling at Labor and Delivery or Immediately After Delivery**

Many women in resource-limited countries present at labor and delivery (L&D) with unknown HIV status. In some settings, these women may be at higher risk of HIV than those tested during prenatal care. Rapid testing and counseling at L&D or immediately after delivery enables women that might have been missed during prenatal care to also know their HIV status and access PMTCT interventions. Testing in these settings also allows access to treatment and care for the HIV-infected mother and other family members. The provision of routine testing and counseling in L&D and postpartum wards for women not tested during the antenatal periods is a crucial safety net for maximizing PMTCT programs and has been found to increase uptake of PMTCT services.

**Table**

<table>
<thead>
<tr>
<th>Study/location</th>
<th>Client-initiated testing and counseling</th>
<th>Provider-initiated testing and counseling</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005, Van’t Hoog et al</td>
<td>2278/4142 (55%) (12 months)</td>
<td>2799/4089 (68%) (12 months)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2004, Centers for Disease Control and Prevention</td>
<td>381/506 (75%) 3 months in 2003</td>
<td>314/347 (90%) 4 months in 2004</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>National Data Botswana</td>
<td>67%, 2003</td>
<td>92%, 2005</td>
<td>—</td>
</tr>
<tr>
<td>2001, Stringer et al</td>
<td>2561/3415 (75%) 12 months, 1998-1999</td>
<td>3324/ 3778 (88%) 12 months 1999-2000</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1999, Simpson et al</td>
<td>35% United Kingdom</td>
<td>88%</td>
<td>—</td>
</tr>
<tr>
<td>2006, Sherr et al</td>
<td>2309/2710 (85%), 2002</td>
<td>774/850 (91%) 2004</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
The Mother Infant Rapid Intervention at Delivery (MIRIAD) study evaluated the feasibility of offering rapid testing to women of unknown HIV status at L&D in 16 hospitals in the United States. MIRIAD found that rapid testing and counseling is acceptable and feasible and that the rapid tests deliver accurate and timely test results. Based on this study, the United States now recommends routine HIV testing and counseling at L&D to women with unknown status.

A few studies in large provincial hospitals in resource-limited countries such as Uganda and Kenya found that testing and counseling at L&D and immediately after delivery is acceptable and feasible and increases HIV testing uptake. However, concerns have been expressed that women may be pressured to give consent, may not understand the testing and counseling process at the time of labor, or may feel coerced to test for HIV. On the contrary, an evaluation to determine whether participants in the MIRIAD study actually understood from the consent process that they could opt out of HIV testing and counseling found that approximately 70% of participants were able to state in their own words the benefits of testing. Over 80% accepted rapid HIV testing and knew they had the right to opt out, indicating that they were not being forced or coerced. It is important, however, to ensure that providers are trained to conduct the pretest session, offer the test, and ensure consent without unduly pressuring the patient. This may be particularly important when working in settings in which patients may not feel free to question their health care provider.

Rescreening Women Who Test HIV Negative During the Prenatal Period
Recent studies show high rates of seroconversion among women who test negative early in pregnancy in some sub-Saharan African settings. Depending on local HIV incidence, consideration should be given to retesting HIV-negative women in the third trimester or during labor. Recent evidence also indicates that HIV rescreening late in pregnancy in high-prevalence, resource-limited settings is a cost-effective strategy for reducing MTCT. These findings illustrate the need for stronger posttest counseling messages that include risk reduction and encourages partner testing, and they highlight the benefits of retesting later in pregnancy, especially in high-prevalence settings.

Human Resource Capacity
Despite the above approaches, the human resource crisis facing many African countries may affect the capacity to scale up HIV testing and counseling. Innovative strategies can be implemented to support staff, typically nurses who are tasked with testing and counseling in PMTCT settings. The paper by Sripipatana et al in this supplement clearly outlines the need to utilize lay counselors such as traditional birth attendants, mothers living with HIV infection, community health care workers, and off-duty workers to provide PMTCT services including HIV testing and counseling. People in other fields can also be rapidly trained as counselors to help to alleviate the human resources crisis. For example, in Botswana, high school graduates serve as counselors after receiving a 4-week HIV-counseling training.

Ongoing training and utilization of job aids such as videos, algorithms, protocols, and flip charts with text messages and action steps will help these various cadres of staff to provide quality and standardized HIV testing and counseling services. The Centers for Disease Control and Prevention (CDC) in collaboration with the WHO, United Nations Children’s Fund, and the United States Agency for International Development have developed the Testing and Counseling for PMTCT Support Tools, which provide educational materials, job aids, and training resources to support the integration of testing and counseling into prenatal, L&D, and postdelivery settings as well as linking PMTCT services with care, treatment, and community services. These tools are available online, can be used as an orientation package for new providers, and are being adapted in several countries including Mozambique, Cambodia, Nigeria, Kenya, and Botswana.

Male Partner Involvement and Couples Counseling
One major factor that prevents some women from accepting testing is the need to seek their partner’s consent or assent. More than 50% of pregnant women who refused HIV testing in a PMTCT setting in Uganda reported the need for their partner’s assent or presence before they could test. Studies have shown that when male partners are involved or couples counseling is provided, HIV testing uptake is higher and women are more likely to implement PMTCT and treatment and care interventions. Involving men has been one of the most difficult strategies to implement, yet there have been some successful efforts. One study in Tanzania showed a 30% increase in male partner counseling when men were sent a letter of invitation to participate in PMTCT programs. Studies in Uganda and Kenya have shown that routine offer of testing and counseling to male partners as part of couples counseling during labor or immediately after delivery is highly acceptable and has resulted in higher rates of HIV testing.

In Swaziland, lower infant transmission rates were recorded when the male partner was involved and participated in support group activities for people living with or affected by HIV. Additionally, utilization of PMTCT interventions, including the receipt of antiretrovirals, avoidance of breast-feeding, and condom use, have also been reported to be higher when couples are counseled together, emphasizing the need to further support couples counseling within PMTCT settings. Other strategies include extending clinic hours so that men can visit in late afternoon or reducing wait times for men or couples who visit MCH clinics. A combination of these strategies is needed to increase testing uptake and involve the male partner.

Concern has been raised that women who disclose to their partners, whether through couples counseling or other circumstances, have an increased likeli-
hood of adverse social outcomes such as abandonment or violence. A recent study in Zambia showed that this is not always the case because adverse social events were reported regardless of disclosure or counseling status. The rate of adverse social events were similar in women who received couples counseling, women who disclosed after individual testing, and women who did not disclose their HIV status. Although adverse social events of up to 4-16% have been reported after disclosure in sub-Saharan African settings, the experience from multiple African countries have shown that more women actually experienced beneficial outcomes and support after disclosing their HIV status to their partner. However, it will be extremely important to establish support mechanisms for the women who may experience negative outcomes, and additional data from resource-poor settings would help to further understand the depth of social adverse events following HIV testing and disclosure.

**COMMUNITY INVOLVEMENT**

Scaling up testing and counseling within PMTCT settings is influenced by not only policies, staffing, and infrastructure but also the community. Community norms, ideas, and support for a particular program or activity can influence a woman’s decision to test for HIV. However, experience with involving the community is limited. One such experience is from a comprehensive rural PMTCT program in Zimbabwe. Community activities included informational meetings about testing and counseling for PMTCT and provision of educational materials for community members. This program was successful in increasing testing uptake, and community education was seen as a contributor to increasing awareness of HIV and PMTCT services and to decreasing the stigma surrounding HIV.

For women in rural settings or those who do not have easy access to health centers, testing and counseling for PMTCT can be integrated into community prenatal and immunization outreach services. Other innovative practices involving the community include mobile testing and counseling services provided in Uganda and the traveler tester and counselor program in Kenya in which counselors use bicycles to reach remote settings to provide HIV testing and counseling services. These strategies can target pregnant women and can offer testing and referral for other PMTCT interventions. Models for increasing community involvement such as communication strategies to increase knowledge and awareness of HIV and PMTCT services are needed to reduce stigma and to increase the acceptability of testing and PMTCT interventions.

**CONCLUSION**

Testing and counseling in prenatal, L&D, and postdelivery settings is an important gateway to providing PMTCT and treatment and care services to women and their families. Uptake of HIV testing and counseling can be greatly increased with provider-initiated testing and counseling, group pretest counseling sessions, and rapid HIV testing with same-day results. These services should be integrated into every component of reproductive health and MCH services. Finally, international and national policies that promote use of provider-initiated testing and counseling and rapid HIV testing should be widely adopted to further encourage scale-up of HIV testing and counseling in PMTCT settings.

Training health care providers in key elements of HIV testing and counseling and distributing work to appropriately trained lay providers can help alleviate the human resources crisis faced in many resource-limited countries as discussed elsewhere in this supplement (Sripipattana et al). Tools such as flip charts, wall charts, videos, and written information can assist lay personnel in conducting standardized testing and counseling activities. Male partner involvement should also be encouraged because men can affect women’s decisions to be tested and treated for HIV infection. Involving male partners will increase uptake of HIV testing and PMTCT interventions and will serve as a critical step in involving the family in HIV care. The community should also be involved in program planning and implementation to help reduce stigma and discrimination and to improve community awareness of HIV and PMTCT services beyond MCH settings.

Finally, scale-up of HIV testing and counseling should be accompanied by scale-up of other PMTCT interventions including provision of antiretroviral prophylaxis or treatment, modified obstetric practices, infant feeding counseling, and support for women who test positive as well as prevention counseling and intervention for women who test negative. Continued efforts must also be made to ensure that HIV-positive women have access to other prevention interventions such as cotrimoxazole prophylaxis; counseling to prevent transmission to HIV-negative partners (ie, secondary prevention); linkages or referral for early infant diagnosis; partner referral; and treatment, care, and support for women, their infants, and their families. This will ensure that testing and counseling within PMTCT and MCH settings can serve as points of entry to comprehensive HIV care for entire families.

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Toward elimination of perinatal human immunodeficiency virus transmission in the United States: effectiveness of funded prevention programs, 1999-2001

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Mother-to-infant transmission of human immunodeficiency virus (HIV) in the United States has declined markedly since the early 1990s because of the advent of highly effective interventions to prevent perinatal transmission of HIV. Among an estimated 6000-7000 HIV-infected women who give birth in the United States each year, the number who transmitted HIV to their newborns has decreased from an estimated peak of 1650 infections in 1992 to an estimated range of 144-236 in 2002.1 The sharp decrease reflects the use of antiretroviral (ART) drugs and obstetrical interventions that have reduced the transmission from approximately 25% to less than 2% when the mother’s HIV infection is diagnosed early in pregnancy.2,3 The US Public Health Service recommends 3-part ART prophylaxis: for women during the prenatal and intrapartum periods and for their newborns during the first 6 weeks after birth. Women whose HIV infection is not diagnosed until they are in labor, either because they did not receive prenatal care or were not tested for HIV prenatally, should receive prophylactic ART, if possible, during the intrapartum period, as should their infants during the first 6 weeks.4 Although not as effective as when initiated earlier in pregnancy, ART prophylaxis received during the intrapartum and neonatal periods can cut transmission rates by half.5-8

The objective of the study was to assess the effectiveness of federal funds in preventing perinatal human immunodeficiency virus (HIV) transmission in the United States. We used surveillance data from 1999 and 2001 in 6 funded areas to estimate the proportion of HIV-infected women prescribed perinatal prophylaxis and whose infants were HIV infected. We compared outcomes with 5 unfunded areas in which surveillance data were available. The proportion of funded-area women prescribed prophylaxis increased from 80.1% to 85.9% (P < .01), compared with a decline in unfunded areas from 95.1% to 86.7% (P < .01); the difference in trends between groups was P < .01. The perinatal HIV transmission rate for funded areas declined from 6.5% (105 cases) in 1999 to 3.4% (46 cases) in 2001 (P < .01), compared with a decline in unfunded areas from 4.3% (19 cases) to 3.4% (13 cases) (P = .59); the difference in trends between groups was P = .24). The number of perinatal HIV infections in the funded areas decreased by 56%, achieving the Centers for Disease Control and Prevention’s goal of a 50% reduction in incidence by 2005.

Key words: antiretroviral, perinatal HIV, prevention, surveillance
Survey of Childbearing Women. Enhanced Perinatal Surveillance (EPS) data include information about the receipt of prenatal care, the prescription of prophylactic ART, and HIV status among children born to HIV-infected mothers.

It is important to evaluate the effect of federal prevention dollars on HIV incidence and, in particular, to measure progress toward the CDC’s goal of reducing the incidence by half by 2005. Evaluations of federal programs are challenging, however, because of the frequent lack of comparison groups. In addition, federally funded prevention programs often vary in type and scope in ways designed to best serve individual communities. We did not attempt to evaluate any 1 specific program type but the potential effect of federal funding in general. Using national surveillance data, we assessed trends in the prescription of prophylactic ART and in perinatal transmission rates in 6 areas with perinatal HIV prevention program and surveillance funding and compared the trends with those in 5 areas with perinatal surveillance funding only.

Materials and Methods
This evaluation covered the period 1999 through 2001. The program funds were made available in late 1999; most programs did not begin until 2000 or later. Enhanced perinatal surveillance data were available from 1999 though 2001; most areas discontinued surveillance for years after 2001. We provide process measures on program implementation for the years 2000 and 2001. We provide outcome measures for 1999, a baseline year before programs began, and for 2001, the last year for which surveillance data were available in most areas. Because CDC policy is to report aggregate surveillance data, we combined process and outcome measures across the 6 areas funded for prevention programs and surveillance and across those funded for surveillance only. Institutional review board approval or exemption for the collection of surveillance data was obtained as appropriate by each area.

Areas receiving CDC perinatal HIV prevention and/or surveillance dollars were included if the annual number of mother-infant pairs on whom data were collected was 70% or greater of the number of HIV-infected child-bearing women. We used data from the 1994 Survey of Childbearing Women, or more recent serosurvey data if available, to estimate the completeness of EPS data in each state. Among the 16 health departments awarded CDC program funds for perinatal HIV prevention, we included 6 in the analysis. Two were excluded because they were not funded for perinatal surveillance during the time of analysis, so outcome data were not available. Four were excluded because EPS data were collected on an insufficient proportion (less than 70%) of mother-child pairs for the analysis period; 2 were provided surveillance funds but were unable to conduct it on all HIV-exposed children because of state law, and 2 did not implement their prevention programs until 2001. The 6 funded areas included in this analysis are the states of Connecticut, Louisiana, New Jersey, New York, and South Carolina and the city of Philadelphia. The number of HIV-infected women giving birth in these 6 areas represented 49.6% of the 4804 annual births among HIV-infected women in all 16 funded areas, according to the 1994 Survey of Childbearing Women.

Among the 7 health departments funded for perinatal surveillance only, 5 were included and 2 were excluded because EPS data were collected on an insufficient proportion of mother-child pairs for the period under analysis. The included health departments were those for Michigan, Mississippi, North Carolina, Tennessee, and Virginia. The number of HIV-infected women giving birth in these areas represented 71.0% of the 663 annual births among HIV-infected women in all 7 unfunded areas, according to the 1994 Survey of Childbearing Women.

Our process measures include a program type and size. Program types were described as 1 of the following: (1) social marketing to inform women about the need to be tested for HIV during pregnancy and the availability of interventions to dramatically reduce transmission rates; (2) provider training to promote HIV testing of pregnant women and appropriate treatment or referrals for infected women; (3) case management of HIV-infected pregnant women to ensure proper prenatal and HIV care; (4) outreach or 1-on-1 contact between a community worker and a woman of childbearing age at risk for HIV infection to promote HIV testing, pregnancy testing, risk reduction, and referrals to prenatal and HIV care as appropriate; and (5) rapid HIV testing of women in labor who did not have a documented prenatal HIV test. Program size was assessed by the following: (1) the number and types of social marketing programs, (2) the number of providers trained, (3) the number of HIV-infected women enrolled in case management during their pregnancy, (4) the number of women of childbearing age who were contacted by outreach workers, and (5) the number of hospitals engaged in rapid HIV testing at labor and delivery.

For both groups, we analyzed age at delivery, race, and ethnicity of HIV-infected women for 1999 and 2001. For the year 1999 only, we compared those characteristics for the funded and unfunded areas, using a χ² test. We estimated the outcome measures of receipt of any perinatal care, the prescription of prophylactic ART stratified by receipt of prenatal care, and the proportion of infants diagnosed as HIV infected.

We defined the receipt of prenatal care as yes, no, or unknown. We included in the analysis the number of HIV-infected women for whom data on the prescription of antiretroviral agents were available and defined as known prescription or known nonprescription of these drugs. We assessed the prescription of prophylactic ART in 2 ways. In a best-case scenario, among women who received prenatal care, we assessed the proportion of mother-infant pairs prescribed ART during the prenatal, intrapartum, and neonatal periods. In a worst-case scenario, among women who did not receive prenatal care but who delivered their babies in a hospital, we examined the proportion of pairs who were not prescribed any ART, despite the opportunity during labor and after deliv-
ery. We used the revised CDC surveillance HIV case definition for adults and children to classify infants as infected with HIV, not infected with HIV, or indeterminate. The case definition is available as an appendix to this supplement.

We conducted a 2-tailed Fisher’s exact test to determine whether the difference in proportions within a group between 1999 and 2001 was statistically significant. To determine whether an outcome’s changes over time differed significantly between groups, we used a multiple logistic regression model, with variables for year, funded or unfunded, and an interaction term. For the proportion of women without prenatal care who were prescribed no antiretroviral agents, we used an exact logistic regression model because of the small sample size.

In a separate analysis, we assessed receipt of prenatal care and of ART among women in both groups who delivered in 2001 and whose infants were HIV infected. The purpose of this analysis was to better understand the extent to which perinatal HIV infections in either group might have been prevented.

**Results**

All of the 6 funded areas conducted provider training in 2000 and 2001; some, but not all, areas implemented other types of perinatal HIV prevention. Program size with respect to the number and types of social marketing programs, the number of providers trained, the number of HIV-infected women enrolled in case management during their pregnancy, and the number of women of childbearing age who were contacted by outreach workers increased in 2001, compared with 2000 (Table 1).

Age at delivery, race, and ethnicity varied significantly (P < .01) among the 2 groups in 1999, using a χ² test (data not shown). The funded areas had a smaller proportion of births among 13- to 19-year-olds and among black women that year and a larger proportion of births among women 35 years old and older and among Hispanic women than did the unfunded areas.

In the funded group, the proportion of women who received prenatal care and who, with their infants, were prescribed the 3 recommended parts of prophylactic ART increased from 80.1% in 1999 to 85.9% in 2001 (P < .01), whereas in the unfunded group, the proportion decreased from 95.1% to 86.7% (P < .01) (Table 2 and Figure 1). In the multiple logistic analysis, the change in proportions from 1999 to 2001 between the 2 groups was statistically significant (P < .01).

Perinatal HIV transmission in the funded group declined from 6.5% (105 cases) to 3.4% (46 cases) (P < .01), a 56% reduction in new cases (Table 2 and Figure 2). The rate in the unfunded group declined from 4.3% (19 cases) to 3.4% (13 cases), a 32% reduction in new cases, but the decline was not statistically significant. Although transmission rates dropped sharply in the funded areas, the change in proportions over time between the 2 groups was not statistically significant, partly because of the small number of transmissions overall.

In 2001, 46 women in the funded areas transmitted HIV to their infants, as did 13 women in the unfunded areas. Nine of the women in the funded areas (19.6%) received no prenatal care, compared with 2 (15.4%) in the unfunded areas. Among 27 women in the funded areas who received prenatal care and had data on prophylactic ART prescription, 19 (66.7%) were prescribed 3-part ART, as were 5 of 10 women in the unfunded areas.

**Comment**

Our analysis suggests that federal funding earmarked for perinatal HIV prevention programs was associated with an increase in the proportion of HIV-infected women and their infants who received recommended prophylactic ART. Federal funding may also be associated with larger reductions in perinatal HIV transmission rates, compared with areas in which prevention program funding was not available. Both groups showed reductions in their rates of perinatal HIV transmission, and both had the same transmission rate in the final year of the evaluation, but the steepest decline occurred for the funded group. That group exceeded the CDC’s goal of a 50% reduction in new HIV infections by 2005 for the targeted group, newborns.

Whereas the evaluation of federal HIV prevention dollars is critical, this evaluation demonstrates some of the obstacles. As is often the case with prevention program funds, we did not have a rigorous comparison group of areas with similar prevalence of HIV among women of childbearing years but that did not re-

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**TABLE 1**

Perinatal HIV prevention programs aggregated across 6 areas that received federal funding for programs, 2000-2001

<table>
<thead>
<tr>
<th>Program</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider training: number of providers trained</td>
<td>CDC-funded perinatal HIV prevention programs begin in 2000</td>
<td>1634 (6)*</td>
<td>2319 (6)*</td>
</tr>
<tr>
<td>Outreach: number of women contacted</td>
<td>97,076 (3)*</td>
<td>109,148 (4)*</td>
<td></td>
</tr>
<tr>
<td>Case management: number of HIV-infected pregnant women enrolled</td>
<td>45 (1)*</td>
<td>81 (3)*</td>
<td></td>
</tr>
<tr>
<td>Social marketing: number of and type of media distributed</td>
<td>700 brochures (1)*</td>
<td>132 bus shelter posters</td>
<td>25,000 outreach cards 5252 brochures (3)*</td>
</tr>
<tr>
<td>Rapid HIV testing during labor: number of hospitals offering</td>
<td>2 (1)*</td>
<td>2 (1)*</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses indicate how many of the 6 funded areas offered the program.
receive program funding. In addition, the small number of perinatal HIV transmissions in the United States makes it difficult to detect statistically significant differences in rates between groups. We note differences in maternal age, race, and ethnicity between our funded and unfunded groups that may have influenced outcomes. However, the direction of these hypothetical influences is unclear.

The available surveillance data did not permit us to examine differences in maternal characteristics such as health insurer, country of birth, substance abuse, or mental illness, which could have influenced receipt of prenatal care or the prescription of antiretroviral drugs. Knowledge of these characteristics could be important to understand why outcomes differed between groups and how to improve programs. Nonetheless, our comparison group of unfunded areas suggests trends that might have occurred in the funded group had it not received federal prevention funds.

In addition, we had to limit our evaluation to a subgroup of both the funded and unfunded areas. Most areas were eliminated from the analysis because of their lack of surveillance data to calculate outcomes. Funded areas included in our evaluation captured 50% of HIV-infected women of childbearing age in all of the funded areas, according to the 1994 Survey of Childbearing Women. Unfunded areas included in our evaluation captured 71% of the estimated total. It is difficult to assess the potential impact on outcomes if the additional areas had been able to provide surveillance data. However, areas that were unable to

| TABLE 2 | Receipt of prenatal care, prescription of antiretroviral therapy, and perinatal HIV transmission rates, in 1999 and 2001, among 6 areas receiving perinatal HIV prevention program funds and 5 areas not receiving program funds |
|-----------------|-----------------|-----------------|-----------------|
| Prevention program grantee areas (6) | Nongrantee areas (5) |
| 1999 | 2001 | 1999 | 2001 |
| Total number of mother-child pairs | 1608 | 1372 | 447 | 379 |
| Received any prenatal care | 1436 | 89.3 | 1220 | 88.9 | .77 | 301.05 | .01 | 19 | 4.3 | .59 | .24 |
| Received any prenatal care and 3 arms of ART | 1052 | 80.1 | 949 | 85.9 | .01 | 330 | 95.1 | 261 | 86.7 | .01 | .01 |
| Received no prenatal care and no arms of ART | 13 | 16.3 | 11 | 13.3 | .01 | 1 | 7.7 | 5 | 18.5 | .64 | .47 |
| HIV infected | 105 | 6.5 | 46 | 3.4 | .01 | 19 | 4.3 | 13 | 3.4 | .59 | .24 |

* This P value measures the statistical significance of changes in proportions between 1999 and 2001 between areas federally funded to conduct perinatal HIV prevention programs and those not funded. Differences with P < .05 are considered to be statistically significant.

** FIGURE 1 **
Proportion of HIV-infected women in prenatal care prescribed 3-part antiretroviral prophylaxis


** FIGURE 2 **
Proportion of HIV-infected women whose infants are HIV-infected

provide complete surveillance data often were affected by local laws that made difficult the matching of HIV-infected mothers to their infants as required to conduct perinatal surveillance. We do not believe these laws would have affected program performance.

Even in areas able to perform perinatal surveillance, these surveillance funds were available only to measure 3 consecutive years of outcome and impact measures. For the key measures of prescription of ART among HIV-infected women in prenatal care and perinatal HIV transmission, the funded and unfunded groups had reached nearly the same point in 2001, as Figures 1 and 2 indicate. However, for the proportion of women prescribed ART, the funded group made significant progress over the 3 years, whereas the proportion shrank in the unfunded group. The funded group shows the steeper decline in perinatal HIV transmission rates (an additional 27% relative reduction in the transmission rate above the decline in the unfunded areas). In both cases, additional years of surveillance data would be needed to determine if these trends continue.

Perinatal surveillance funds were renewed in 2006, but they will be available only for a subset of the areas receiving funds for HIV prevention programs. Data on key characteristics of HIV-infected pregnant women and perinatal HIV transmission in funded as well as unfunded areas for several consecutive years would be useful for continued assessment of impact and to help pinpoint which areas might most benefit from new or continued funding.

The economic perspective also is important in the evaluation of HIV prevention programs. We did not conduct a formal cost-effectiveness analysis, but note that CDC distributed $11 million in perinatal HIV prevention dollars to the funded areas included in our evaluation from 1999 through 2001, including resources for coordination and administration at the national level. The 27% relative improvement in transmission rates, compared with the unfunded group, indicates that 48 perinatal HIV transmissions might have been prevented with the help of federal funding. We calculate that each perinatal HIV transmission translates into $163,324 in lifetime treatment costs, assuming 15 years of survival, and 18.3 quality-adjusted life-years saved. Thus, federal funds allocated to the prevention areas minus lifetime treatment costs associated with prevented infections were $3.1 million, or $65,226 per infection prevented and $3,560 per quality-adjusted life-year saved, a value that is well below the median cost for other life-saving interventions. Although this analysis does not account for state and local funds that may have supplemented perinatal HIV prevention in the 6 areas, the federal contribution appears to be a good investment.

This evaluation shows that opportunities remain to prevent transmission through more rigorous identification and treatment of HIV-infected pregnant women and increased prenatal care. For women who received prenatal care, the proportion prescribed the full course of recommended prophylaxis was only 85.9% in 2001 at the funded areas (and 66.7% among those whose infants were infected). A substantial proportion of the HIV-infected women in both groups, more than 8%, received no prenatal care during 2001. Among women whose infants became infected, the proportion that received no prenatal care was 19.6% and 15.4% in the funded and unfunded areas, respectively. In contrast, only 1.0% of all women delivering in the United States in 2001 received no prenatal care.

The evaluation also indicates that some women continue to transmit HIV to their infants despite receiving prenatal care and being prescribed ART. More research needs to be conducted to discover why such transmissions continue to occur and to what extent additional prevention can be achieved through better programs vs more efficacious antiretroviral prophylactic regimens. Perinatal HIV transmission among women prescribed ART is associated with factors that either could not be assessed by available surveillance data or fell outside the scope of our analysis. Those factors include, but are not limited to, adherence, viral load at the time of delivery, viral resistance to antiretroviral medications, breastfeeding, and mode of delivery.

Our analysis suggests that federal funding can be effective in preventing perinatal HIV transmission in the United States. The data evaluated here also point to missed opportunities for prevention and future avenues for research. The continued evaluation of the impact of federal HIV prevention funds is important. For perinatal HIV prevention, specifically data collection on all HIV-infected pregnant women and their infants with regard to receipt of prenatal care, prescription of and adherence to ART prophylaxis and treatment, and HIV transmission will be vital to the evaluation of program effectiveness and identification of additional opportunities for prevention.

ACKNOWLEDGMENTS
The authors acknowledge data analysis support by Suzanne Whitmore, DrPH, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, CDC; and leadership in perinatal HIV prevention by the participating health department program and surveillance teams, including the following: Tamika Jackson, Heather Noga, Aaron Roome, and Janis Spurlock-McLendon, Connecticut Department of Public Health; Jamie Segura, Cheryl Wheeler, Billy Robinson, and the HAP Perinatal Work Group, Louisiana Department of Health and Hospitals; Hollie Malamud-Price and Linda Scott, Michigan Department of Community Health; Patricia Doyle, Roberta Glaros, Lou Smith, and Barbara Warren, New York State Department of Health; Vicki Peters, New York City Department of Health and Mental Hygiene; William Graham and Anne-Lyne McCalla, North Carolina Department of Health and Human Services; Jane Baker, Kathleen Brady, Phil DiBar- tolo, Diane Gatson, Olara Marshall, James McAnaney, and Geneva Vaughan-Harris, Philadelphia Department of Public Health; Linda Kettinger, South Carolina Department of Health and Environmental Control; Laurealee Killingsworth and Thomas Shavor, Tennessee Department of Health; and Carol Burnham, Betsy Coleburn, Dena Ellison, and Lisa Weymouth, Virginia Department of Health.

REFERENCES


Cesarean delivery for HIV-infected women: recommendations and controversies

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In the United States, the rate of cesarean delivery, defined as cesarean deliveries per 100 live births, has increased markedly over the past 10 years. A variety of factors have contributed to this increase, which includes an expansion of indications for cesarean delivery, increased reliance on continuous fetal monitoring (leading to increased diagnosis of fetal distress), obstetrician-gynecologist concerns regarding medical liability, and, possibly, maternal requests for elective cesarean deliveries without a specific indication. Paralleling the increase in the overall rate of cesarean delivery, an increasing proportion of HIV-infected women are having cesarean deliveries. In this article, we review evidence for the prevention of mother-to-child transmission (MTCT) of HIV through cesarean delivery before labor and before ruptured membranes, the evolution of recommendations regarding the mode of delivery for HIV-infected women, trends in the mode of delivery for HIV-infected women, and the associated risks and cost-effectiveness of cesarean delivery for the prevention of MTCT of HIV. Finally, we summarize unanswered questions regarding the role of cesarean delivery among HIV-infected women.

Benefits of Cesarean Delivery and Evolution of Recommendations Regarding the Mode of Delivery for HIV-Infected Women

Early observational studies suggested there might be a role for cesarean delivery in the prevention of MTCT of HIV. Several studies of twins who were born to HIV-infected women noted that, among twins who were born vaginally, first-born twins were more likely to be infected with HIV compared with second-born twins. Because first-born twins are the first to pass through the birth canal, it was assumed that they would have the greatest exposure to infectious blood and genital tract secretions. In addition, first-born twins remain in the birth canal for a longer period of time. This supported the theory that exposure to HIV in the birth canal may play an important role in MTCT of HIV and that cesarean delivery could be protective by limiting exposure to blood and genital secretions in the birth canal. Additional retrospective and prospective studies yielded inconsistent results; some studies reported that cesarean delivery was associated with a decreased risk of MTCT of HIV, and other studies failed to show any association of the mode of delivery with transmission.

These early observational studies may have had conflicting results for several reasons. One critical issue was that it is often not easy to differentiate between cesarean deliveries that are performed before labor from those that are performed after the onset of uterine contractions, when microtransfusions of maternal blood into fetal circulation may occur. In addition, to have maximal effect, cesarean deliveries should be performed before the rupture of membranes, because once the integrity of the membranes is compromised the risk of infection increases. To standardize terminology, the term elective cesarean sec-

Two studies that were published in 1999 demonstrated that cesarean delivery before labor and before the rupture of membranes (elective cesarean delivery) reduces the risk of mother-to-child transmission of the human immunodeficiency virus (HIV). On the basis of these results, the American College of Obstetricians and Gynecologists and the US Public Health Service recommend that HIV-infected pregnant women with plasma viral loads of >1000 copies per milliliter be counseled regarding the benefits of elective cesarean delivery. Since the release of these guidelines, the cesarean delivery rate among HIV-infected women in the United States has increased dramatically. Major postpartum morbidity is uncommon, and cesarean delivery among HIV-infected women is relatively safe and cost-effective. However, a number of important questions remain unanswered, including whether cesarean delivery has a role among HIV-infected women with low plasma viral loads or who receive combination antiretroviral regimens.

Key words: cesarean delivery, HIV transmission
was adopted widely to refer to a cesarean delivery that was performed before the onset of labor and before the rupture of membranes. Alternatively, the American College of Obstetricians and Gynecologists (ACOG) uses the term scheduled cesarean delivery so that it is not confused with other uses of the term elective in obstetrics. Hereafter in this article, the term elective cesarean delivery is used to denote cesarean delivery before labor and before ruptured membranes.

A turning point came in June 1998, when the preliminary results from both a multicenter randomized clinical trial and a large individual patient data meta-analysis were presented at the 12th World AIDS Conference in Geneva, Switzerland, and published subsequently in 1999. Results from the randomized trial, which was conducted in 6 European countries, demonstrated an 80% reduction in the rate of MTCT of HIV among women who were allocated to the elective cesarean delivery group. When the actual mode of delivery was analyzed, cesarean delivery after labor and/or after ruptured membranes resulted in an intermediate rate of MTCT of HIV (8.8%), compared with vaginal delivery (10.2%) and to elective cesarean delivery (2.4%). In this study, although elective cesarean delivery was associated with a decreased odds of transmission compared with vaginal delivery (odds ratio, 0.3; 95% CI, 0.1-0.8), cesarean delivery after labor and/or after ruptured membranes was not associated with a significant decreased odds of transmission compared with vaginal delivery (odds ratio, 1.0; 95% CI, 0.3-3.7). Results from the large metaanalysis of individual patient data from 15 prospective cohort studies indicated that elective cesarean delivery was associated with an approximately 50% reduction in the risk of MTCT of HIV. The results from the randomized trial and the individual patient data metaanalysis were sufficient for ACOG to issue new guidance regarding the role of cesarean delivery in perinatal HIV prevention. In August 1999, ACOG issued a committee opinion that recommended that HIV-infected women be offered a scheduled cesarean delivery at 38 completed weeks of gestation. The original 1999 ACOG committee opinion was updated in 2000. The current recommendations by ACOG and the US Public Health Service recommend that HIV-infected pregnant women with plasma loads of >1000 copies/mL be counseled regarding the benefits of an elective cesarean delivery. Elective cesarean deliveries should be performed at 38 completed weeks of gestation, based on the best clinical estimate of gestational age. A woman’s prenatal antiretroviral regimen should not be interrupted around the time of delivery. In addition, for most women, an infusion of zidovudine should be started at least 3 hours before the operation.

Trends in Cesarean Delivery Rates Among HIV-Infected Women
Since the release of the results of the randomized clinical trial in Europe and the individual patient data metaanalysis from North America and Europe and of subsequent guidelines, the cesarean delivery rate among HIV-infected women has increased dramatically. In the United States, the cesarean delivery rates in a pediatric surveillance system and a pediatric HIV longitudinal cohort study demonstrated a doubling of cesarean delivery rates after June 1998, from 20% to nearly 50%. Unfortunately, it was not possible in this study to distinguish between elective cesarean deliveries and cesarean deliveries performed after the onset of labor or rupture of membranes. In addition, such studies of trends in the mode of delivery in the United States have not been updated recently, so it is unknown whether cesarean delivery rates among HIV-infected women have continued to increase or have stabilized over the last few years. In Europe, where cesarean delivery rates among HIV-infected women have been higher traditionally than in the United States, similar increases in cesarean delivery rates have been reported after 1998. For example, in a recent report from Sweden, the cesarean delivery rate for HIV-infected women increased from 8% in 1985-1993 to 44% in 1994-1998 and to 80% in 1999-2003. These higher rates may reflect a more aggressive policy of offering cesarean delivery to all women, regardless of viral load. The European Collaborative Study reported that the elective cesarean delivery rate among HIV-infected women increased from 1997-2000, then decreased slightly, and finally began increasing again in 2003. The authors speculate that these fluctuations were, in part, due to an increase in nonelective cesarean deliveries among women who had planned an elective procedure but were seen in labor or after rupture of membranes. These results led to a policy shift towards the scheduling of elective cesarean deliveries earlier in gestation.

 Associated Risks and Cost-Effectiveness of Cesarean Delivery for the Prevention of the MTCT of HIV
In weighing the risks and benefits of elective cesarean delivery, the benefit of the prevention of MTCT must be carefully weighed against any increase of morbidity or mortality for either the woman or her infant, as well as increased costs and recovery time. A number of studies have addressed the question of whether HIV-infected women have higher postcesarean complication rates compared with HIV-uninfected control subjects. Most studies demonstrate an increased risk of postoperative morbidity, mostly infectious, in HIV-infected women compared with uninfected control subjects, and the risk of complications is correlated with the degree of immunosuppression.

However, from a clinical perspective, the pertinent question is whether elective cesarean delivery increases an HIV-infected woman’s risk of complications compared with a vaginal delivery or with a nonelective cesarean delivery. Six studies that address this issue were recently summarized in a Cochrane review. This review concluded that, among HIV-infected women, nonelective cesarean delivery was associated with the highest rate of postpartum morbidity, that elective cesarean delivery was intermediate in risk, and that vaginal de-
livery had the lowest risk of morbidity. Much of the postpartum morbidity was relatively minor, including postoperative fever, anemia, endometritis, and wound infection. Findings from this review reinforce the importance of the ACOG recommendations that all women who undergo cesarean delivery, regardless of HIV infection status, should receive prophylactic antibiotics. Maternal deaths are rare, and these studies did not have adequate sample sizes to assess potential differences in maternal mortality rates. Although short-term postoperative morbidity may be increased among HIV-infected women, it does not appear that mode of delivery is associated with more long-term effects, such as subsequent HIV disease progression.

In resource-limited settings, there are limited data to suggest that the risks of postpartum morbidity and mortality among HIV-infected women who undergo cesarean delivery may be magnified. In addition, there may be inadequate resources available to provide cesarean deliveries for all HIV-infected women in settings of high HIV seroprevalence among pregnant women.

In terms of risks to the infant that are associated with cesarean deliveries, there are no studies to address this among infants born to HIV-infected women. However, we know from studies of HIV-uninfected women that the primary risk to infants that is associated with elective cesarean delivery is iatrogenic prematurity and its sequela. To reduce the likelihood of onset of labor or rupture of membranes before delivery, ACOG recommends that elective cesarean delivery for HIV-infected women be scheduled at 38 completed weeks of gestation, which is 1 week earlier than for HIV-uninfected women. Because amniocentesis should be avoided in HIV-infected women, clinicians should rely on best clinical estimates of gestational age, rather than documentation of fetal lung maturity. In HIV-infected pregnant women, earlier delivery (38 vs 39 weeks) without documentation of fetal lung maturity may lead theoretically to more iatrogenic prematurity, although there are no data to support or refute this. It will be important to monitor the rate of infant morbidity because of iatrogenic prematurity in this setting.

Elective cesarean delivery has been shown to be relatively cost-effective and, in some cases, cost-saving. However, these analyses focused primarily on women who were receiving prenatal and intrapartum zidovudine only and assumed relatively high transmission rates. Because these cost-effectiveness models are very sensitive to changes in the baseline rate of MTCT, if assumptions about the increased effectiveness of combination antiretroviral regimens are included, the cost/benefit of cesarean delivery is reduced markedly. By contrast, because the cost of treating postpartum morbidity is relatively low compared with treatment of pediatric HIV disease, these models are relatively stable over a wide range of postpartum morbidity rates. However, over a broad range of assumptions, elective cesarean delivery remains relatively cost-effective.

Unanswered Clinical Questions

The initial ACOG guidelines were circumspect about the role of elective cesarean delivery in pregnant women with low HIV viral loads, and neither the randomized trial nor the metaanalysis could address this issue. Because these studies were conducted before the advent of viral load testing, these studies could not incorporate adjustment for viral load, which is now known to be critically important in the determination of the risk of MTCT. When the ACOG guidelines were updated in May 2000, they further specified that women with viral loads of >1000 copies/mL should be counseled regarding the benefits of cesarean delivery. These updated guidelines cited results from the Women and Infants Transmission Study, a prospective cohort study. In this analysis, no transmissions were reported among the 57 women with viral loads of <1000 copies/mL. For women with viral loads of <1000 copies/mL, the ACOG guidelines state that there are insufficient data with which to make recommendations regarding mode of delivery. The US Public Health Service guidelines are consistent with the ACOG guidelines and support elective cesarean delivery for women with viral loads of >1000 copies/mL and encourage additional clinical research regarding the potential role of elective cesarean delivery in decreasing MTCT among women with undetectable viral loads.

Another related unanswered question is whether there is any benefit of elective cesarean delivery in the prevention of MTCT of HIV among women who receive combination antiretroviral regimens, including highly active antiretroviral therapy (HAART). Both the randomized clinical trial and the individual patient data metaanalysis included mostly women who were receiving either no antiretrovirals or zidovudine only. In the randomized trial, although more than one half of the women received zidovudine during pregnancy, few women received combination antiretroviral regimens. In the individual patient data metaanalysis, >70% of mother-child pairs did not receive any antiretrovirals during the prenatal, intrapartum, or neonatal periods. Because the risk of transmission already is reduced substantially for women who take HAART prenatally (ie, 1%-2% transmission rate), a study with a very large sample size would be needed to detect a further reduction in transmission because of elective cesarean delivery.

However, there are some studies that shed some light on the issue of whether elective cesarean delivery confers additional benefit among women with low viral loads while receiving HAART. In an individual patient data metaanalysis of 1202 women with plasma viral loads of <1000 copies/mL, cesarean delivery was an independent predictor of transmission risk in analyses that controlled for maternal receipt of antiretrovirals. Of note, among women who underwent cesarean deliveries, there were no transmissions among 270 women who received antiretroviral therapy, whereas there were 5 transmissions among 66 women who had not received antiretrovirals. However, this study was unable to
distinguish elective from nonelective cesarean deliveries. In a recent report from the European Collaborative Study, elective cesarean delivery was associated independently with transmission risk in analyses that adjusted for maternal viral load and maternal antiretroviral therapy. When restricted to 560 women with undetectable viral loads, elective cesarean delivery was protective in univariate analyses. However, when adjusted for maternal antiretroviral use (none vs any), the association between elective cesarean delivery and transmission risk was no longer statistically significant (adjusted odds ratio, 0.52; 95% CI, 0.14-2.03). It is unclear whether these results mean there is no true protective effect or whether the study lacked adequate statistical power to reveal an association because of the small sample size. Because of their limitations, neither of these studies definitively answers the question of whether elective cesarean delivery is associated with a decreased risk of MTCT of HIV among women with undetectable viral loads in the era of HAART.

Another unanswered clinical question is how soon after the onset of labor or the rupture of membranes that the benefit of cesarean delivery is lost. Although early studies dichotomized the length of membrane rupture and found that rupture of membranes for >4 hours was associated with a nearly 2-fold increase in transmission risk, a subsequent individual patient data metaanalysis demonstrated a continuously increasing risk of MTCT, with the transmission risk increasing approximately 2% for every additional hour of ruptured membranes. Therefore, how does one counsel a woman who planned for an elective cesarean delivery but who arrives in early labor or shortly after rupture of membranes? In such a situation, if a long period of labor is anticipated, some clinicians may choose to proceed with cesarean delivery; others may choose to proceed with an expedited vaginal delivery. What about the case of an HIV-infected woman with a high viral load who arrives with preterm labor or with premature preterm rupture of membranes? In these cases, the preferred mode and timing of delivery should be individualized on the basis of the specific clinical situation.

Other questions arise from clinical situations in which there is incomplete information about plasma viral load. For example, suppose a woman arrives late in pregnancy; she has not been receiving antiretroviral therapy, and viral load results are unlikely to be available before delivery. In this case, it is unlikely that her viral load will be suppressed adequately before delivery, and the woman should be counseled that elective cesarean delivery is likely to reduce her risk of transmission.

COMMENT

Among HIV-infected pregnant women, cesarean delivery before labor and before the rupture of membranes has been shown to be safe and effective in reducing the risk of MTCT of HIV. However, the benefits of cesarean delivery in preventing MTCT of HIV must be weighed against potential increases in maternal and infant morbidity and the costs of cesarean delivery. In the United States, the benefits of cesarean delivery for women with viral loads of >1000 copies/mL generally outweigh the increased risk of minor postpartum morbidity. However, a number of important unanswered questions remain, such as how soon after labor onset or rupture of membranes the benefit of cesarean delivery is lost and whether cesarean delivery has a role in women with low HIV viral loads while receiving HAART. Furthermore, the appropriate role, if any, of elective cesarean delivery among HIV-infected women in various resource-limited settings with variable degrees of medical infrastructure and HIV prevalence rates will need to be better defined, particularly given the expanding availability of HAART in these settings.

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Prevention of mother-to-child transmission services as a gateway to family-based human immunodeficiency virus care and treatment in resource-limited settings: rationale and international experiences

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With more than 15 million human immunodeficiency virus (HIV)-infected women living in developing countries and more than 500,000 HIV-infected infants born each year, the HIV/AIDS epidemic presents an unprecedented challenge to maternal and child health.1 In response, there have been important steps in the areas of HIV prevention and treatment towards mitigating the impact of the epidemic among women and children in developing countries.

Efforts to identify HIV-infected women during pregnancy and prevent the mother-to-child transmission (PMTCT) of HIV have made important inroads in the prevention of pediatric HIV, primarily through the use of single-dose nevirapine (SD-NVP).2 Although SD-NVP programs have proven feasible to implement in a wide range of antenatal care settings, further efforts to prevent the vertical transmission of HIV face significant hurdles. In many countries, low levels of uptake of antenatal and obstetric services mean that only a fraction of HIV-infected women can receive PMTCT interventions.3 There is also evidence to suggest that the effectiveness of PMTCT programs in preventing pediatric HIV may be somewhat less than that demonstrated in clinical trials. This may be due in large part to difficulties in maintaining high levels of compliance with SD-NVP protocols in busy public sector services where HIV-infected pregnant women do not receive intensive education and adherence support. One analysis of an urban PMTCT service in Zambia suggested that approximately one-third of HIV-infected women who were dispensed SD-NVP did not take it.4 In this light, initiatives to further reduce the vertical transmission of HIV around the world will require more intensive interventions delivered on a broader scale.

There have also been recent advances in many developing countries in the accessibility of HIV care and antiretroviral treatment services. A number of reports have demonstrated that the use of highly active antiretroviral therapy (HAART) in these settings can achieve outcomes comparable to those in United States and Europe,5,6 and experience in the use of antiretroviral drugs is increasing rapidly in many developing countries.

In many developing countries, services to prevent the mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) operate with limited contact with HIV care and treatment programs, despite significant advances in the accessibility of both services. There is a need to deliver more complex multidrug PMTCT interventions that extend beyond single-dose nevirapine, particularly for pregnant women with advanced HIV disease who are at high risk of transmitting HIV to their children and require rapid initiation of life-long highly active antiretroviral therapy. We argue for strengthened ties between PMTCT services and HIV care and treatment programs in resource-limited settings, viewing PMTCT programs as a gateway to family-based HIV care and treatment. Existing experiences from the multicountry MTCT-Plus Initiative suggest that close ties between PMTCT services and HIV care and treatment programs are feasible and can lead to significant advances in reducing the vertical transmission of HIV and promoting the health of HIV-infected women, children, and families.

Key words: antiretroviral therapy, child health, health systems, human immunodeficiency virus, mother-to-child transmission, women’s health

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Received Feb. 2, 2007; accepted March 15, 2007.

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The MTCT-Plus Initiative is supported through a consortium of foundations including the Bill and Melinda Gates Foundation, William and Flora Hewlett Foundation, Robert Wood Johnson Foundation, Henry J. Kaiser Family Foundation, John D. and Catherine T. MacArthur Foundation, David and Lucile Packard Foundation, Rockefeller Foundation, and Starr Foundation, and is administered through the International Center for AIDS Care and Treatment Programs at the Mailman School of Public Health, Columbia University.

0002-9378/$32.00
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doi: 10.1016/j.ajog.2007.03.068
The parallel expansion of PMTCT and HIV treatment around the world has challenged many national and international health programs to consider the practical interactions between these services. In many local health services and national health systems, PMTCT is the concern of maternal and child health. HIV care and treatment services have generally been developed as stand-alone clinical services, often with limited integration with HIV prevention efforts or existing primary health care services.

This separation may prevent both services from achieving their overall aims of preventing new HIV infections and providing optimal care to individuals who are HIV-infected. Here, we review the potential interface between PMTCT services and HIV treatment programs in developing countries. After discussing the benefits of integrating these services, we argue for an approach in which PMTCT services are viewed as a gateway for HIV-infected women and their families to comprehensive HIV care and treatment.

The rationale for linking PMTCT and HIV treatment services

In many developing countries, particularly in sub-Saharan Africa, antenatal care clinics (ANC) are among the most frequently utilized services of the public sector health system. Primary care antenatal and obstetric services are usually run by nurse-midwives with minimal access to specialists, and high patient-to-provider ratios are the norm. The simplicity of SD-NVP has allowed widespread coverage of PMTCT in this context, but delivering more complex multidrug PMTCT interventions may be less straightforward. Enhanced linkages between HIV treatment programs and PMTCT services can facilitate the introduction of more complex antiretroviral regimens, including HAART for women with advanced HIV disease who require treatment for their own health, as well as 2- and 3-drug combinations for pregnant women who do not yet need chronic therapy.

Women with advanced HIV disease, as defined by high viral load, low CD4 count, and AIDS, are at the greatest risk of transmitting the virus during pregnancy and delivery as well as postpartum through breastfeeding. Maternal viral load was the strongest predictor of vertical transmission of HIV in a study of PMTCT in Thai women. Similarly, in an analysis of late postnatal transmission, lower maternal CD4 count was associated with a significantly higher risk of transmission through breastfeeding. It is in this subset of pregnant women with advanced HIV disease in which HAART, beyond simpler 1- or 2-drug strategies, can have the greatest impact on reducing MTCT.

There are also significant advantages to the use of more complex regimens for women with less advanced disease. In settings in which HAART is used during pregnancy for almost all HIV-infected women, such as the United States and Western Europe, MTCT rates have dropped dramatically. However, several simpler and less costly PMTCT regimens, such as SD-NVP with either short-course zidovudine or zidovudine and lamivudine, have demonstrated efficacy greater than SD-NVP alone and are highly effective for preventing transmission, particularly in women with less advanced disease.

If PMTCT programs in developing countries are to achieve successes in preventing pediatric infections similar to those seen in well-resourced countries, PMTCT services need to be able to deliver more complex antiretroviral regimens. In addition to access to the appropriate antiretroviral drugs, this will require the ability to assess HIV disease state, rapidly identify the subset of pregnant women with advanced HIV disease who require HAART, expedite the initiation of treatment, and closely monitor drug toxicity. While short-course regimens are less demanding than HAART therapy, they will also require a level of monitoring and support not routinely needed for the administration of SD-NVP. Given the limited capacity of most ANC and PMTCT services, it is unlikely that these activities will be integrated successfully into PMTCT programs without significant support. For this reason, it will be critical to link HIV care and treatment services, in which the expertise to administer multidrug regimens is well established, with PMTCT services, thereby enhancing the capacity of PMTCT programs to offer more complex regimens and more comprehensive services.

One example of the potential interface between PMTCT and HIV care and treatment services in a low-resource setting comes from the Western Cape Province of South Africa. All HIV-infected pregnant women identified through PMTCT services undergo immunologic testing. Pregnant women with CD4-positive counts greater than 200 cells/μL receive a 2-drug regimen of short-course zidovudine and SD-NVP for PMTCT, whereas those with CD4-positive counts of 200 or fewer cells/μL are immediately referred to separate HIV treatment facilities for a “fast-track” evaluation and HAART initiation. This dual strategy has now been implemented on a wide scale and has contributed to the Province’s overall low rate of vertical transmission of HIV, estimated at approximately 6% to 8%. In addition to the enhanced PMTCT benefits, this dual strategy facilitates the entry of women into chronic HIV treatment.

Despite the success of this approach, there have been concerns that the need to refer women requiring HAART from PMTCT services to separate HIV treatment centers may lead to delays in HAART initiation because of administrative complexities and the difficulties that women face in seeking care at another facility. For example, at many sites in the Western Cape, the separate location of PMTCT and HIV treatment services means that HIV-infected women with CD4 counts below 200 cells/μL are referred to initiate HAART at facilities that are several kilometers away from the ANC/PMTCT service and are expected to regularly attend separate follow-up visits at both ANC/PMTCT and HIV treatment services.

Anecdotal evidence suggests that there is substantial loss to follow-up of pregnant women with advanced HIV disease in this referral system (with women not completing distant referrals and failing to initiate HAART during the antenatal period as a result). In response to this,
public sector PMTCT services in the community of Khayelitsha in Cape Town, which are managed with support from Médecins Sans Frontières, have instituted a different approach to linking services. Pregnant HIV-infected women with advanced HIV disease initiate HAART and clinical follow-up entirely within PMTCT clinics, through “outreach” or satellite clinics operated within PMTCT programs by the local HIV treatment service. This approach streamlines the rapid initiation of HAART during pregnancy and reduces the likelihood that women will be lost or treatment will be delayed. This approach also requires more intensive involvement of providers from HIV treatment services and active coordination between the 2 services.

Other models to link PMTCT and HIV care and treatment services have been explored within the Columbia University Mailman School of Public Health MTCT-Plus Initiative, a multicenter program in sub-Saharan Africa and Thailand that uses PMTCT as a platform to provide comprehensive HIV care to women and their families. In several sites, peer workers trained to provide support and education to newly diagnosed HIV-infected women, also play the role of patient navigator, assisting and accompanying pregnant women as they make and attend appointments in HIV care clinics.

In some programs, HIV clinics have identified a weekly session during which pregnant women are seen so that their enrollment and treatment initiation can be expedited. At most sites, multidisciplinary teams of HIV providers, including staff from PMTCT as well as HIV treatment clinics, meet weekly to review and discuss new patients, creating a venue to discuss, track, and assure that eligible pregnant women are successfully initiating treatment. Although the advantages and limitations of different models for the provision of HAART to pregnant women require further investigation and will need to be tailored to a variety of settings, these experiences suggest the types of linkages that are possible between PMTCT and HIV care and treatment programs.

PMTCT services as a gateway to family-based HIV care and treatment

The rationale for linking these services also extends beyond enhancing PMTCT interventions. Antenatal services are a critical venue for the identification of HIV-infected women for long-term HIV care and treatment. For example, 1 recent analysis from Lusaka, Zambia suggests that more than 10,000 HIV-infected women could be identified annually through the city’s PMTCT services. PMTCT services provide one of the few opportunities to identify women across the spectrum of HIV disease, including asymptomatic patients and those with advanced disease. In addition to HAART and prophylaxis against opportunistic infections, there are important interventions that can promote the long-term health of HIV-infected women with earlier stages of HIV disease by reducing morbidity and delaying HIV disease progression. These include case finding and treatment for tuberculosis, malaria prevention interventions, nutritional supplementation, and family planning.

To date, most HIV care and treatment services in resource-limited countries have approached HIV-infected adults and children as individual patients, with little recognition of the effect of HIV on entire families. In many health systems, pediatric and adult HIV services are often in different locations, provided by distinct groups of providers, with little effort to coordinate care for mothers, children, and families. Such an approach overlooks the potential benefits of directing services toward families. By recognizing the mother–child dyad as a principal unit of care, PMTCT services can help to change this view of HIV care and treatment to increase the emphasis on family-centered services.

A family-centered approach offers the ability to reach and retain a greater number of HIV-infected family members. Throughout the world, women are at the center of families and households. By identifying HIV-infected women through PMTCT programs and enrolling them into family-based care, health services are more likely to access other HIV-infected household members. A family-centered approach may be particularly important for pediatric care because children frequently receive less attention in HIV care and treatment services than adults. With postnatal follow-up, PMTCT programs afford the opportunity to identify and follow up both HIV-exposed and infected children; with appropriate links to care and treatment, these children can receive routine health interventions such as cotrimoxazole and isoniazid prophylaxis.

For HIV-infected children, a family-based approach may help ensure better access to services and retention in care than if parents’ and children’s services are provided separately and in different locations. Also, engaging families affords an opportunity to identify family and household members at earlier stages of HIV disease and to provide interventions aimed at slowing disease progression. Late entry into care for adults has been associated with poor outcomes in response to HAART. More generally, the retention of patients in long-term primary care services is a ubiquitous concern for HIV treatment programs, and having families receiving care at the same facility facilitates patient follow-up over time. For example, among patients on antiretroviral therapy (ART), the support provided by family members is likely to be an important determinant of treatment adherence.

The MTCT-Plus Initiative

Despite the potential benefits of using PMTCT services as an entry point to long-term HIV care and treatment, few programs in resource-limited settings have recognized this unique potential of PMTCT programs. The MTCT-Plus Initiative provides a leading example of the feasibility and benefits of such integration. The concept of MTCT-Plus builds on existing PMTCT programs, which often offer limited medical care to HIV-infected women and their families. MTCT-Plus programs enroll HIV-infected women identified through antenatal or postnatal PMTCT services. Women receive a comprehensive pack-
age of care adapted to their stage of HIV disease, and they serve as the index patient for family-centered HIV care and treatment services. Women enroll their newborn infants; other HIV-infected family and/or household members, including male partners, are also enrolled into the same program of long-term HIV care.

The interventions that are included in the MTCT-Plus Initiative are delivered as part of a comprehensive package of HIV primary care (Figure). This approach to comprehensive care is necessary to address the different needs of HIV-infected family members, which are likely to change through time with the progression of HIV disease and improvements in health that come with initiating ART. To deliver this kind of comprehensive HIV primary care and address the complex needs of families with HIV, the MTCT-Plus Initiative emphasizes multidisciplinary teams to provide care, incorporating nurses, counselors, doctors, community health workers, social workers, pharmacists, and peers. Coordinating the efforts of these different types of service providers is a significant challenge, and regular team meetings are an important tool for addressing the needs of patients and families.

Currently, there are 13 programs in sub-Saharan Africa and Southeast Asia participating in the MTCT-Plus Initiative. As of September 2006, more than 12,000 individuals have been enrolled into care. Approximately half of the patients are index women identified through PMTCT services; of these, 45% initiated care during the antenatal period, whereas the remainder enrolled postpartum. More than two-thirds of index women have enrolled another family member, usually an HIV-infected or HIV-exposed child. Across MTCT-Plus sites, 69% of women enrolled into the program received SD-NVP for PMTCT, but a substantial proportion received multidrug PMTCT combinations (12%) or HAART (7%).

At sites that have developed the capacity to initiate HAART during pregnancy, up to 30% of pregnant women are eligible and receive triple-drug therapy and low MTCT rates at several sites suggest the effectiveness of this approach for both prevention of MTCT as well as enhancement of maternal health. Early virologic testing of all HIV-exposed infants is supported within MTCT-Plus to identify infected infants within the first months of life, and there is an emphasis on retaining exposed babies in care throughout the first years of life until a final infection status is determined. More than 2000 infants, 90% of those who have reached 18 months of age, have been determined to be uninfected. Of 761 infected children enrolled in MTCT-Plus, including children of the index pregnancy as well as older siblings, 65% are currently receiving HAART. Thirty-seven percent of infected children are less than 12 months of age. This is an unusually high proportion of young babies, reflecting the success of the attention to follow-up of exposed babies and early identification and diagnosis of those who are infected. Overall, retention of patients and adults as well as children in MTCT-Plus programs is excellent, with fewer than 600 adults leaving the program, including 190 reported deaths.

The MTCT-Plus Initiative has provided several valuable lessons regarding the provision of woman-centered, family-based HIV care and treatment services linked to PMTCT programs (Table). The rapid expansion of MTCT-Plus services at participating sites and the high levels of patient retention in services demonstrate that PMTCT programs are valuable settings to engage women and families in long-term HIV care and treatment services. For women with advanced HIV disease who require HAART, several sites have made rapid evaluation and initiation of treatment available, with promising results. For other sites, the links between PMTCT programs and HIV treatment services allow the delivery of multidrug PMTCT regimens that would not otherwise be possible through standard antenatal care services. And across all MTCT-Plus sites, women, their children, and their families from across the spectrum of HIV disease receive comprehensive HIV care and treatment services. With growing evidence that providing health care services to HIV-infected individuals before they require HAART can yield important benefits, the use of PMTCT services as a gateway to family-based HIV care and treatment is likely to gain increasing attention in many resource-limited countries.

**Conclusion**

There is a strong rationale for linking PMTCT and HIV care and treatment
services. Enormous benefits can be garnered that will result in markedly decreased morbidity and mortality for women, their children, and their families. PMTCT programs identify large numbers of HIV-infected women and, ultimately, HIV-exposed and infected children and provide the ideal opportunity to engage women, their partners, and their children in long-term care. HIV care and treatment services, when linked with PMTCT programs, can facilitate the use of highly potent ART regimens during pregnancy, further diminishing the risks of vertical transmission and can engage families in long-term preventive and therapeutic care. Perinatal HIV prevention efforts will not be able to attain the successes seen in more resourced settings without comprehensive integration with care and treatment services. HIV care and treatment programs will miss the opportunity to provide critical, lifesaving services to large numbers of women and children unless they are effectively linked to PMTCT services.

In light of the clear benefits of linked systems, there is a pressing need for greater insight into how such integration may take place. There are few well-documented public sector experiences that can be used as a basis for scaling-up programs. There are important outstanding questions regarding how resource constraints, human capacity, national agendas, and community preferences influence the feasibility of linkages between services. With countless lives of women, children, and families at stake, addressing these questions and developing reproducible models for using PMTCT programs as a gateway to HIV care and treatment services may represent one of the most significant interventions to improve the lives of HIV-infected individuals around the globe.

ACKNOWLEDGMENTS

MTCT-Plus has supported the following sites: Cote d’Ivoire: Formation Sanitaire Urbaine de Yopougon-Attie, Abidian; Cameroon: Mbomo and Banso Baptist Hospitals, Bamenda; Kenya: Moi Hospital and Mosoriot Rural Health Center, Eldoret, Nyansa Provincial General Hospital, Kisumu; Mozambique: Beira and Chimoio Day Hospitals; Rwanda: Treatment and Research AIDS Center, Kicukiro Health Center, Kigali; South Africa: Ekupheni Clinic, Cato Manor, Durban, Langa Clinic, City of Cape Town Health Department, Cape Town, Perinatal HIV Research Unit, Chris Han Baragwanath Hospital, Soweto; Thailand: Thai Red Cross Research Center, Bangkok; Uganda: Mulago Hospital, Kampala, St. Francis Nsambya Hospital, Kampala; Zambia: Chelstone and Mtwendere District Health Clinics, Lusaka.

REFERENCES


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Site-specific interventions to improve prevention of mother-to-child transmission of human immunodeficiency virus programs in less developed settings

Tabitha Sripipatana, MPH; Allison Spensley, MPH, MSW; Anna Miller, MD; James McIntyre, MD; Gloria Sangiwa, MD; Frederick Sawe, MD; David Jones; Catherine M. Wilfert, MD

Worldwide, 530,000 children became infected with the human immunodeficiency virus (HIV) in 2006, an estimated 90% as a result of mother-to-child transmission (MTCT). In 2001, the UN General Assembly set a target of reducing the proportion of infants infected with HIV by 20% by 2005 and 50% by 2010. This article explores the experiences of prevention of mother-to-child HIV transmission (PMTCT) programs designed to meet these targets in resource-constrained settings. The following sections highlight the various interventions used, with the successes and challenges faced along the way. The strategies described draw from the published literature and the last 6 years of experience with the Elizabeth Glaser Pediatric AIDS Foundation’s (EGPAF) PMTCT program, initially entitled “Call to Action.”

The World Health Organization (WHO) recommendations for PMTCT (revised in 2006) include a 4-pronged comprehensive strategy. Although we acknowledge the critical role that all approaches play in reducing pediatric HIV infection, the focus of this article is on site-specific strategies that address the third prong: preventing HIV transmission from infected mothers to their infants. Programmatic experiences in sub-Saharan Africa are the primary focus here, but the lessons learned from these examples apply to other resource-constrained settings.

METHODS

EGPAF requires a quantitative progress report quarterly for US government-funded PMTCT sites and every 6 months for privately funded sites. Each site records patient data about counseling, testing, HIV status, antiretroviral (ARV) prophylaxis, and other indicators. A standardized form is submitted to the in-country technical advisor or the EGPAF program officer. Data are reviewed for inconsistencies, trends over time, site variability, and discussion of challenges and improvements. Queries are sent to in-country staff for appropriate corrections. All corrected data are entered in FileMakerPro 6 (Filemaker Inc, Santa Clara, CA). Qualitative data reports are submitted every 6 months and are reviewed alongside the quantitative data to provide context and explanation regarding site successes and challenges.

Programmatic experience and innovations

Despite many challenges, 6 years of EGPAF’s program experience with PMTCT service delivery in 13 African
nations has shown that high uptake of HIV counseling, testing, and delivery of an intervention is possible in resource-poor settings (Figure 1). Statistical analyses on program data regarding uptake in HIV counseling, HIV testing, women receiving test results, and provision of ARV to mother and infant show significance in improvement over the years.\textsuperscript{4}

PMTCT and maternal and child health services

The defined minimum package for antenatal care (ANC) usually includes health education, a physical examination, urinalysis, laboratory blood tests, including syphilis screening, vitamin and iron supplementation, tetanus immunization, and malaria prophylaxis. However, the availability of supplies and staff to provide basic services is dependent on the economic reality of the country. The availability of test kits, drugs, and other commodities, essential to providing PMTCT services, is inevitably linked to procurement, distribution, and supply chain management capacity. These aspects of program management are fundamental for the entire continuum of HIV services and need strengthening in most countries. Sites benefit from technical assistance to develop a clear procurement system and from support to hire and train individuals with the responsibility for ordering and distributing essential commodities.

Human capacity and space constraints

PMTCT is part of the complete package of quality health care services that should be offered to mothers and infants. To ensure integration, PMTCT services should be provided by the regular maternal and child health (MCH) staff, not by a separate cadre of health care providers. However, adding PMTCT services increases the time demands on staff, and additional personnel may be required to handle the workload. Equally important, all staff in the facility must be appropriately trained in PMTCT and involved in service delivery so that every mother has access to services, regardless of which provider she sees at the facility. The addition of counseling alters patient flow and creates a need for confidential space. National programs should incorporate PMTCT curricula into the preservice training of physicians, nurses, and clinical officers to ultimately diminish training needs of personnel providing services.

Strategies that have been used include:

- Paying trained staff to work overtime, as sites have done in Zambia.\textsuperscript{5}
- Reapportioning the work and using staff of the highest skill level for tasks only they can perform. For example, nurses do not need to register patients when a clerk can do so. In Malawi and Zimbabwe, nurses provide rapid tests at the time of counseling.
- Training new cadres of workers, such as lay counselors, as sites have done in Zimbabwe and South Africa.
- Engaging community workers, such as traditional birth attendants (TBA), in the program, as sites have done in Tanzania and Cameroon.\textsuperscript{6,7}

The availability of sufficient space to provide services is often a challenge to already stretched health facilities. Adding the need to accommodate every woman in confidential space for counseling has changed facilities and patient flow. Where feasible, sites have constructed new buildings; when resources and property restrictions do not allow for a new building, sites have used other innovative strategies:

In Kenya, sites have used partitions creatively within the existing facility and have brought in trucking containers modified with windows and air conditioning to serve as counseling rooms.

In Zambia, counselors set up tents to provide space when PMTCT service initiation could not wait for new construction.

In Uganda, the Ministry of Health (MOH) abandoned traditional ANC days and provided services to women five days a week to alleviate crowding on any given day.
HIV counseling

The initial presentation of PMTCT concepts to pregnant women is critically important in the uptake of services. Initially, many sites provided counseling and testing in an opt-in fashion, meaning clients elected to be counseled and tested for HIV. Discussion and testing for HIV were treated as a special service that mothers needed to actively accept. Many programs are now shifting to provide HIV counseling as a routine service. Women have the right to actively refuse or “opt out” of testing. The EGPAF/Cameroon Baptist Convention Health Board program has provided opt-out counseling and testing for 5 years. Through 2005, 100% (111,322) of eligible women have been counseled, and 91.6% of those counseled have accepted testing in more than 200 facilities.

Pretest HIV counseling may be offered individually or to groups, with group counseling reducing the number of staff needed. A Burkina Faso study comparing group and individual HIV counseling found that pregnant women receiving group counseling had higher posttest knowledge about HIV/AIDS in all but 1 topic area. In early 2005, the Malawi EGPAF/University of North Carolina PMTCT program shifted from an opt-in to an opt-out approach to HIV counseling and testing and initiated group pretest counseling. In 1 year the program increased counseling from 75-100%, whereas testing remained at 98% of those counseled. With a seroprevalence of 15% in a population of 20,100 pregnant women using ANC services, an estimated 96% of HIV-positive women were provided nevirapine.

The national PMTCT program in Kenya also experienced a dramatic increase in uptake of HIV testing when MOH policy shifted from opt in to opt out. Uptake of testing in the first 3 months of the new policy significantly improved, but testing rates declined with stock-outs of HIV test kits. Because policy and procurement were not coordinated, the dramatic increase in testing uptake rapidly depleted the supply of kits, undermining the uptake improvements within the first 6 months of the policy change (Figure 2) (D. Mbori-Ngacha, CDC/MOH, personal communication, 2006).

HIV testing

HIV tests are administered in accordance with national policy and there is considerable variability in approach among countries. Most sites use rapid HIV testing by using a serial algorithm and deliver results to women on the same day that testing takes place. In the district of Hlabisa, South Africa, 14 rural MCH clinics seeing 7000 women over 21 months were able to give results to only 66% because blood was sent for enzyme-linked immunosorbent assay testing and same day results were not available. When rapid testing became available, 93% of women obtained their results over the ensuing 24 months. Programs should consider counseling and testing in labor and delivery to provide PMTCT services for women without ANC care or with unknown serostatus. A study in Kenya showed that a high percentage (79%) of women delivering in the maternity of a large tertiary facility had no prior ANC visits or attended ANC in facilities in which PMTCT services were not offered.

The Rwanda EGPAF PMTCT sites have achieved high coverage of the intervention, including counseling and testing in ANC and in maternity settings. By including PMTCT services in maternity hospitals, the program identified 1983 (27.7%) of a program total of 7150 HIV-positive pregnant women through December 2005; these women would not have been counseled and tested if the intervention was limited to the ANC setting. Likewise, 15% of 40,204 women in Kenya, 28% of 10,645 women in Swaziland, and 11% of 94,633 women in Tanzania accessed services in maternity. Counseling and testing should become a routine service at each contact point in MCH clinics, including ANC, maternity, well-child, family planning, and postnatal clinics. The personnel are often the same as in ANC and trained in the provision of these services.

Provision of ARV prophylaxis to HIV-positive mothers and HIV-exposed infants

The choice of prophylactic regimen is determined by the MOH within each country. Generally, countries have opted for the most feasible effective regimen that can be administered on a large scale. To date, that often means single-dose nevirapine (SD-NVP). SD-NVP dispensing practices have been modified over time to maximize the number of HIV-infected women who receive ARV prophylaxis.
In most locations, HIV-infected women are encouraged to deliver in a maternity setting where they may be observed ingesting the NVP tablet. Initially, NVP was dispensed only in maternity when women arrived for delivery. However, sites in Uganda, Zimbabwe, and elsewhere recognized that women might not deliver in facilities or might arrive too late to receive the NVP tablet because delivery is imminent or they deliver before reaching the facility. As a result, policies evolved toward dispensing NVP for the mother to take home during ANC at a fixed point in gestation, such as 28 weeks. However, women do not always return to ANC to receive NVP late in gestation. In Kericho, a tea estate region in Western Kenya, 72.5% of 1600 HIV-positive women received their dose of NVP after 28 weeks’ gestation. This improved to 94.4% of 1100 HIV-positive women when the policy was changed to providing the NVP dose when women tested HIV positive. Similarly, in Cameroon 40.8% of 7171 HIV-positive women received NVP in delivery but subsequent to a policy change, 87.4% of 1735 women received NVP at the time of testing HIV positive. Thus, many sites now give SD-NVP to the mother during the antenatal visit at time of diagnosis, advising her to take it at the onset of active labor.

Sites have acknowledged the difficulty of delivering the infant dose when a high proportion of mothers deliver at home and it is often impossible to bring their infants for NVP dosing within 1 week of birth. Transportation and cultural barriers are particular impediments. Note in Figure 1 that only 43.6% of HIV-exposed infants received ARV prophylaxis. An increasing number of sites have started to dispense NVP doses for both infant and mother simultaneously, with instructions to the mother about dosing her infant. The infant dose is not yet available in single-dose packaging so it is dispensed in an oral syringe. Stability of NVP has been demonstrated for 2 months in the donated Baxa syringe. Stability of NVP has been demonstrated for 2 months in the donated Baxa syringe.16

In Kericho, Kenya (Figure 3), the PMTCT program has started to provide infant prophylaxis in ANC at the time of the mother’s HIV test. The NVP-filled, capped syringes are wrapped in foil and placed in a black plastic bag for mothers to take home with their NVP tablet; mothers are instructed to give the syrup to their infant within 3 days of birth. The program began with 2 sites toward the end of 2003 and with more sites dispensing NVP-filled syringes by the end of 2004. By mid-2005, the majority of 52 sites were providing NVP-filled syringes. From April to December 2005, 76.5% of the infants of identified HIV-positive mothers received ARV prophylaxis. In July 2005, Kericho District rapidly increased the number of new sites providing PMTCT services. These new sites received conflicting information regarding when to dispense NVP and some of the health care workers were not confident enough to dispense the infant NVP for the mothers to take home. During this quarter, the percentage of infants receiving NVP decreased to 54.6%, but as procedures were clarified, the infant NVP uptake increased to 82.0% the following quarter. The NVP doses provided in ANC are not directly observed being swallowed and there is no guarantee that all will take their medication. However, women and infants must have access to the medication in order to take it.

**AZT and combined regimens**

As many countries scale-up ART programs, additional infrastructure and staffing are being put into place. Providing HAART to treatment-eligible persons has enhanced the possibility of providing more complex and effective prophylactic regimens. Countries in sub-Saharan Africa have reviewed and revised policies for PMTCT and started to selectively pilot administration of AZT/NVP prophylactic regimens and screen and provide HAART for eligible women. However, the experience of delivering complex regimens in these settings remains limited. Research is needed to determine how best to operationalize delivery of complex prophylactic regimens.17,18 Some concerns expressed by sites that must be addressed include the need for training, appropriate staffing, feasible prescribing policy and reliable logistics systems. In 2006, WHO revised its recommendations for ARVs for PMTCT in resource-limited settings. (See WHO’s revised guidelines for regimen recommendations.)

---

**FIGURE 3**  
Kericho, Kenya

Infant feeding practices
Addressing infant feeding options for mothers is as important as ARV prophylaxis because one-third to one-half of all MTCT occurs postnatally through breastfeeding. WHO recommends avoiding all breastfeeding from birth only if replacement feeding is “AFASS” (acceptable, feasible, affordable, sustainable, and safe) and has recently released a consensus statement supporting breastfeeding where AFASS conditions are not met. Many national guidelines continue to recommend exclusive breastfeeding because the majority of women in their countries do not meet AFASS requirements. A recommendation for early weaning at 6 months is also dependent on the AFASS criteria, requiring availability of supplementary foods and mother’s appropriate knowledge of nutritional needs for the infant. Understanding and assessing the AFASS conditions for individual mothers has proven to be very challenging for many health care workers. An infant feeding algorithm to help health providers counsel individual women has been developed.

All feeding choices for HIV-infected mothers carry some risk. Although breastfeeding exposes infants to HIV, replacement feeding carries the risks of increased morbidity and mortality. In a Botswana study that included free formula for participants, there was increased mortality in the first 7 months of life for nonbreastfed infants, and HIV-free survival was the same at 18 months of age. The provision of formula reduced HIV infections but added risk for other morbidity and mortality in infants who were not HIV infected.

Longitudinal care
Introducing the concept and practice of longitudinal care to both health care providers and clients is critical to bridging the gap between PMTCT services and continued follow-up and appropriate HIV care and treatment. Integrated family services would involve coordination of ANC and long-term care of the mother, infant, and additional family members.

Follow-up of HIV-exposed children is best performed in the MCH setting, where they normally return for immunizations and well-child care. Knowing which infants have been HIV exposed (born to HIV positive women) is essential to providing optimal care so that cotrimoxazole can be administered as recommended, the infant’s infection status can be assessed, and ART can be provided when available. A system for sharing this knowledge is not often a part of well-child care. However, some countries, including Zimbabwe and Tanzania, are including the mother’s serostatus routinely on the infant health card. Capacity of the staff in MCH clinics in facilities providing ARV should be developed so that HIV care can be provided in MCH during pregnancy, the early postnatal period, and for infants.

Involving men
There has been little or no male involvement at most sites. This is related to deep-seated sex imbalances, as well as institutional factors within health system delivery. Some women believe they need partner consent before agreeing to HIV testing, and perceptions about the husband’s approval have been shown in a rural Ugandan context to be a strong predictor of their willingness to be tested.

Some sites have introduced “male-friendly” interventions with varying success. Efforts include:

- Allowing pregnant mothers to go to the front of the line in ANC if they bring their male partners.
- Offering testing to men at evening or weekend clinics, when they are most likely to be available.
- Sending an invitation home with the partner with a direct request that the man attend ANC with his partner.
- Coordinating with local companies to provide paid leave for male partners who accompany their wives to the antenatal clinic.
- Providing couples testing and counseling.

Community involvement
Local leadership is required to ensure PMTCT services are acceptable to the community. Lessons learned from the first 18 months of a rural PMTCT program in Zimbabwe suggest the importance of community education to raise awareness of HIV in general, as well as of specific PMTCT services, and to lessen the stigma surrounding HIV. The community activities were designed to pre-
pare mothers for HIV counseling and testing in ANC and include informational meetings and the development of materials for multiple community targets, such as pregnant women, community leaders, and men and women of childbearing age.26

CONCLUSION

PMTCT was initially viewed as an independent service unrelated to continued care for mothers, their infants and other children, and their partners. With the global rollout of HIV services, PMTCT services need to become an integral part of the continuum of care. The pregnant women who are diagnosed as HIV infected can serve as an entry point for families, promoting early diagnosis, particularly of women and young infants who have not yet become ill, and linking them into long-term care. PMTCT is the single most effective program available to prevent HIV transmission, and preventing new infections is essential if the course of the epidemic is to be altered. The outcomes of the interventions discussed are very encouraging and need continued attention and improvement. The Table outlines key future directions and recommendations for PMTCT programming. Expanding access to interventions that effectively prevent MTCT is an urgent priority and one that must be maintained and strengthened in parallel with increasing availability of ARV treatment.

ACKNOWLEDGMENT

We would like to acknowledge the tireless efforts of the PMTCT partners in all 22 countries whose work made this article possible. Ellen Piwoz of AED provided substantial technical input to the infant feeding section. We thank the following reviewers and their helpful comments: Chuck Hoblitelle of EGPAF, Peter Savosnick of EGPAF, Heather Bergmann of EGPAF, Lucy Alcalá of EGPAF, Charlotte Colvin of EGPAF, Nathan Shaffer of CDC, Rabia Mathai of CMMB, and Chewu Luo of UNICEF. EGPAF’s PMTCT program appreciates the generous financial support of the US Agency for International Development, Johnson & Johnson, and Ronald McDonald House Charities.

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Prevention of human immunodeficiency virus-1 transmission to the infant through breastfeeding: new developments

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Currently about 800,000 children become infected with human immunodeficiency virus type 1 (HIV) every year through mother-to-child transmission (MTCT); 90% of these children live in resource-limited countries. Breastfeeding transmission accounts for about one third to one half of all HIV transmission from mothers to their infants in resource-limited settings in which breastfeeding into the second year of life is the norm.2-5

A number of studies have documented the risk of transmission per month of breastfeeding and cumulative risk after the first 1-2 months of age. Some studies suggested that the highest risk of breastfeeding transmission of HIV is in the immediate neonatal period.7,8 A more recent metaanalysis suggested a more constant risk of about 0.9% per month after the first month of life.9 There is limited information on risk of transmission during the early weeks of life, due in part to the difficulty in differentiating early breast milk transmission from intrapartum transmission. Two studies have been able to estimate postpartum transmission based on differences in transmission between mothers who breast fed and those who used formula from birth.10,11 Both studies demonstrated a very high risk of transmission for the breastfed, compared with the formula-fed infant in the early weeks of life: 6.3% difference in the risk of transmission in the randomized trial in Nairobi from birth to 6 weeks (or about 1% per week) and about 5.6% difference in the South African study over an 8-week period (or about 0.7% per week).10,11 In contrast, in the Mashi trial, in which infant prophylactic zidovudine was used during breastfeeding, no difference in the risk of HIV transmission to the infant at 1 month was detected in the formula-fed (5.0%) and breastfed infants (4.6%).12

Risk factors for postnatal transmission include higher deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) viral load in milk and plasma8,13,14; decreased maternal CD4 cell count; increased maternal illness severity, mastitis and breast milk stasis15-17; thrush and other infant coinfections; type of infant feeding (exclusive breastfeeding [EBF] versus mixed feeding [MF])18,19; longer duration of breastfeeding9; and maternal seroconversion or HIV-1 superinfection during lactation.20,21

Breastfeeding accounts for up to half of all infant human immunodeficiency virus (HIV) infections worldwide and carries an estimated transmission risk of about 15% when continued into the second year of life. Because replacement feeding is not safely available, culturally acceptable, or affordable in many parts of the world and because breastfeeding provides protection against other causes of infant mortality, approaches that reduce breastfeeding mother-to-child transmission of HIV are being explored. These include exclusive breastfeeding for the infant’s first few months of life followed by rapid weaning, treatments of expressed milk to inactivate the virus, and antiretroviral prophylaxis taken by the infant or mother during breastfeeding, which are strategies currently being tested in clinical trials. Passive (antibodies) and active (vaccine) immunoprophylaxis will also soon begin to be tested. This paper focuses on current and planned research on strategies to prevent breastfeeding transmission of HIV.

Key words: breast milk, human immunodeficiency virus, infant, prevention, transmission

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Received December 15, 2006; revised February 12, 2007; accepted March 1, 2007.
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The views expressed herein are those of the authors and do not necessarily reflect those of the Centers for Disease Control and Prevention or the World Health Organization.

0002-9378/32.00 © 2007 Mosby, Inc. All rights reserved. doi: 10.1016/j.ajog.2007.03.003

Biology of breastfeeding transmission of HIV to the infant

Virology. HIV is detected in both the liquid phase of breast milk and in breast milk cells.15,22 Free virus can be derived from blood, or it can be produced by local replication in macrophages and in ductal and alveolar mammary epithelial cells.23 Evidence of HIV compartmentalization between blood and breast milk has been conflicting.24,25 HIV is detected in the breast milk of HIV-infected moth-
ers at varying frequencies across studies (39–89%);26,27 intermittent shedding and differences in viral load between the 2 breasts have been noted by several investigators.26,27 The concentration of HIV in cell-free breast milk is generally lower than that in plasma by 1–2 logs.7 Studies have shown that breast milk viral load is highest immediately after birth and that both clinical and subclinical mastitis are associated with increased viral loads in breast milk.16,26–28

Recently a 3-fold increase in transmission was demonstrated for every 10-fold increase in cell-free or cell-associated viral load in breast milk,28,29; however, no lower threshold for transmission could be determined. Cell-associated virus was found to be a stronger predictor for HIV transmission to the infant than cell-free virus.29,30 Recent evidence also indicates that highly active antiretroviral therapy (HAART), started during pregnancy or postpartum, suppresses HIV RNA,30,31 but not DNA, in breast milk.30 In fact, part of the efficacy of the peripartum single-dose nevirapine (sdNVP) regimen may be attributable to its effects in lowering breast milk viral loads early during lactation.32

Emerging data on the pharmacokinetics of antiretroviral agents in breastfeeding mothers indicate that nevirapine (NVP), zidovudine (ZDV), and lamivudine (3TC) achieve HIV inhibitory concentrations in the breast milk (similar or higher than those of serum) and that NVP in addition achieves inhibitory concentrations in the serum of breastfed infants.33 These data suggest that a maternal regimen may be sufficient to provide prophylaxis from breastfeeding transmission to the infant but also that adverse effects of antiretroviral (ARV) therapy (toxicities, development of resistance) could theoretically be seen among breastfed infants exposed to them.

**Immunology.** Breast milk contains a multitude of antimicrobial and immunomodulatory factors, including lactoferrin, lysozyme, fibronectin, mucin, lipids, epidermal growth factor, interleukin (IL)-1β, IL-6, IL-8, and IL-10, transforming growth factor (TGF)-β, secretory leukocyte protease inhibitor (SLPI), defensins, adhesion molecules, selectins, and chemokines.34–38 These soluble factors have diverse effects on HIV; some have in vitro anti-HIV activity (SLPI, lactoferrin, regulated upon activation, normal T cell expressed, and secreted, interferon-γ, α- and β-defensins) and others have proinflammatory activity that might promote local HIV replication (IL-6, IL-8, IL-1β, tumor necrosis factor-α). HIV-specific antibodies have been detected in the breast milk of HIV-infected mothers, predominately of the immunoglobulin (Ig) G isotype.39 Often the specificity of IgG and IgA HIV antibodies in the breast milk differs from that of antibodies in the serum of the same person.40

Breast milk also contains a large number of lymphocytes, macrophages, and other mononuclear cells (ranging from 105 to 107/mL in colostrum and declining up to 10-fold during the subsequent 2–3 months of lactation). The breast milk lymphocytes have an activated phenotype40–42 and express chemokine receptors and mucosal homing markers such as CD103 in high frequency. They thus seem to bear a mucosal phenotype and are thought to migrate to the breast from distant mucosal sites such as the gastrointestinal or genital tract. The macrophages in the breast milk are distinct in their phenotypic characteristics.43 IL-4–stimulated breast milk macrophages express DC-SIGN, a dendritic cell receptor for HIV. Recent findings indicate that HIV virions captured by dendritic cell-specific ICAM-3 grabbing nonintegrin (DC-SIGN) may be transmitted more efficiently through the gastrointestinal tract,44 suggesting a role in transmission to the infant.

**Role of mucosal factors.** Two nonrandomized studies from southern Africa have suggested that type of infant feeding has a substantial effect on the risk of postnatal HIV transmission from mothers to their infants. Both studies presented observational data suggesting that exclusive breastfeeding is associated with a lower risk of transmission than mixed feeding (breastfeeding and other liquids or solids) among HIV-infected mothers. First, Coutsoudis et al17 in South Africa found that at 6 months of age, there was a substantially lower risk of transmission among infants who had been exclusively breastfed during the first 3 months, compared with infants who had received mixed feeding. Recent data from the Zvitanumbo trial in Zimbabwe found that exclusive breastfeeding in the first 3 months of life was associated with only a 1.3% risk of transmission from 6 weeks to 6 months, which is significantly lower than the transmission risk of 4.4% associated with mixed feeding.45

Possible explanations for this finding include damage to the intestinal mucosa from early introduction of other foods, leading to the delayed closure of the enterocyte junctions in the intestinal mucosal barrier or intestinal immune activation from early introduction of foreign antigens or pathogens, both mechanisms that can enhance transmission of HIV to the infant.46 Similar to the structure of intestinal epithelia, tight junctions form barriers between adjacent epithelial and endothelial cells in the mammary gland that restrict passage of serum components into milk.47 Mammary epithelial permeability is increased during the immediate postpartum period and during weaning48 as well as during periods of inflammation such as mastitis, when pericellular sodium and albumin can move into breast milk, resulting in elevated levels of these compounds in breast milk.47,48 Infrequent breast emptying, such as might occur with nonexclusive breastfeeding, may increase the risk of ductal inflammation and mammary permeability and may also lead to subclinical mastitis and a higher risk of HIV transmission to the infant.

**General feeding recommendations in resource-limited settings**

Prevention of HIV transmission through breastfeeding should be considered against a backdrop of promoting appropriate feeding for all infants and young children. According to current World Health Organization recommendations, infants should be exclusively breastfed for the first 6 months of life to achieve optimal growth, development, and health. Thereafter infants should receive nutritionally adequate and safe comple-
mentary foods while breastfeeding continues up to 24 months or beyond.49 However, given the need to reduce the risk of HIV transmission to infants and minimizing the risk of other causes of morbidity and mortality, the guidelines also state that “when replacement feeding is acceptable, feasible, affordable, sustainable, and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended. Otherwise, exclusive breastfeeding is recommended during the first months of life” and should then be discontinued as soon as it is feasible. This would normally imply the same conditions as for replacement feeding from birth, that is, acceptable, feasible, affordable, sustainable, and safe.49 For most HIV-infected mothers in resource-limited settings, breastfeeding remains the only feasible and sustainable option, given a societal context of unsafe water and unsanitary or nutritionally deficient home-modified animal milk substitutes, cultural norms for mothers to breastfeed with the risk of stigmatization if not breastfeeding, and prohibitive costs of breast milk substitutes.

For an individual HIV-infected mother, balancing risks and benefits is complex. Mothers should receive counseling that includes information about both the risks and benefits of various infant feeding options based on local assessment and guidance in selecting the most suitable option for their situation. The above recommendations on infant feeding and HIV are the same, whether or not the women receive ARV regimens for their own health. Women receiving ARV drugs for their own health who are breastfeeding should continue their ARV regimen. Currently World Health Organization–recommended ARV prophylactic regimens for women who do not need HAART for their own health are based on a short antepartum, intrapartum, postpartum, and postnatal component. The short postpartum and postnatal components are mainly designed to reduce the risk of developing maternal resistance to sdNVP and as a postexposure prophylaxis regimen for the child.

**Approaches to decrease mother-to-child HIV transmission during breastfeeding**

Exclusive replacement (formula) feeding is the most widely used and effective method to prevent MTCT of HIV-1 through breastfeeding in resource-rich settings and is recommended in situations in which this is acceptable, feasible, affordable, sustainable, and safe. In the United States, obstetricians/gynecologists counsel their HIV-infected patients not to breastfeed and to use formula feeding instead. However, in many resource-constrained settings, the above conditions are rarely all met. Based on findings from the studies mentioned above, exclusive breastfeeding for a few (3-6) months with rapid weaning has been advocated as a strategy that balances optimal nutritional source for the infant’s first few months of life with lessening the risk of MTCT of HIV. This approach is currently being evaluated in a number of clinical trials.

Recently concerns have arisen that early weaning of HIV-exposed infants may increase infant morbidity and mortality. For example, two studies from Malawi and Kenya have noted spikes in growth faltering of infants following weaning at around 6 months of age, and the Kenya study has also noted increased rates of failure to thrive and growth faltering of infants following weaning. Results from the MASHI study demonstrated a near doubling of infant mortality at 7 months in infants who were formula fed from birth when compared with those who were breastfed and received ZDV prophylaxis for 6 months; at 12 months, overall HIV-free survival was comparable between the 2 infant-feeding strategies. If these findings concerning the deleterious effects of early weaning are further substantiated, alternative strategies including the need for an effective perinatal vaccine or other strategies that would allow breastfeeding safely throughout the first year of life will be emphasized.

Subclinical mastitis is associated with higher breast milk HIV viral copy number and MTCT of HIV. This condition has been shown to be common among HIV-infected, breastfeeding women in Malawi, Zambia, and Zimbabwe. It has been hypothesized that mastitis might contribute to transmission in such populations and that empiric treatment for the condition might play a role in the prevention of MTCT. A recent study in Zimbabwe, however, demonstrated that empiric treatment of HIV-infected, breastfeeding women with amoxicillin/clavulanate did reduce breast milk leukocyte counts but was accompanied by only a small reduction in breast milk viral load at 4-12 weeks.

Health care providers should counsel breastfeeding. HIV-infected women about the proper breastfeeding technique, treat clinical mastitis with antibiotics, and expressing and discarding breast milk from the affected breast while also continuing feeding from the unaffected breast, and treating infant oral thrush or nipple candidiasis with nystatin. The efficacy of these methods in reducing MTCT, however, has not been formally assessed.

Poor maternal nutritional status has been shown in observational studies to be associated with the increased risk of HIV disease progression and MTCT of HIV. Low maternal serum vitamin A levels have been associated with increased breast milk viral load and MTCT of HIV. However, clinical trials of prenatal vitamin A supplementation have shown no effect on MTCT of HIV with at least 1 study showing an increase in transmission. Similarly, a single large dose of vitamin A postpartum was shown to have no effect on HIV transmission and in fact may increase mortality in infants who remained HIV negative at 6 weeks. An ongoing study in Malawi (the Breastfeeding Antiretrovirals Nutrition [BAN] trial) is currently assessing the value of maternal calorie, protein, and micronutrient supplementation during breastfeeding in preventing maternal wasting and the postnatal transmission of HIV to the infant.

Inactivation of HIV in breast milk by either chemical means or heat has also been proposed as a means of preventing...
breastfeeding MTCT of HIV. A preclinical study of treating breast milk with sodium dodecyl sulphate has shown some promise.\(^{63}\) Boiling or pasteurization of breast milk appears to decrease HIV infectivity of milk.\(^{64,65}\) Pretoria pasteurization, in which breast milk in a glass jar is placed in boiling water for 12-15 minutes, is a simple method for maintaining breast milk at 56-62.5°C by heat transfer.\(^{66}\) This method, which can be done in the home has been shown to reduce bacterial contamination of unrefrigerated breast milk for up to 12 hours.\(^{67}\)

There is also some evidence that Pretoria pasteurization can inactivate HIV in breast milk.\(^{66,68}\) In a small study in Cote d’Ivoire,\(^{69}\) 76% of women felt breast milk pasteurization would be an acceptable way to reduce transmission of an infectious disease to the infant if a convenient method could be found for pasteurization. The effects of such pasteurization on MTCT and on other biological components of breast milk and the feasibility of the method’s widespread uptake in real-world settings is unknown but faces obvious obstacles, given cultural norms and logistical barriers.

The antimalarial agent chloroquine and its hydroxyl analogue have in vitro activity against HIV-1 replication and against several acquired immunodeficiency syndrome (AIDS)-related opportunistic microorganisms.\(^{70,71}\) Chloroquine also tends to concentrate in breast milk, with the highest concentration appearing in breast milk cells.\(^{72}\) Given that this drug is inexpensive, widely available, and has a low toxicity profile in prophylactic doses, it might have potential as a means of reducing HIV transmission to the breastfeeding infant. However, preliminary work has not shown a significant effect of chloroquine on breast milk virus loads\(^{73}\) in the dosage used.

**Current clinical trials**

Several peripartum strategies including short-course ZDV,\(^{74,76}\) short-course ZDV/3TC,\(^{77}\) or the use of sdNVP\(^{78,79}\) given to mothers at labor and to their newborns have demonstrated a substantial reduction in the risk of perinatal HIV transmission. The use of combination short-course antiretroviral drugs appears to have a synergistic effect in lowering the risk of transmission. Studies from Thailand and France, respectively, demonstrated that the combined use of either short-course ZDV from 28 weeks of gestation plus sdNVP\(^{80}\) or ZDV plus 3TC from 32 weeks\(^{81}\) can reduce transmission to about 2% among non-breastfeeding women, which is similar to rates achieved in the United States and Europe with the use of HAART. In breastfeeding settings, however, the risk of transmission remained substantially higher.\(^{10,45,75,77,79}\)

Reducing the risk of HIV transmission during lactation in a safe manner for HIV-infected women in resource-limited settings who opt to breastfeed remains 1 of the major challenges facing perinatal HIV researchers, policy makers, and HIV-infected mothers in resource-limited settings.

Several current or planned randomized trials are designed to test strategies aimed at reducing the risk of transmission during the breastfeeding period. These include using antiretroviral drugs given to either the mother or infant during lactation; using passive and/or active immune strategies given to mothers and/or their infants; or assessing various infant feeding and weaning methods. The trials are summarized in the Table and will be presented here.

**Antiretroviral intervention studies**

Several clinical trials investigating the role of antiretroviral drugs during breastfeeding to mothers or infants to reduce MTCT of HIV are ongoing. The Breastfeeding Antiretrovirals Nutrition (BAN) study is a randomized, phase III, 2 × 3 factorial clinical trial of 2400 mother-infant pairs evaluating the effect of a maternal nutritional supplement and antiretroviral prophylaxis during 6 months of exclusive breastfeeding followed by rapid weaning. All mothers and infants receive the perinatal sdNVP regimen plus a week of postpartum/postnatal ZDV/3TC. The antiretroviral regimens tested include a combination maternal regimen (ZDV/3TC/lopinavir/ritonavir) or daily infant NVP during breastfeeding vs standard of care. Only mothers with a CD4+ T cell count greater than 200/mm\(^3\) are enrolled. Outcomes include infant HIV infection at 6 and 12 months, maternal weight loss during breastfeeding, infant survival at 12 months, and the feasibility of exclusive breastfeeding for 6 months followed by rapid weaning.

Second, the Kisumu Breastfeeding Study (KiBS) in Kisumu, Kenya, is a phase II single-arm, open-label clinical trial using ZDV, 3TC, and nelfinavir or NVP (depending on CD4+ count) beginning at 34 weeks of gestation and continuing until 6 months postpartum. In addition to safety, end points include cumulative infant HIV infection risk at 6 weeks, 9 months, and 18 months and infant HIV-free survival at 24 months. Target sample size is 520 mother-infant pairs.

Third, the Kesho-Bora study (Swahili for a better future) is a phase III, randomized, open-label clinical trial comparing ZDV, 3TC, and lopinavir/ritonavir beginning at 28 weeks of gestation through 6 months of breastfeeding to short-course ZDV (also beginning at 28 weeks) and sdNVP at labor among HIV-infected women with CD4 counts between 200 and 500 cells/mm\(^3\) at enrollment. The infant receives sdNVP and a week of ZDV. This multinational clinical trial is taking place in Burkina Faso, Kenya, and may also include a site in South Africa. End points include HIV-free infant survival at 6 weeks and 12 months, maternal AIDS-free survival, and incidence of serious adverse events in both mother and infant. The target sample size is 1000 mother-infant pairs.

Fourth, the Post-Exposure Prophylaxis for Infants (PEPI-Malawi) trial in Blantyre, Malawi, is a phase III, randomized clinical trial comparing 3 different regimens of antiretroviral drugs given to infants of HIV-infected breastfeeding mothers. The control arm receives sdNVP and 1 week of ZDV. The 2 intervention arms both receive the control regimen but then receive NVP alone or...
### TABLE
Summary of ongoing or planned trials for prevention of mother-to-child transmission of HIV through breastfeeding

<table>
<thead>
<tr>
<th>Trial (location, status)</th>
<th>Study arm</th>
<th>Antepartum (AP)</th>
<th>Intrapartum</th>
<th>Postpartum (mother)</th>
<th>Postnatal (infant)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BAN (Malawi, ongoing) phase III</strong></td>
<td>Arm 1a</td>
<td>No drug</td>
<td>sdNVP</td>
<td>Nutritional supplement $\times 6$ mo</td>
<td>EBF $\times 6$ mo with rapid weaning sdNVP plus ZDV/3TC $\times 1$ wk</td>
</tr>
<tr>
<td></td>
<td>Arm 2a</td>
<td>No drug</td>
<td>sdNVP</td>
<td>Nutritional supplement $\times 6$ mo ZDV/3TC $\times 1$ wk</td>
<td>EBF $\times 6$ mo with rapid weaning sdNVP plus ZDV/3TC $\times 1$ wk plus NVP daily $\times 6$ mo</td>
</tr>
<tr>
<td></td>
<td>Arm 3a</td>
<td>No drug</td>
<td>sdNVP</td>
<td>Nutritional supplement $\times 6$ mo ZDV/3TC $\times 1$ wk</td>
<td>EBF $\times 6$ mo with rapid weaning sdNVP plus ZDV/3TC $\times 1$ wk</td>
</tr>
<tr>
<td></td>
<td>Arm 1b</td>
<td>No drug</td>
<td>sdNVP</td>
<td>ZDV/3TC $\times 1$ wk, then ZDV/3TC/LPV/rv $\times 6$ mo</td>
<td>EBF $\times 6$ mo with rapid weaning sdNVP plus ZDV/3TC $\times 1$ wk</td>
</tr>
<tr>
<td></td>
<td>Arm 2b</td>
<td>No drug</td>
<td>sdNVP</td>
<td>ZDV/3TC $\times 1$ wk</td>
<td>EBF $\times 6$ mo with rapid weaning sdNVP plus ZDV/3TC $\times 1$ wk</td>
</tr>
<tr>
<td></td>
<td>Arm 3b</td>
<td>No drug</td>
<td>sdNVP</td>
<td>ZDV/3TC $\times 1$ wk</td>
<td>EBF $\times 6$ mo with rapid weaning sdNVP plus ZDV/3TC $\times 1$ wk</td>
</tr>
<tr>
<td><strong>KiBS (Kenya, ongoing) phase II</strong></td>
<td>Arm 1</td>
<td>ZDV/3TC/NVP (or NFV*) from 34 wks</td>
<td>ZDV/3TC/NVP (or NFV*) $\times 6$ mo</td>
<td>sdNVP</td>
<td>Exclusive breastfeeding $\times 6$ mo</td>
</tr>
<tr>
<td><strong>Kesho Bora (Burkina Faso, Kenya, ongoing) phase III</strong></td>
<td>Arm 1</td>
<td>ZDV/3TC/LPV/rv from 28 wks</td>
<td>ZDV/3TC/LPV/rv $\times 6$ -mo as long as breastfeeding continues</td>
<td>sdNVP plus ZDV $\times$ 1 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2 (control)</td>
<td>ZDV from 28 wks</td>
<td>sdNVP</td>
<td>ZDV/3TC $\times 7$ d</td>
<td>sdNVP</td>
</tr>
<tr>
<td><strong>PEPI (Malawi, ongoing) phase III</strong></td>
<td>Arm 1</td>
<td>Background maternal ARV for treatment allowed</td>
<td>sdNVP</td>
<td>No drug</td>
<td>NVP plus ZDV $\times$ 1 wk, then NVP $\times$ 14 wk EBF with abrupt weaning at 6 mo</td>
</tr>
<tr>
<td></td>
<td>Arm 2</td>
<td>Background maternal ARV for treatment allowed</td>
<td>sdNVP</td>
<td>No drug</td>
<td>NVP plus ZDV $\times$ 14 wk EBF with abrupt weaning at 6 mo</td>
</tr>
<tr>
<td></td>
<td>Arm 3 (control)</td>
<td>Background maternal ARV for treatment allowed</td>
<td>sdNVP</td>
<td>No drug</td>
<td>sdNVP plus ZDV $\times$ 1 wk EBF with abrupt weaning at 6 mo</td>
</tr>
<tr>
<td><strong>HPTN 046 (South Africa, Tanzania, Uganda, Zimbabwe, ongoing) phase III</strong></td>
<td>Arm 1</td>
<td>ZDV or maternal ARV for own treatment$^{**}$</td>
<td>Same as AP and/or sdNVP</td>
<td>As needed for maternal treatment</td>
<td>NVP $\times$ 6 mo or for the duration of breastfeeding</td>
</tr>
<tr>
<td></td>
<td>Arm 2 (control)</td>
<td>ZDV or maternal ARV for own treatment$^{†}$</td>
<td>Same as AP and/or sdNVP</td>
<td>As needed for maternal treatment</td>
<td>sdNVP</td>
</tr>
</tbody>
</table>

Continued on page S118.
NVP/ZDV for 14 weeks thereafter. End points include infant HIV infection rates (at various points up to 24 months), HIV-free survival rates (at 6, 12, 18, and 24 months), safety, and tolerability. The target sample size is 3500 mother-infant pairs.

Fifth HIV Prevention Trials Network (HPTN) 046 is a multisite, phase III, blinded, randomized clinical trial in Uganda, Zimbabwe, Tanzania, and South Africa with a planned enrollment of 1576 mother-infant pairs. This trial will provide either daily NVP prophylaxis or placebo to infants during breastfeeding through their first 6 months of life. Mothers and newborns will receive the background standard prevention regimen used at each site, such as sdNVP or short-course ZDV, and some mothers will be receiving HAART for their own treatment.

### TABLE

**Summary of ongoing or planned trials for prevention of mother-to-child transmission of HIV through breastfeeding**

<table>
<thead>
<tr>
<th>Trial (location, status)</th>
<th>Study arm</th>
<th>Antepartum (AP)</th>
<th>Intrapartum</th>
<th>Postpartum (mother)</th>
<th>Postnatal (infant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEBS (Zambia, ongoing)</td>
<td>Arm 1</td>
<td>No drug</td>
<td>sdNVP</td>
<td>No drug</td>
<td>sdNVP EBF with abrupt cessation at 4 mo</td>
</tr>
<tr>
<td></td>
<td>Arm 2 (control)</td>
<td>No drug</td>
<td>sdNVP</td>
<td>No drug</td>
<td>sdNVP EBF with gradual weaning after 6 mo</td>
</tr>
<tr>
<td>PROMISE-PEP (Burkina Faso, Uganda, Zambia, South Africa, planned) phase III</td>
<td>Arm 1</td>
<td>ZDV or maternal ARV for own treatment</td>
<td>Same as AP and sdNVP (or ZDV/3TC if first seen in labor)</td>
<td>ZDV/3TC × 7 d or maternal ARV for own treatment</td>
<td>sdNVP plus ZDV × 7 d plus 3TC up to month 9 EBF with weaning between 6 and 8 mo</td>
</tr>
<tr>
<td></td>
<td>Arm 2 (control)</td>
<td>ZDV or maternal ARV for own treatment</td>
<td>Same as AP and sdNVP (or ZDV/3TC if first seen in labor)</td>
<td>ZDV/3TC × 7 d or maternal ARV for own treatment</td>
<td>sdNVP plus ZDV × 7 d plus placebo from day 8 to month 9 EBF with weaning between 6 and 8 mo</td>
</tr>
<tr>
<td>HIVIGLOB (Uganda, ongoing) phase II/III</td>
<td>Arm 1</td>
<td>HIV hyperimmune globulin at 36-37 wk</td>
<td>sdNVP</td>
<td>No drug</td>
<td>NVP × 6 wk This arm will be pooled with data from Ethiopia and India trials</td>
</tr>
<tr>
<td></td>
<td>Arm 2</td>
<td>HIV hyperimmune globulin at 36-37 wk</td>
<td>sdNVP</td>
<td>No drug</td>
<td>sdNVP plus HIV hyperimmune globulin within 18 h of birth</td>
</tr>
<tr>
<td></td>
<td>Arm 3 (control)</td>
<td>HIV hyperimmune globulin at 36-37 wk</td>
<td>sdNVP</td>
<td>No drug</td>
<td>sdNVP This arm will be pooled with data from Ethiopia and India trials</td>
</tr>
<tr>
<td>Nevirapine for prevention of MTCT (Ethiopia, ongoing) phase III</td>
<td>Arm 1</td>
<td>No drug</td>
<td>sdNVP</td>
<td>No drug</td>
<td>Daily NVP plus MVit × 6 wk</td>
</tr>
<tr>
<td></td>
<td>Arm 2 (control)</td>
<td>No drug</td>
<td>sdNVP</td>
<td>No drug</td>
<td>sdNVP plus MVit × 6 wk</td>
</tr>
<tr>
<td>Prevention of MTCT in India (India, ongoing) phase III</td>
<td>Arm 1</td>
<td>ZDV from 36 wk</td>
<td>sdNVP</td>
<td>No drug</td>
<td>Daily NVP plus MVit × 6 wk</td>
</tr>
<tr>
<td></td>
<td>Arm 2 (control)</td>
<td>ZDV from 36 wk</td>
<td>sdNVP</td>
<td>No drug</td>
<td>sdNVP plus MVit × 6 wk</td>
</tr>
</tbody>
</table>

Continued on page S119.
Immune strategies to reduce the risk of transmission during breastfeeding

The first strategy, an ongoing trial in Uganda, which is a 3-arm phase II/III trial (HIV immune globulin [HIVIGLOB]), is assessing the possible protective effect of an HIV hyperimmune globulin product given as an infusion to mothers at 36-37 weeks of gestation and to the newborn; in another arm NVP is given daily to the newborn for 6 weeks. Safety and HIV transmission rates in both arms will be compared with those for sdNVP. Data from the HIVIGLOB 6-week infant NVP prophylaxis arm will be pooled with data from trials in Ethiopia and India, which are also looking at the relative efficacy of 6 weeks of infant NVP prophylaxis, compared with sdNVP. The sample size enrolled across the 3 sites is 2222 (Table).

Second, a planned phase I/II trial in South Africa will assess the use of monoclonal antibodies for the prevention of postpartum mother-to-child HIV transmission.82-84

Third, in Uganda, a phase 1 trial (HPTN 027) with a sample size of 50 evaluable infants is an ongoing trial looking at the safety of a perinatal HIV vaccine candidate using a canary pox vector (ALVAC-HIV vCP1521), which is given to infants as 4 injections during the first 3 months of life. If the data suggest this product to be safe and immunogenic, then a phase II/III trial would be the next step to evaluate whether the vaccine could allow mothers to breastfeed safely through the first year of life.

Other studies on exclusive breastfeeding

All of the current trials described above are in the background of recommendations for EBF followed by early weaning at around 3-6 months postpartum. The PROMISE for Exclusive Breastfeeding (EBF) research consortium is running a randomized trial of the safety and efficacy of EBF promotion by peer-counselors among both HIV-uninfected and infected mothers in Burkina-Faso, Uganda, Zambia, and South Africa. The plan is to add, in a factorial design, the assessment of 3TC given to the child during the breastfeeding period. All HIV-infected mothers will have received 1 month of ZDV and sdNVP. ZEBS, an ongoing study in Zambia, is addressing whether abrupt vs gradual weaning has a lower risk of transmission.85

The Future

There are still significant gaps in our understanding of how HIV is transmitted to the infant through breastfeeding, such as whether cell-free or cell-associated virus is the primary mode of transmission and characterizing the immunologic and other properties in breast milk, which help protect most breastfed infants from such transmission despite daily exposure. It is recommended that HIV-infected women should be advised not to breastfeed in parts of the world in which safe substitutes for breast milk exist, but the ideal strategy for the developing world is less clear.

Exclusive breastfeeding for 6 months, followed by rapid weaning, has been advocated as a measure to reduce breastfeeding transmission of HIV and is currently being evaluated in clinical trials. However, the balance of risk and benefit for the health, development and survival of the infant and the implementation of this strategy in many resource-limited settings needs to be carefully assessed.
given social and cultural practices as well as the economic and logistic challenges. Furthermore, if the current or planned trials demonstrate efficacy of maternal combination antiretroviral treatment or infant antiretroviral prophylaxis during breastfeeding, operational challenges of implementing these programs widely in resource-limited settings will need to be addressed. If antiretroviral drugs for both maternal therapy and prevention of MTCT become more widely available and are demonstrated to be safe, efficacious, and cost effective, extended breastfeeding with antiretroviral prophylaxis could indeed be considered for as long as the mother wishes to breastfeed.

Pharmacokinetic and safety information of newer antiretroviral agents for nursing mothers and their infants that have less potential for resistance (such as tenofovir) should be encouraged. Finally, passive and ideally active immunization, alone or in combination with peripartum antiretroviral regimens, might be a good future approach to protect breastfed infants from HIV transmission. Support for and completion of the above described research needs to receive high priority if we are to conquer this remaining challenge in prevention of mother-to-child HIV transmission and reduce the number of pediatric HIV infections worldwide.

REFERENCES


Young, seropositive, and pregnant: epidemiologic and psychosocial perspectives on pregnant adolescents with human immunodeficiency virus infection

Linda J. Koenig, PhD; Lorena Espinoza, DDS, MPH; Krystal Hodge, MPH, CHES; Nan Ruffo, BS

The number of young people in the United States with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) has been increasing. It is estimated that 1 of 1000, or 21,400 persons aged 18-24 years, in the United States have HIV infection. In 2005, based on data from 33 states with confidential name-based reporting to the Centers for Disease Control and Prevention, 1268 youth aged 13-19 years received a diagnosis of HIV infection; 5322 13- to 19-year-olds were living with HIV or AIDS. Although declining, the U.S. teen pregnancy rate is startlingly high; one third of young women in the United States (34%) become pregnant at least once before they reach the age of 20 years; 81% of these pregnancies are to unmarried teens. Although teen pregnancy is more prevalent than teen HIV infection, the 2 health outcomes share a number of behavioral and epidemiologic features, with similarities according to race/ethnicity, geographic region of residence, and risk behavior.

Adolescents of minority races and ethnicities are disproportionately affected by both HIV/AIDS and pregnancy. Population estimates reveal a 20-fold gap in the prevalence of HIV among non-Hispanic blacks, compared with youth of other racial and ethnic groups, and blacks account for more than half of all reported HIV infections among 18- to 24-year-olds. In the United States in 2005, 16% of the adolescent population was black, yet 69% of reported AIDS cases in 13- to 19-year-olds were in blacks. Girls of minority race or ethnicity are also disproportionately affected by teen pregnancy. Pregnancy and birth rates for black and Hispanic teens are 2-3 times higher than rates for white teens. Twenty-four percent of Hispanics and 20% of non-Hispanic blacks have a birth before the age of 20 years, compared with 8% for non-Hispanic whites.

The 2 epidemics also share geographical similarities. Perhaps not unrelated to issues of race and ethnicity, the highest concentration of teen births and a growing number of HIV infections are occurring in the southern region of the United States. In 2003 the rate of new AIDS diagnoses for adolescents and young adults was highest in the South (22 per 100,000 population), and case reports suggest that the rate of AIDS may be increasing for African-American adolescents and adults in this region.

Females are exclusively at risk for pregnancy and increasingly at risk for HIV/AIDS. Girls make up a larger proportion of both AIDS cases and new HIV infections among teens than they do...
among adults. As with pregnancy, heterosexual contact is the mode of transmission for most adolescents with HIV, accounting for 63% of AIDS cases among female teens in 2001-2005. Unprotected intercourse is the proximal risk behavior for both pregnancy and sexually transmitted infections (STIs) including HIV. Behaviors that increase risk for pregnancy among sexually experienced girls (initiating sex before age 15 years, having 3 or more sexual partners, and failing to use contraception the first time they had sex) are also risk factors for HIV infection among adolescent females. Contextual factors such as poverty, history of child sexual abuse, and older partner age are risk factors for teen pregnancy that also characterize females with HIV. Health risks associated with teen pregnancy (late/no prenatal care, preterm and low-birthweight-infants) have also been identified as health risks for pregnant women with HIV.

Despite these similarities and a vast literature on adolescent sexual risk behavior and its relation to unplanned pregnancy and STIs, few studies address the combined occurrence of pregnancy and HIV. Prenatal HIV screening is a common venue for detecting HIV, but we do not know how many females have been both pregnant and HIV seropositive during their adolescent years or how many pregnancies have occurred among HIV-seropositive adolescents. Almost nothing is known about the characteristics of seropositive pregnant adolescents.

In this paper, we examine 2 data sources (the national HIV/AIDS Reporting System [HARS, 2001-2004] and the Perinatal Guidelines Evaluation Project [PGEP, 1997-1999]) to identify and characterize seropositive pregnant adolescents according to maternal (sociodemographic, health and pregnancy, behavioral, and psychosocial) and infant characteristics. Births to HIV-seropositive adolescents aged 13-21 years are reported to HARS through the pediatric case report form. We used these data to estimate cases of seropositive pregnant adolescents. Because HARS contains minimal information on maternal psychosocial and behavioral characteristics, we also conducted secondary analyses of data from PGEP, a well-characterized study of HIV-seropositive and HIV-seronegative at-risk pregnant women. By comparing seropositive adolescents with the cohort of seronegative but at-risk adolescents, as well as with seropositive adults, we were able to consider some of the unique psychosocial and behavioral characteristics of pregnant adolescents with HIV.

Cases of Co-Occurring HIV and Pregnancy Among Adolescents

Materials and methods

Using pediatric case report forms from their perinatally exposed infants, we analyzed maternal characteristics of adolescents, aged 13-21 years, delivering a live infant during 2001-2004 and reported to the Centers for Control and Prevention (CDC) through December 2005 from the 28 states (Alabama, Arizona, Arkansas, Colorado, Connecticut, Indiana, Iowa, Kansas, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nebraska, Nevada, New Jersey, New Mexico, New York, Ohio, Oklahoma, South Carolina, Tennessee, Texas, Utah, Virginia, West Virginia, Wisconsin, and Wyoming) that had conducted confidential, name-based perinatal HIV exposure reporting since at least 2001. HIV/AIDS surveillance data have been determined to be exempt from institutional review board approval.

We examined the following maternal characteristics: number of births, age, timing of HIV diagnosis, risk factors, and prenatal care. Infant characteristics included race/ethnicity, birth weight, receipt of zidovudine (ZDV), and caretaker information. Race/ethnicity was categorized into non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, and American Indian/Alaska Native.

Results

In the years 2001-2004, 1090 seropositive females aged 13-21 years (in the 28 states with confidential, name-based perinatal HIV exposure reporting) had at least 1 pregnancy, which resulted in 1183 live births (87 had 2 pregnancies, 3 had 3 pregnancies). Of the 98.7% of exposed infants whose race/ethnicity was known, 74.4% were non-Hispanic black, 14.0% were Hispanic, 11.1% were non-Hispanic white, and 0.4% were other races/ethnicities. From age 14 years to age 21 years, the number of births increased with each increasing year of maternal age: 26 births (2.2%) were to young adolescents (aged 13-15 years), 246 (20.8%) were to girls in the midadolescent years (aged 16-18 years), and 911 (77%) were to older adolescents (aged 19-21 years).

The majority of infants (622, 52.6%) were born to mothers who acquired their infection through sex with someone known to have, or be at risk for, HIV. For a large proportion of infants (491, 41.5%), the mothers' source of infection was unknown. Fifteen cases (1.3%) occurred to mothers known to have been perinatally HIV infected. Fifty births (4.2%) occurred to mothers who acquired HIV through injection drug use, and 5 (0.4%) through blood transfusion.

Information on timing of HIV diagnosis relative to the current pregnancy was known for 97.9% of births (excluding 13 births to mothers known to be infected before delivery but exact timing was not known and 1 birth to a mother who refused HIV testing). Of these, 609 births (52.6%) were to mothers who knew their positive serostatus before the index pregnancy. Of the 549 remaining births to mothers who learned of their positive serostatus during the index pregnancy or later, 451 (82.2%) were to mothers who received an HIV diagnosis during the pregnancy. Information on receipt of prenatal care was available for 76.8% of the births; of these, prenatal care was not received in 4.7% of cases (43). Of the 99.7% of births to mothers with information on prophylaxis, 90.3% were associated with receipt of ZDV during pregnancy, labor/delivery, or both.

One quarter of the infants born to adolescent mothers (25.7%) had low birthweight (less than 2500 g); 10.1% had a birthweight of less than 1500 g. Of those with available information (94.9%), 18.3% of infants were born premature.
taker was known for 84.8% of the sample; of these, 94.2% were with a biological parent at the time of the initial report. The remainder were with a foster/adoptive relative or nonrelative (2.5%), another relative (1.9%), or a social service agency (1.1%).

**Psychosocial and Behavioral Characteristics of HIV-Infected Pregnant Youth**

Materials and methods

From 1995 to 2000, the CDC funded the PGEP to examine, among other things, psychosocial consequences of HIV diagnosis and infection during pregnancy. Between 1996 and 1999, 634 HIV-seropositive and HIV-seronegative but at-risk pregnant women were interviewed and then followed up for 6 months after delivery. This well-characterized cohort has been the subject of multiple reports on psychosocial and behavioral aspects of HIV and pregnancy in the eras of perinatal prophylaxis and highly active antiretroviral therapy (HAART). However, no analyses ever concentrated on unique issues of youth. We conducted secondary analyses to identify the unique ways in which the seropositive adolescents differed from the seropositive adults and the at-risk but seronegative adolescents.

The cohort, design, procedures, and measures of the PGEP have been described in detail elsewhere. In brief, HIV-infected women were recruited from infectious disease, high-risk, or general prenatal care clinics in New York City; Connecticut; North Carolina; and Dade County, Florida. To identify characteristics unique to HIV diagnosis or illness, the seronegative comparison sample was recruited from clinics serving women with demographic and behavioral characteristics similar to the women with HIV. They were frequency matched (at a within-state level of ± 5%) to the seropositive women on HIV sexual transmission risk behavior (defined as a history of crack cocaine use, sexual intercourse with a male injection drug user [IDU], or exchange of sex for drugs or money), injection drug use, race/ethnicity, and late entry into prenatal care (20 or more weeks of gestation). Participants were interviewed at 24 weeks of gestation or later and again at 6 weeks and 6 months postpartum using a standardized assessment. Medical records of seropositive women were abstracted by trained reviewers. The study was approved by the Institutional Review Boards at the Centers for Disease Control and Prevention and each of the participating institutions.

The baseline assessment included interview questions and administration of psychosocial scales covering the following categories: demographics and socioeconomic indicators, health care factors (including timing of HIV diagnoses relative to index pregnancy), pregnancy and motherhood factors (including reproductive history and maternal-fetal attachment), behavioral factors (including sex and drug risk behaviors), partner factors (including partner support and abuse), and psychosocial factors (including social support, depression, social isolation, perceived stress, negative life events, and recent experiences of violence). Questions regarding the baby’s caretaker and support for the mother were asked at follow-up interviews (see Ethier et al for a full description of measures and scales).

**Results**

PGEP included 147 participants 13-21 years of age; 48 (32.6%) were aged 13-18 years and 99 (67.3%) were aged 19-21 years. HIV serostatus did not differ according to age category. Of the 61 HIV-infected participants (mean age 19.8 years), 29.5% were aged 13-18 years and 70.5% were aged 19-21 years. Nearly half (49.2%) received a diagnosis of HIV before the current pregnancy. Approximately two thirds (67.2%) had been pregnant before, and more than half (52.5%) had previously given birth. Compared with younger seropositive adolescents (aged 13-18 years), older seropositive adolescents (aged 19-21 years) were more likely to have been pregnant before ($\chi^2 [1] = 6.01, P = .01$), and, for those with a main male partner, to report that the baby’s father was their current partner ($\chi^2 [1] = 4.60, P = .05$). Most (83.3%) of the index pregnancies were unplanned; 43.3% of girls had used no pregnancy prevention.

Of girls who answered condom use questions, inconsistent use before and during pregnancy was reported by 88.7% and 77.3%, respectively. More than 15% missed 3 or more prenatal care appointments, and 29.5% had inadequate prenatal care as assessed by the Kotchuck index. The Table presents a description of demographic, health, behavioral, and psychosocial characteristics of the HIV-seropositive adolescents and comparison samples. With 1 exception (older seropositive adolescents reported more stress than younger seropositive adolescents [$\chi^2 (1) = 4.41, P = .04$]), there were no other differences among adolescents with HIV according to age category.

HIV-seropositive adolescents differed from HIV-seropositive adults in predictable ways. They had lower income, were somewhat more likely to be Medicaid recipients, had less education, and were more likely to be currently in school. The proportion of women who were Hispanic was somewhat smaller for the adolescent group than the adult group. The adolescents were less likely to have ever engaged in known HIV sexual transmission risk behavior (ever used crack, traded sex for money or drugs, or had sex with a male IDU) or to have had a previous pregnancy or birth. The adolescents were less likely to have ever used tobacco, alcohol, marijuana, or crack/cocaine, or to have been in a drug rehabilitation program. In addition, they were also less likely to be current cigarette smokers and were somewhat less likely to have used alcohol or drugs during the current pregnancy. Although the length of relationship with their male partner was shorter than that of their adult peers (we did not adjust scores for age), HIV-seropositive adolescents reported their partners to be more supportive and less abusive than partners of HIV-seropositive adults. Adolescents reported fewer recent negative life events and 6 weeks after the birth of their child they were more likely than the adults to have help with child care.

The HIV-seropositive adolescents were similar to the seronegative at-risk
### TABLE
Demographic, health, behavioral, and psychosocial characteristics of HIV-seropositive adolescents, HIV-seropositive adults, and HIV-seronegative adolescents, PGEP, 1997-1999

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 HIV infected aged 13-21 y % (n) (total = 61)</th>
<th>Group 2 HIV infected age &gt; 22 % (n) (total = 273)</th>
<th>Group 3 HIV uninfected aged 13-21 y % (n) (total = 86)</th>
<th>P value* (1 vs 2)</th>
<th>P value* (1 vs 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (mean y)</td>
<td>19.8</td>
<td>30.2</td>
<td>19.3</td>
<td>NA</td>
<td>.12†</td>
</tr>
<tr>
<td>Race‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black (non-Hispanic)</td>
<td>78.7 (48/61)</td>
<td>70.0 (191/273)</td>
<td>64.0 (55/86)</td>
<td>&gt;.17</td>
<td>.06</td>
</tr>
<tr>
<td>Other</td>
<td>21.3 (13/61)</td>
<td>30.0 (82/273)</td>
<td>36.0 (31/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity§</td>
<td>11.5 (7/61)</td>
<td>21.2 (58/273)</td>
<td>20.9 (18/86)</td>
<td>.08</td>
<td>.13</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>.04</td>
<td>.86</td>
</tr>
<tr>
<td>Less than high school</td>
<td>68.4 (39/57)</td>
<td>53.0 (132/249)</td>
<td>69.8 (60/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school/GED or more</td>
<td>31.6 (18/57)</td>
<td>47.0 (117/249)</td>
<td>30.2 (26/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently attending school</td>
<td>18.0 (11/61)</td>
<td>8.4 (23/273)</td>
<td>37.2 (32/86)</td>
<td>.03</td>
<td>.01</td>
</tr>
<tr>
<td>Monthly income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than $1000</td>
<td>85.2 (52/61)</td>
<td>72.5 (198/273)</td>
<td>74.4 (64/86)</td>
<td>.04</td>
<td>.11</td>
</tr>
<tr>
<td>$1000 or more</td>
<td>14.8 (9/61)</td>
<td>27.5 (75/273)</td>
<td>25.6 (22/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of times moved in the prior year</td>
<td>.16</td>
<td>.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41.0 (25/60)</td>
<td>49.8 (134/269)</td>
<td>37.2 (32/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>23.0 (14/60)</td>
<td>27.1 (73/269)</td>
<td>25.6 (22/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or more times</td>
<td>34.4 (21/60)</td>
<td>23.0 (62/269)</td>
<td>37.2 (32/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received public assistance</td>
<td>39.3 (24/61)</td>
<td>44.4 (122/273)</td>
<td>25.6 (22/86)</td>
<td>.45</td>
<td>.08</td>
</tr>
<tr>
<td>Received Medicaid</td>
<td>93.4 (57/61)</td>
<td>84.2 (230/273)</td>
<td>93.0 (80/86)</td>
<td>.06</td>
<td>1.00</td>
</tr>
<tr>
<td>Pregnancy characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous pregnancies</td>
<td>&lt;.01</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32.8 (20/61)</td>
<td>8.4 (23/273)</td>
<td>54.7 (47/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or more</td>
<td>67.2 (41/61)</td>
<td>91.6 (250/273)</td>
<td>45.3 (39/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous live births</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>47.5 (29/61)</td>
<td>22.0 (60/273)</td>
<td>74.4 (64/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or more</td>
<td>52.5 (32/61)</td>
<td>78.0 (213/273)</td>
<td>25.6 (22/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate prenatal care§</td>
<td>29.5 (18/61)</td>
<td>26.4 (72/273)</td>
<td>33.7 (29/86)</td>
<td>.62</td>
<td>.59</td>
</tr>
<tr>
<td>Missed 3+ prenatal care visits</td>
<td>15.3 (9/59)</td>
<td>10.7 (29/271)</td>
<td>11.6 (10/85)</td>
<td>.32</td>
<td>.54</td>
</tr>
<tr>
<td>Pregnancy planning</td>
<td>.94</td>
<td>.18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned</td>
<td>16.7 (10/60)</td>
<td>18.3 (49/268)</td>
<td>15.1 (13/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unplanned, not prevented</td>
<td>43.3 (26/60)</td>
<td>43.7 (117/268)</td>
<td>58.1 (50/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unplanned, failed prevention</td>
<td>40.0 (24/60)</td>
<td>38.1 (102/268)</td>
<td>26.7 (23/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV diagnosed before pregnancy</td>
<td>49.2 (30/61)</td>
<td>59.6 (110/272)</td>
<td>NA</td>
<td>.21</td>
<td>NA</td>
</tr>
<tr>
<td>Risk behaviors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>34.4 (21/61)</td>
<td>56.4 (154/273)</td>
<td>41.9 (36/86)</td>
<td>&lt;.01</td>
<td>.36</td>
</tr>
<tr>
<td>During current pregnancy</td>
<td>16.4 (10/61)</td>
<td>31.9 (87/273)</td>
<td>17.4 (15/86)</td>
<td>.02</td>
<td>.87</td>
</tr>
</tbody>
</table>

Continued on page S127.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 HIV infected aged 13-21 y % (n) (total = 61)</th>
<th>Group 2 HIV infected age &gt; 22 % (n) (total = 273)</th>
<th>Group 3 HIV uninfected aged 13-21 y % (n) (total = 86)</th>
<th>P value* (1 vs 2)</th>
<th>P value* (1 vs 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>39.3 (24/61)</td>
<td>58.2 (159/273)</td>
<td>60.5 (52/86)</td>
<td>&lt;.01</td>
<td>.01</td>
</tr>
<tr>
<td>During current pregnancy</td>
<td>8.3 (5/60)</td>
<td>17.6 (47/267)</td>
<td>9.6 (8/83)</td>
<td>.08</td>
<td>.79</td>
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<tr>
<td>Marijuana use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>29.5 (18/61)</td>
<td>45.1 (123/273)</td>
<td>40.7 (35/86)</td>
<td>.03</td>
<td>.16</td>
</tr>
<tr>
<td>During current pregnancy</td>
<td>1.6 (1/61)</td>
<td>7.3 (19/259)</td>
<td>8.5 (7/82)</td>
<td>.14</td>
<td>.14</td>
</tr>
<tr>
<td>Crack/cocaine, ever</td>
<td>13.1 (8/61)</td>
<td>36.3 (99/273)</td>
<td>15.1 (13/86)</td>
<td>&lt;.01</td>
<td>.73</td>
</tr>
<tr>
<td>Injection drugs, ever‡</td>
<td>3.3 (2/61)</td>
<td>7.0 (19/273)</td>
<td>1.2 (1/86)</td>
<td>.28</td>
<td>.57</td>
</tr>
<tr>
<td>Used any drug, current pregnancy</td>
<td>8.2 (5/61)</td>
<td>17.6 (48/273)</td>
<td>12.8 (11/86)</td>
<td>.07</td>
<td>.39</td>
</tr>
<tr>
<td>Previous drug rehabilitation</td>
<td>8.2 (5/61)</td>
<td>32.2 (88/273)</td>
<td>11.6 (10/85)</td>
<td>&lt;.01</td>
<td>.50</td>
</tr>
<tr>
<td>Any sex risk (ever used crack, had sex with IDU male, or bartered sex)‡</td>
<td>21.3 (13/61)</td>
<td>45.4 (124/273)</td>
<td>17.4 (15/86)</td>
<td>&lt;.01</td>
<td>.56</td>
</tr>
<tr>
<td>Inconsistent condom use before current pregnancy</td>
<td>88.7 (47/53)</td>
<td>83.8 (196/234)</td>
<td>89.5 (77/86)</td>
<td>.37</td>
<td>.88</td>
</tr>
<tr>
<td>Partner characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main male partner</td>
<td>72.1 (44/61)</td>
<td>78.8 (215/273)</td>
<td>76.7 (66/86)</td>
<td>.26</td>
<td>.53</td>
</tr>
<tr>
<td>Partner is baby’s father</td>
<td>86.4 (38/44)</td>
<td>93.0 (200/215)</td>
<td>83.3 (55/66)</td>
<td>.14</td>
<td>.67</td>
</tr>
<tr>
<td>Partner relationship length†</td>
<td>65.9 (29/44)</td>
<td>47.4 (101/213)</td>
<td>67.7 (44/65)</td>
<td>.03</td>
<td>.85</td>
</tr>
<tr>
<td>Shorter</td>
<td>34.1 (15/44)</td>
<td>52.6 (112/213)</td>
<td>32.3 (21/65)</td>
<td>.01</td>
<td>.04</td>
</tr>
<tr>
<td>Longer</td>
<td>27.3 (12/44)</td>
<td>53.3 (114/214)</td>
<td>47.0 (31/66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physically or emotionally abusive partner</td>
<td>72.7 (32/44)</td>
<td>46.7 (100/214)</td>
<td>53.0 (35/66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced physical or sexual violence in the last 6 mo</td>
<td>6.8 (4/59)</td>
<td>7.4 (20/270)</td>
<td>8.1 (7/86)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Social support</td>
<td></td>
<td></td>
<td></td>
<td>.95</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Low</td>
<td>86.9 (53/61)</td>
<td>12.8 (35/273)</td>
<td>90.7 (78/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>13.1 (8/61)</td>
<td>87.2 (238/273)</td>
<td>9.3 (8/61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social isolation†</td>
<td></td>
<td></td>
<td></td>
<td>.31</td>
<td>.03</td>
</tr>
<tr>
<td>Low</td>
<td>55.9 (33/59)</td>
<td>48.7 (130/267)</td>
<td>37.2 (32/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>44.1 (26/59)</td>
<td>51.3 (137/267)</td>
<td>62.8 (54/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression‡</td>
<td></td>
<td></td>
<td></td>
<td>.24</td>
<td>.97</td>
</tr>
<tr>
<td>Lower</td>
<td>56.7 (34/60)</td>
<td>48.4 (132/273)</td>
<td>57.0 (49/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher</td>
<td>43.3 (26/60)</td>
<td>51.6 (141/273)</td>
<td>43.0 (37/86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued on page S128.
### Table

**Demographic, health, behavioral, and psychosocial characteristics of HIV-seropositive adolescents, HIV-seropositive adults, and HIV-seronegative adolescents, PGEP, 1997-1999**

Continued from page S127.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 HIV infected aged 13-21 y % (n) (total = 61)</th>
<th>Group 2 HIV infected age &gt; 22 % (n) (total = 273)</th>
<th>Group 3 HIV uninfected aged 13-21 y % (n) (total = 86)</th>
<th>P value* (1 vs 2)</th>
<th>P value* (1 vs 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived stress(^1)</td>
<td>Low: 55.2 (32/58)</td>
<td>Low: 51.5 (139/270)</td>
<td>Low: 57.0 (49/86)</td>
<td>.61</td>
<td>.83</td>
</tr>
<tr>
<td></td>
<td>High: 44.8 (26/58)</td>
<td>High: 48.5 (131/270)</td>
<td>High: 43.0 (37/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative life events, prior 6 mo(^2)</td>
<td>Low: 67.2 (41/61)</td>
<td>Low: 51.6 (141/273)</td>
<td>Low: 44.2 (38/86)</td>
<td>.03</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>High: 32.8 (20/61)</td>
<td>High: 48.4 (132/273)</td>
<td>High: 55.8 (48/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal-fetal attachment(^3)</td>
<td>Low: 54.7 (29/53)</td>
<td>Low: 42.2 (97/230)</td>
<td>Low: 64.0 (55/86)</td>
<td>.10</td>
<td>.28</td>
</tr>
<tr>
<td></td>
<td>High: 45.3 (24/53)</td>
<td>High: 57.8 (133/230)</td>
<td>High: 36.0 (31/86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes(^4)</td>
<td>Gestational age at delivery</td>
<td>Less than 38 wks: 21.4 (9/42)</td>
<td>24.1 (48/199)</td>
<td>16.7 (10/60)</td>
<td>.71</td>
</tr>
<tr>
<td></td>
<td>38 wks or longer: 78.6 (33/42)</td>
<td>75.9 (151/199)</td>
<td>83.3 (50/60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight(^5)</td>
<td>Less than 2500 g: 14.3 (8/56)</td>
<td>14.1 (37/262)</td>
<td>9.7 (6/62)</td>
<td>.98</td>
<td>.44</td>
</tr>
<tr>
<td></td>
<td>2500 g or greater: 85.7 (48/56)</td>
<td>85.9 (225/262)</td>
<td>90.3 (56/62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Help with childcare at 6 wks</td>
<td>91.1 (41/45)</td>
<td>73.1 (152/208)</td>
<td>87.1 (54/62)</td>
<td>.01</td>
<td>.52</td>
</tr>
<tr>
<td>Help with child care at 6 mo</td>
<td>93.0 (40/43)</td>
<td>84.4 (162/192)</td>
<td>90.7 (49/54)</td>
<td>.14</td>
<td>1.00</td>
</tr>
<tr>
<td>Baby living with you at 6 wks</td>
<td>97.8 (44/45)</td>
<td>90.0 (207/230)</td>
<td>98.4 (62/63)</td>
<td>.14</td>
<td>1.00</td>
</tr>
<tr>
<td>Baby living with you at 6 mo</td>
<td>97.7 (42/43)</td>
<td>90.1 (191/212)</td>
<td>89.7 (52/58)</td>
<td>.14</td>
<td>.23</td>
</tr>
</tbody>
</table>

\(^1\) Perceived stress based on the Kotelchuck index.\(^2\)

\(^2\) Low birthweight was calculated by using the procedure previously reported by Ickovics et al.\(^1\) Specifically, chart review data were used when available, otherwise, mothers’ reports were used. \(^3\) Includes first baby only for any multiple births.

\(^4\) P value for comparisons are based on \( \chi^2 \) analyses or Fisher’s exact tests to determine significant differences between groups.

\(^5\) Variables used as matching characteristics in the overall PGEP study sample.

\(^6\) Based on the Kotelchuck index.\(^8\)

\(^7\) Scores were dichotomized based on a median split using data from the entire PGEP study sample.

\(^8\) Includes first baby only for any multiple births.

GEO, general equivalency diploma; IDU, injection drug use; PGEP, Perinatal Guidelines Evaluation Project.

### Adolescents with respect to sociodemographics. Although matched in the full cohort according to race and ethnicity, a somewhat larger proportion of the HIV-seropositive than seronegative adolescents were black. However, the 2 samples did not differ significantly according to Hispanic ethnicity and also did not differ with respect to age, income, work status, household stability, or completion of high school/general education degree. However, compared with the seronegative sample, adolescents with HIV were significantly less likely to still be in school and somewhat more likely to be receiving public assistance. Although the 2 cohorts did not differ according to pregnancy planning or inconsistent condom use before or during this pregnancy, HIV-seropositive adolescents were more likely to have previously been pregnant and to have given birth than the seronegative adolescents. Again, the 2 (full) cohorts were matched according to history of injection drug use and the HIV sexual transmission risk behaviors of either using crack cocaine, trading sex for drugs or money, or having sex with a male IDU. Not surprisingly, the groups didn’t differ on these behaviors. With the exception of alcohol use (HIV-seropositive adolescents were less likely to have ever used alcohol), there were no differences in any of the other drug use or sex risk behaviors assessed. Although there were no differences in
partner characteristics, HIV-seropositive adolescents reported more partner support; they also reported more social support in general, less social isolation, and fewer negative life events, compared with seronegative adolescents. There were no differences in infant birthweight or gestational age at delivery.

**COMMENT**

Pregnancy is not uncommon among adolescents with HIV, particularly among older adolescents (aged 19–21 years) who accounted for approximately three quarters of the participants in these studies. During 2001–2004, we identified 1183 births to seropositive adolescents in the 28 states with confidential, name-based perinatal HIV exposure reporting. Multiple pregnancies characterized 90 adolescents. Although we cannot say whether the prior pregnancies reported by PGEP participants occurred subsequent to HIV infection, more than two thirds of the seropositive PGEP adolescents were previously pregnant, and just over half had given birth. This high prevalence of pregnancy and childbearing among HIV-seropositive youth is consistent with findings from other studies. For example, in a study of seropositive 13- to 24-year-olds participating in a psychosocial program, 42% of participants reported at least 1 pregnancy since learning their HIV status. Moreover, 38% of teens (13–18 years old) in the multisite Reaching for Excellence in Adolescent Care and Health (REACH) study had children at enrollment. The higher rate found for the PGEP cohort, as compared with the REACH cohort, is likely due to the inclusion of older adolescents in the PGEP cohort; indeed, one quarter of the REACH teens became pregnant in the 3 years after enrollment.

Contrary to expectations related to younger age, seropositive adolescents were no more likely than seropositive adults to have received an HIV diagnosis as part of their current prenatal care. Across both studies, in approximately half of the births to adolescents, a diagnosis of HIV occurred before the current pregnancy (49% PGEP, 53% HARS). (Some adolescents may have tested seropositive during a previous pregnancy because more than half of the adolescents who already knew their serostatus had been pregnant before [data not shown].) Moreover, consistent with national data on teen pregnancy, 83.3% of pregnancies in PGEP adolescents were unplanned. Although some pregnancies can be attributed to contraception failures, 43% of PGEP adolescents who did not plan their pregnancies also reported using no prevention. Taken together, these findings indicate that many HIV-seropositive adolescents who know their positive serostatus are engaging in unprotected sex and are not using any pregnancy prevention methods. The results argue strongly for risk reduction interventions specifically for young HIV-seropositive females, not only to prevent unplanned pregnancy but also to decrease HIV transmission.

Supporting published case reports documenting pregnancies among the aging cohort of perinatally infected adolescents, we found that 1.3% of infants born to adolescents during 2001–2004 had perinatally HIV-infected mothers. In the short term, these numbers are likely to increase as surviving children enter adolescence and young adulthood.

In 1 study of 28 perinatally HIV-infected females aged 13–24 years, 10 were sexually active; 5 of the 10 had been pregnant. Most of the females in that study (70.8%) reported a desire to have children. However, in the largest case series to date, 83% (15/18) of the pregnancies among perinatally HIV-infected adolescents were unintended, a proportion equivalent to that reported by the behaviorally infected adolescents in the PGEP study.

These data document the need for developmentally targeted and aggressive anticipatory guidance regarding reproduction and HIV transmission along with tested risk reduction interventions appropriate for perinatally HIV-infected adolescents. Guidance that emphasizes the often neglected issue of planning a future pregnancy would be beneficial for males with perinatally acquired HIV as well as for females. Providers caring for these youth, and those who deliver their infants, can play an important role in providing risk behavior counseling and guidance on future childbearing. The difficult struggle experienced by these teens as they attempt to balance the realities of HIV disease with their developing sexuality, normal desires to have children, and strong social pressures to have sex are illustrated by a case example reported by Levine et al. Of a perinatally HIV-infected teen who was an active participant in her clinic support groups, the authors write that she was “an outspoken advocate of sexual abstinence until her pregnancy was diagnosed.”

In addition to health risks, pregnant teens face unique psychosocial challenges related to education, child care, and finances. For example, teen mothers are at risk for poor educational outcomes. Of older teen mothers (aged 18–19 years), only 74% finish high school or obtain a general education degree, and only 3% complete college. Relative to their risk-taking but seronegative peers, the seropositive teens in PGEP had had more children, were less likely to be in school, and were more likely to be on public assistance. Although this financial assistance may be directly related to their serostatus, these adolescents will likely need extra help completing their education, locating affordable child care, and obtaining higher education and/or developing the vocational skills necessary to obtain work and achieve the financial stability necessary to support their families.

On the other hand, the seropositive adolescents felt more supported than the seronegative adolescents (in general and from their male partners) and were less lonely. It is not clear why this was the case; however, research on serostatus disclosure has suggested that many women receive unexpected support after disclosing their positive serostatus to loved ones. If a majority of seropositive adolescents are living with family (which could explain increased child care assistance relative to adults), they may have recently disclosed this information. Thus, these reports may reflect this increased experience of support. In addition, pregnant women with HIV are typically connected to an array of social
services, including support groups, which also may have contributed to their relative lack of perceived social isolation.

To date, very little has been written specifically about pregnant adolescents with HIV. These data represent the first estimate of cases of co-occurring HIV infection and pregnancy among adolescents in the United States and some of the first information about their psychosocial and behavioral characteristics. Nevertheless, each source of information is subject to several limitations.

The national HIV/AIDS surveillance system data are subject to at least 3 limitations. First, HIV infection surveillance data from all states are not included in the national surveillance system. Although pediatric HIV infection surveillance is currently being conducted in 48 areas that use name-based HIV infection reporting, only 28 states also conduct population-based perinatal HIV exposure surveillance for infants born to HIV-seropositive mothers. Although our data are from the largest set of population-based data currently available for persons infected with HIV, the 28 states used in this analysis may not be nationally representative because they reported only 55.3% of all AIDS cases diagnosed among adolescents in the United States during 2001-2004. Second, risk behavior information about partners is limited; therefore, surveillance data cannot effectively be used to evaluate the effect of sexual behaviors on transmission of HIV infection. Last, the surveillance data do not include HIV-seropositive women who were not reported or their HIV-exposed children who tested negative or were not tested but were presumed to be negative.

The PGEP data are also subject to limitations. The study was not designed to focus on adolescents, and no attempts were made to identify representative samples of youth or to conduct matching within age groups. Because of matching criteria, the lack of differences between the 2 cohorts cannot be interpreted as a statement on the level of risk behavior in HIV-seropositive girls relative to the general population. Finally, some of these data were collected as many as 9 years ago. Although both perinatal prophylaxis to prevent mother-to-child transmission and HAART were available at that time, advances in HIV treatment and obstetric care, as well as changes in societal knowledge and attitudes about HIV, may influence the behavior and experiences of today’s seropositive pregnant youth.

Seropositive pregnant adolescents need strong pregnancy and HIV transmission prevention counseling as well as educational, vocational, and financial counseling. At the same time, these adolescents may possess certain psychosocial strengths, such as support from partners, friends, or family, that can and should be used to help them cope with the complex array of health and social demands they will face as they manage their HIV disease while parenting their newborn.

REFERENCES


The missing link: documentation of recognized maternal human immunodeficiency virus infection in exposed infant birth records, 24 United States jurisdictions, 1999-2003

Allan W. Taylor, MD, MPH; Nan Ruffo, BS; Judy Griffith, RN, MS; Athena P. Kourtis, MD, PhD, MPH; Jill Clark, MPH; Michael Lindsay, MD, MPH; Donata Green, PhD; Denise J. Jamieson, MD, MPH

Reduction in perinatal transmission of the human immunodeficiency virus (HIV) in the United States since the mid 1990s has been a tremendous public health success. Annual cases of perinatal HIV transmission in the United States are estimated to have peaked in 1991 at approximately 1650 cases. By 2002 the estimated number of annual perinatal transmissions had decreased to an estimated range of 144–236 cases. This decline can be attributed in large part to the rapid adoption of important interventions by prenatal care providers, such as routine voluntary prenatal HIV testing, effective use of antiretroviral treatment and prophylaxis, and scheduled cesarean delivery when appropriate. However, maximal reduction of perinatal HIV transmission has not yet been achieved in the United States.

Risk factors for perinatal HIV transmission have been reviewed extensively elsewhere. These factors include inadequate antiretroviral prophylaxis for mother and infant, prematurity, chorioamnionitis, use of instrumentation during delivery, and prolonged rupture of membranes. The first steps in the prevention of perinatal HIV infection are primary prevention for women and recognition of existing HIV infection among women. Despite recommendations for universal HIV screening for pregnant women from the Centers for Disease Control and Prevention (CDC) and other authorities, some women are not screened for HIV during prenatal care, and some women who are identified as HIV infected do not receive appropriate treatment or prophylaxis.

It is recommended that any woman at labor and delivery without documentation of an HIV test during pregnancy (eg, if records are unavailable) be screened routinely with a rapid HIV test, unless she declines. Women who are found to be HIV infected should receive prophylactic therapy to prevent transmission to the infant and be evaluated for the need for treatment for their own infection.

The final crucial step in the perinatal HIV prevention cascade is for the HIV-exposed newborn infant to receive appropriate antiretroviral prophylaxis; several other measures must occur during the first year of life to assure that a definitive diagnosis of HIV infection is made or ruled out in the infant and to assure that HIV-infected infants are protected against opportunistic infections.
that can occur within the first 6 months of life. These interventions cannot occur if the infant’s HIV exposure is not recognized and communicated in a timely manner to the care providers. Failure to communicate HIV exposure status of infants from maternal care providers to pediatric providers constitutes a preventable medical error that results in a small, but unacceptable, number of infected infants. The purpose of this study was to examine the extent to which incomplete communication between obstetric and pediatric care providers represents an important missed opportunity for the prevention of mother-child HIV transmission and the effects of this missed opportunity among infants whose cases are reported to the Enhanced Perinatal Surveillance System (EPS) of the Centers for Disease Control and Prevention.

**MATERIALS AND METHODS**

We examined the extent of missed communication among providers for HIV-exposed infants who were reported to the EPS system, which is coordinated by the CDC, for births that occurred between 1999 and 2003. EPS has collected prenatal care and diagnostic and treatment-related data regarding HIV-exposed and -infected infants in select jurisdictions since 1999. These 24 sites represented 89% of the cumulative perinatal acquired immunodeficiency syndrome (AIDS) cases that were reported through 2003 in the United States. Infants were determined to be HIV infected or uninfected or of indeterminate status with the use of the revised CDC surveillance HIV case definition for adults and children.\(^1\) A detailed description of the methods that were used and participating jurisdictions, which includes case definitions and reporting procedures, can be found in an accompanying article in this Journal.\(^2\) This project was deemed exempt from the CDC institutional review board review because it was determined that the project constituted data collection for the purposes of disease surveillance and program evaluation and thus was not classified as human-subjects research. Data were collected by trained health department personnel or their agents from existing medical and ancillary records. There was no contact with individual patients, and no names of individuals were reported to the CDC.

We examined all reports of HIV-exposed infants who were born between 1999 and 2003 to determine whether any association existed between documentation of maternal HIV infection in the infant’s medical record at the time of birth and evidence of antiretroviral medications to the infant in the first 6 weeks of life or infant infection status. We considered maternal HIV status to be known before delivery on the basis of the relationship between the timing of the woman’s HIV diagnosis and the date of the infant’s birth. Bivariate and multivariate logistic regression analyses were used to explore associations between the receipt of infant antiretroviral medications in the first 6 weeks of life or infant HIV infection and other risk factors for perinatal HIV transmission. Model variables included (1) the receipt of any prenatal antiretroviral medications by the woman, (2) the receipt by the woman of any antiretroviral medication during labor or delivery, (3) the duration (in hours) from rupture of membranes to delivery, (4) the use of forceps or vacuum extraction instrumentation during delivery, and (5) the infant’s estimated gestational age at birth, as noted in the neonatal medical record. All analyses were performed with the SAS System software (version 9.1; SAS Institute, Cary, NC).

**RESULTS**

Of 12,309 HIV-exposed infants who were reported to the EPS between 1999 and 2003, 8552 infants had complete data regarding the timing of maternal HIV diagnosis. Maternal HIV infection had been diagnosed by the time of the infant’s birth for 8115 of these infants (95%). Of these 8115 infants, maternal HIV infection was documented in 96% of infants’ charts, which left 4% (307 infants) without such documentation. Mothers of these 307 infants were less likely to have received any prenatal or labor and delivery antiretroviral medica-

**COMMENT**

We found that, for infants whose mothers had been diagnosed with HIV before or at the time of delivery, documentation...
of maternal HIV infection was in the infant’s chart in most cases. However, we found that, in 4% of cases, this communication did not occur. This lack of appropriate documentation, although rare, often was associated with a failure of appropriate neonatal treatment and prevention of mother-child HIV transmission. Such cases represent sentinel events, which indicate areas in which simple system changes can result in improved care for women and infants.

Documentation in the medical record is critical for the communication of HIV-exposure status to the newborn infant’s healthcare providers. Information from recent focus groups of obstetrician/gynecologists in Memphis, Tenn, and Cleveland, Ohio, indicated that clinicians relied primarily on medical record documentation (maternal chart) and neonatal nursing reports as the primary means to communicate the maternal HIV status (CDC unpublished data, 2006).

A variety of factors might have contributed to the uncommon but important cases described in this study in which this communication was lacking. Misunderstandings about confidentiality requirements may cause some providers to hesitate to document a mother’s HIV test results in her infant’s chart. The CDC recommends that maternal HIV results be documented in their infants’ charts; these recommendations should be communicated clearly to all staff. Some facilities may not have well-established channels of communication for conveying maternal prenatal care information to the neonatal team, or there may be cases in which such channels malfunction. Perinatal steering committees can be established at birthing facilities with membership from obstetric and neonatal providers and the hospital pharmacy to refine protocols and address any observed exceptions. Some health delivery systems conduct perinatal clinical meetings to review challenging maternal case histories (such as
perinatal HIV infection) for the development of a joint obstetric/pediatric treatment plan. Finally, obstetricians and pediatricians must take shared responsibility to ensure that all mothers and newborn infants have documentation of maternal HIV status in their charts and ensure that this information is communicated clearly to the newborn infant care providers. Educational activities, such as grand rounds presentations, and periodic quality control activities, such as chart reviews, may enhance consistency of documentation. Current guidelines regarding treatment, prophylaxis, and documentation are available from the CDC[9] and the US Public Health Service (www.aidsinfo.nih.gov). In addition, there is a national perinatal HIV consultation service that is operated by the University of California, San Francisco, with a 24-hour toll-free hotline as a resource for clinicians with questions about perinatal HIV treatment and prevention (1-888-448-8765).

This study was subject to important limitations. EPS is not a representative sample of HIV-exposed infants in the United States, and these results therefore cannot be taken to be statistically representative of all such infants. Because EPS is not a random sample of any popula-

### Table 2

Unadjusted and adjusted odds ratios for lack of infant antiretroviral medications by age 6 weeks and infant HIV infection among mothers with known HIV infection, by risk factors for perinatal HIV transmission (EPS, 24 United States jurisdictions, 1999-2003; n = 8115)

<table>
<thead>
<tr>
<th>Documentation of maternal HIV infection in infant birth record</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not documented</td>
<td>148.7</td>
<td>105.3-210.0</td>
<td>37.3</td>
<td>24.6-56.4</td>
</tr>
<tr>
<td>Documented</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prenatal antiretroviral to mother</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>74.5</td>
<td>47.5-116.8</td>
<td>14.3</td>
<td>8.3-24.6</td>
</tr>
<tr>
<td>Yes</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Unknown</td>
<td>38.7</td>
<td>20.3-73.7</td>
<td>8.4</td>
<td>3.6-19.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiretroviral medication in labor and delivery to mother</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>153.5</td>
<td>71.2-330.7</td>
<td>17.1</td>
<td>7.3-40.1</td>
</tr>
<tr>
<td>Yes</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Unknown</td>
<td>22.6</td>
<td>10.5-48.9</td>
<td>10.8</td>
<td>4.7-24.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rupture of membranes duration (hr)</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>1.8</td>
<td>1.2-2.6</td>
<td>1.2</td>
<td>0.7-2.1</td>
</tr>
<tr>
<td>≥18</td>
<td>1.4</td>
<td>1.0-2.0</td>
<td>0.9</td>
<td>0.6-1.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>38.7</td>
<td>20.3-73.7</td>
<td>8.4</td>
<td>3.6-19.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Instrumentation used at delivery</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0.4</td>
<td>0.1-1.5</td>
<td>0.3</td>
<td>0.0-1.8</td>
</tr>
<tr>
<td>Yes</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.4</td>
<td>0.3-0.5</td>
<td>1.2</td>
<td>0.8-1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infant estimated gestational age at birth (wk)</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>Adjusted 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;37</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>≤37</td>
<td>1.5</td>
<td>1.1-2.1</td>
<td>1.1</td>
<td>0.7-1.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>3.6</td>
<td>2.2-5.8</td>
<td>4.5</td>
<td>2.2-9.3</td>
</tr>
</tbody>
</table>
tion, the statistical testing presented in this article cannot be construed as constituting an extrapolation to any underlying population. The system, however, has captured most perinatally acquired AIDS cases reported in the United States and is likely to have captured most cases of HIV-exposed infants as well. A related limitation is that areas with high HIV prevalence are likely overrepresented in the EPS dataset. Such areas may be more likely to have procedures in place for the communication of HIV test results than are areas of lower prevalence. The results of this study may underestimate the magnitude of these missed communication opportunities in lower-prevalence areas.

In addition, for the purposes of this study, HIV-uninfected infants were grouped together with infants whose HIV status was defined for surveillance purposes as “indeterminate.” An infant was classified as indeterminate if the requisite negative viral load or antibody tests do not meet the required specified time periods (ie, ≥4 months old). Because physicians may often rule out infection before 4 months of age, it is likely that most of these infants are uninfected. However, this assumption may have resulted in an underestimate of perinatal HIV infection rates in this study. Further, we did not have data regarding some other known risk factors for perinatal HIV transmission, such as the presence of chorioamnionitis, and were unable to account for these other factors in our analysis. Finally, we defined maternal HIV status to be known on the basis of the relationship of the timing of the mother’s diagnosis and the infant’s date of birth. However, some women may have received a diagnosis of HIV infection before the infant’s birth but were unwilling to disclose their status to their providers. To provide appropriate care to such women and their infants, any woman with undocumented HIV status at labor and delivery (for example, if prenatal care records are unavailable at the time of delivery) should be screened routinely with a rapid HIV test, unless she declines.

Increasingly, the maximal reduction of mother-child HIV transmission is becoming a matter of addressing exceptions to widely adopted recommendations and standards. Universal perinatal screening and prophylaxis can prevent most cases; however, remaining transmissions continue, despite established protocols. Among all the challenges that must still be addressed, failure to communicate an infant’s HIV-exposure status to those caring for newborn infants is an easily addressed missed opportunity for the prevention of perinatal HIV transmission.

REFERENCES
Consultation needs in perinatal HIV care: experience of the National Perinatal HIV Consultation Service

Jessica A. Fogler, MD; Shannon Weber, MSW; Ronald H. Goldschmidt, MD; Megan R. Mahoney, MD; Deborah Cohan, MD, MPH

Perinatal human immunodeficiency virus (HIV) transmission can be reduced from 25% to <1% with optimal medical and obstetric management.\(^1\)\(^-\)\(^4\) Minimizing transmission requires timely recognition of maternal HIV infection, proper prenatal care with correct use of antiretroviral drugs, appropriate intrapartum management, and postexposure prophylaxis for the infant. Universal HIV testing is recommended as routine practice.\(^5\)\(^-\)\(^7\) With broader testing and increased identification of HIV-infected pregnant women, more providers will be faced with the challenge of caring for these women and their infants. Although the care of HIV-infected pregnant women is best managed in concert with perinatal HIV experts, this is not always possible. Many women do not have access to such experts, so their care and the care of their newborn infants will be managed primarily by their obstetricians, family physicians, nurse midwives, and pediatricians. Providers may need expert consultation to ensure that optimal care is being provided.

Formal studies have not been conducted to evaluate the consultation needs of providers who care for HIV-infected pregnant women and HIV-exposed infants. Many women do not have access to such experts, so their care and the care of their newborn infants will be managed primarily by their obstetricians, family physicians, nurse midwives, and pediatricians. Providers may need expert consultation to ensure that optimal care is being provided.

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Received Dec. 15, 2006; accepted Feb. 26, 2007.

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The NCCC is funded by the Health Resources and Services Administration (HRSA) AIDS Education and Training Centers (AETCs) and receives additional funding from the HRSA Division of Community Based Programs and the Centers for Disease Control and Prevention.

0002-9378/$32.00
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doi: 10.1016/j.ajog.2007.02.033

This study evaluates the consultation needs of clinicians who provide perinatal human immunodeficiency virus (HIV) care in the United States. The Perinatal Hotline (1-888-448-8765) is a telephone consultation service for providers who treat HIV-infected pregnant women and their infants. Hotline calls were analyzed for demographics about callers and their patients and information about consultation topics. There were 430 calls to the hotline from January 1, 2005, through June 30, 2006. Most calls (59.5%) were related to pregnant patients; 5.1% of the calls pertained to women currently in labor. The most common topic was HIV care in pregnancy (49.1%), particularly antiretroviral drug use (42.1%). HIV testing was discussed in 21.9%, and intrapartum treatment was discussed in 24.0%. Callers most often requested help choosing antiretroviral drug regimens; many of the discussions were about drug toxicities and viral resistance. Although the hotline received few calls about women in labor, the need for these consultations is expected to increase with the expanding use of rapid HIV testing. Access to 24-hour consultation can help ensure that state-of-the-art care is provided.

Key words: HIV testing, perinatal HIV care, pregnancy, telephone consultation

MATERIALS AND METHODS

The Perinatal Hotline was created in response to the Centers for Disease Control and Prevention (CDC) 2003 Advancing HIV Prevention initiative, which called for a further reduction in mother-to-child HIV transmission as 1 of 4 strategies to limit the spread of the epidemic.\(^10\) The Perinatal Hotline was launched on December 1, 2004, as a new service of the National HIV/AIDS Clinicians’ Consultation Center (NCCC) at the University of California San Francisco–San Francisco General Hospital. The NCCC also includes the National HIV Telephone Consultation Service (HIV Warmline) and the National Clinicians’ Post-Exposure Prophylaxis Hotline (PEPline). The NCCC is part of the Health Resources and Services Administration AIDS Education and Training Centers and receives additional funding from the Health Resources and Services Admini-
For example, public health department, pharmacy, or mental health facility.

For example, social worker, administration, or public safety.

For example, pharmacist, public health, or medical assistant.

TABLE 1

<table>
<thead>
<tr>
<th>Caller demographics</th>
<th>Total (n = 328)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caller profession</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>MD/DO</td>
<td>180</td>
<td>54.9</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>55</td>
<td>30.6</td>
</tr>
<tr>
<td>Obstetrics/gynecology</td>
<td>45</td>
<td>25.0</td>
</tr>
<tr>
<td>Family medicine</td>
<td>41</td>
<td>22.8</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>19</td>
<td>10.6</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>16</td>
<td>8.9</td>
</tr>
<tr>
<td>Emergency medicine</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>MD/DO: other</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Nurse practitioner/physician assistant/</td>
<td>51</td>
<td>15.5</td>
</tr>
<tr>
<td>certified nurse-midwife</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registered nurse/licensed vocational nurse</td>
<td>42</td>
<td>12.8</td>
</tr>
<tr>
<td>Other medical*</td>
<td>28</td>
<td>8.5</td>
</tr>
<tr>
<td>Nonmedical†</td>
<td>23</td>
<td>7.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>1.2</td>
</tr>
<tr>
<td>HIV+ patients cared for by caller</td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>44</td>
<td>13.4</td>
</tr>
<tr>
<td>4-10</td>
<td>20</td>
<td>6.1</td>
</tr>
<tr>
<td>11-25</td>
<td>14</td>
<td>4.3</td>
</tr>
<tr>
<td>26-50</td>
<td>26</td>
<td>7.9</td>
</tr>
<tr>
<td>51-100</td>
<td>31</td>
<td>9.5</td>
</tr>
<tr>
<td>101+</td>
<td>56</td>
<td>17.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>111</td>
<td>33.8</td>
</tr>
<tr>
<td>Not applicable‡</td>
<td>26</td>
<td>7.9</td>
</tr>
<tr>
<td>Caller facility type</td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>176</td>
<td>53.7</td>
</tr>
<tr>
<td>Community clinic</td>
<td>88</td>
<td>50.0</td>
</tr>
<tr>
<td>Private practice</td>
<td>54</td>
<td>30.7</td>
</tr>
<tr>
<td>Outpatient: other</td>
<td>34</td>
<td>19.3</td>
</tr>
<tr>
<td>Hospital</td>
<td>85</td>
<td>25.9</td>
</tr>
<tr>
<td>Hospital: labor and delivery</td>
<td>28</td>
<td>32.9</td>
</tr>
<tr>
<td>Hospital: other</td>
<td>57</td>
<td>67.1</td>
</tr>
<tr>
<td>Other medical‡</td>
<td>36</td>
<td>11.0</td>
</tr>
<tr>
<td>Nonmedical†</td>
<td>23</td>
<td>7.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* For example, pharmacist, public health, or medical assistant.
† For example, social worker, administration, or public safety.
‡ For example, no patient care or nonmedical personnel.
§ For example, public health department, pharmacy, or mental health facility.
‖ For example, social service agency or community organization.

In this analysis, we included Perinatal Hotline calls from January 1, 2005, through June 30, 2006. At the time of each call, hotline staff collected demographic data about the caller and the caller’s patients and recorded a detailed narrative summary that described the caller’s questions and the clinician’s response. Demographic data about callers included profession, number of HIV-positive patients cared for, caller facility type, and locale. Patient demographics included pregnancy status (ie, pregnant, in labor, after delivery); timing of HIV diagnosis for pregnant, intrapartum, and postpartum women; and patient age and race. Demographic information is missing in some instances because hotline clinicians were not able to obtain these data from the callers.

Discussion topics were categorized by keywords, which were developed from a review of themes from Perinatal Hotline calls over the 26 months preceding the study period. Calls in this analysis were reviewed by a hotline clinician (J.A.F.) and assigned ≥1 keywords. Calls were then reviewed by a second unblinded clinician (M.R.M.) to ensure accuracy of coding. When discrepancies occurred, a third clinician (D.C.) met with the first 2 clinicians to arrive at a consensus. Discussions about mother/infant dyads were counted as a single call with 2 separate patients. Calls that anticipated the care of neonates who were not yet born were categorized as discussions about in-
born infants were not included in the pa-
tients in preterm labor (time of the call, with 28.6% of these pa-
calls pertained to patients in labor at the
most one third of these calls coming
practices. Most calls came from outpa-
patients (53.7%). Twenty-six percent
of the calls were from hospitals, with al-
most one third of these calls coming
from labor and delivery units. Approxi-
mately 15% of all calls were from rural
areas.

Most calls (59.5%) related to pregnant
patients (Table 2). Approximately 5% of
calls pertained to patients in labor at the
time of the call, with 28.6% of these pa-
tients in preterm labor (<37 weeks of
gestation). More than 42% of women
were diagnosed with HIV before this in-
dex pregnancy; only 3 women (1.1%) were
diagnosed during labor. The HIV
status was not yet determined in 16.5%
of pregnant women (because of pending
or ambiguous HIV test results). Most
discussions (52.2%) concerned patients ≥20 years of old; 5.6% of the discussions
concerned patients who were 13-19 years
old. The ethnicity of patients included
African American (31.2%), white
(17.5%), Latino/a (10.4%), Asian
(2.2%), other (5.5%), and unknown
(33.2%).

A narrative report of the consultation
was available for 100% of calls. The most
common topic of discussion was HIV
care in pregnancy (49.1%), particularly
the use of antiretroviral drug therapy
(42.1%; Table 3). Of calls about antiretro-
roviral therapy, 13.8% concerned
women who experienced antiretroviral
toxicity or who received potentially ter-
atogenic regimens, and 23.8% of the
calls concerned women with antiretrovi-
ral–drug–resistant HIV. Consultations
about HIV testing in pregnancy com-
prised 21.9% of calls and included ques-
tions about the interpretation of ambigu-
ous HIV test results and the use of rapid
testing. Intrapartum management was
discussed in 24.0% of calls; however,
most of these calls were received during the antepartum period. More than 29% of calls dealt with care of HIV-exposed infants, largely focusing on choice of postexposure prophylaxis regimen (19.5%) or HIV testing protocols (8.8%).

**COMMENT**

This analysis of calls to the Perinatal Hotline highlights the types of clinical questions raised by providers of perinatal HIV care in the United States. Callers most often requested help choosing or modifying antiretroviral drug regimens for their patients. Discussions frequently included antiretroviral side effects and toxicities in pregnancy and toxicity to the exposed fetus. Almost one quarter of the calls about antiretroviral drug use concerned HIV drug resistance. Because data guiding antiretroviral drug selection in the setting of maternal resistance are limited, these calls are some of the most challenging on the hotline. We anticipate an increase in calls about drug-resistant virus as the baseline prevalence of resistance increases in the general population of HIV-infected adults.11,12 The need for these urgent consultations is expected to increase with the expanding use of rapid HIV testing. HIV-infected women in labor who have not received antiretroviral therapy represent a perinatal emergency; transmission can be reduced significantly if the mother and infant receive immediate antiretroviral therapy.13-15 Labor and delivery units must be prepared to provide prompt perinatal HIV care around the clock. More than one quarter of calls about intrapartum patients concerned patients in preterm labor. These difficult situations require clinicians to balance the usual need to prolong gestation with the opposing need to hasten delivery once labor has started to minimize the risk of HIV transmission. Because few data exist to address these issues directly, management decisions are complex and are best made in conjunction with experts.

The most common topic about infant care was choice of postexposure prophylaxis, which can be particularly complex in the setting of maternal viral resistance or persistent viremia. Questions about infant testing usually focused on the type of HIV test (HIV DNA/RNA test vs HIV antibody test) and the timing of follow-up testing.

Many calls about HIV testing involved discordant HIV test results, especially when the screening enzyme-linked immunosorbent assay antibody test was positive and the confirmatory Western blot test was negative or indeterminate. This scenario is particularly common in pregnancy, which increases the number of false-positive HIV test results because of stimulated HLA antibody production.16 Callers have questions about which additional tests are necessary and whether to start antiretroviral treatment. The establishment of a firm diagnosis can take up to several weeks, so these decisions become particularly complex as a woman nears her due date. The revised CDC guidelines, which recommend HIV testing for all pregnant women,5 will likely increase the number of HIV tests performed during pregnancy, which may be accompanied by an increase in the number of discordant test results that require interpretation.

This study has some limitations. Callers to the Perinatal Hotline are providers who are familiar with the service and who requested consultation. Therefore, the types of callers and their patients may not be generalizable to all providers who care for HIV-infected pregnant women or their infants. Nevertheless, the topics that are discussed are likely to be reflective of the issues that providers face in a variety of settings. Demographic data are missing in some cases, the most notable instances of which are the number of HIV-positive patients in the caller’s panel and patient race.

This examination of calls to the Perinatal Hotline provides a first look at the consul-
tation needs of providers who care for HIV-infected pregnant women and HIV-exposed infants in the United States. The main source of guidance for US practitioners is the Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant Women Infected with HIV-1 for Maternal Health and for Reducing Perinatal HIV-1 Transmission in the United States,9 which are updated frequently and are available online and in print. Even providers familiar with these guidelines, however, may appreciate the opportunity to discuss their specific case with an expert. Access to 24-hour consultation can help ensure that state-of-the-art care is provided. In some regions, consultants are available locally and can assist in the treatment of these patients. However, remote consultation might be necessary and is sometimes available through academic or specialty care centers or regional telephone consultation services (such as the 24/7 Illinois Perinatal Hotline).17 Providers of care during labor and delivery may require prompt access to live consultation. This need will become more significant when rapid HIV testing becomes available more widely. The Perinatal Hotline offers around-the-clock consultation on the entire range of questions about perinatal HIV care and can serve as a resource for providers across the country.

REFERENCES