Rapid HIV Testing in Hospital Labor and Delivery

A Maricopa Integrated Health System
RWCA Title IV Initiative

A Nuts and Bolts Technical Assistance Manual for Implementing a Rapid HIV Testing Program in your Hospital Labor and Delivery Unit.

Developed by Maricopa Integrated Heath System’s RWCA Title IV Program, Phoenix Arizona.

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Rapid HIV Testing in Hospital Labor and Delivery


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1. CDC: Rapid HIV Antibody Testing During Labor and Delivery for Women of Unknown HIV Status.
2. CDC Releases Revised HIV Testing Recommendations for in Health-Care Settings.
4. MMR CE Activity re: Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings.
7. MIRIAD Study.
9. US Public Service Task Force Recommendations
Introduction
As a Ryan White Care Act Title IV grantee, Maricopa Integrated Health System (MIHS) is collaborating with Phoenix Children's Hospital (PCH) on a county initiative for implementing Rapid HIV Testing in Hospital Labor & Delivery departments.

The CDC, the American College of Obstetricians & Gynecologists, the Institute of Medicine, and the Public Health Service Task Force all recommend Rapid HIV testing for pregnant women with an undocumented HIV status. By identifying pregnant women with HIV, even late in the pregnancy, a treatment regimen can begin which will greatly reduce the risk of mother-to-child-transmissions (MTCT.) Without Anti-retroviral (ARV) treatment, the estimated MTCT rate is 25%. With ARV in labor, the MTCT rate is reduced to 9-13%.

MIHS and PCH are providing this Technical Assistance Manual free of charge to encourage all hospital labor & delivery departments to implement similar HIV rapid testing programs. We are also available for presentations and speaking engagements.

Thank you for taking this important step. We look forward to working with you.
**HIV/AIDS Statistics**

- Over 1,000,000 people are living with HIV/AIDs in the U.S.¹
- 27% of the new HIV infections are in women.²
- 79% of women with HIV are infected via heterosexual contact.³

**Mother-to-Child Transmission of HIV**

- 7,000 women with HIV give birth every year.
- Historically, 40% of women did not know their status before labor & delivery.
- The majority of Mother-to-Child Transmissions (MTCT) occurs near or during labor & delivery.
- In the majority of states (33), HIV testing is voluntary.⁷
- Mother-to-Child Transmission rates depend on the following:⁸
  - Without treatment → 25%
  - AZT given staring in prenatal care → 8%
  - Prenatal AZT with scheduled C-section → 2%
  - Antiretroviral (ARV) prophylaxis given to mothers during *labor* may reduce MCTC by as much as 42%!
- There were 90 U.S. *reported* cases of HIV in infants born to HIV-infected mothers in 2003, compared to 346 in 1994. This decline is largely due to antiretroviral treatment. The majority of cases (62) are among African-Americans.
- The following agencies have adopted HIV Rapid Testing during pregnancy as the standard of care:
  - The Center for Disease Control and Prevention,
  - The American College of Obstetricians and Gynecologists,
  - The Institute of Medicine, and
  - The U.S. Public Health Service Task Force.

**Cost-effectiveness of HIV Rapid Testing in Pregnant Women**

- Infected as infants, lifetime cost is: $200,000-$300,000
- Infected as adults, lifetime cost is: $370,000-$648,000
- Cost of an OraQuick Rapid Test: $13!

References- All statistics are from the Center for Disease Control and Prevention (CDC), unless otherwise noted.

More Facts, Figures, and References

From Henry J. Kaiser Foundation:
- 16 states have laws regarding HIV testing during pregnancy, AZ isn’t one of them

From PACTG 076 Study (1994)
- Treating patient (pre- & perinatally) & infant (post-partum) with AZT drops
  transmission rate to 8%
- AZT treatment combined with C-section drops transmission rate to 2%

From NY State Study (1998)
- Treating mother & infant only perinatally & post-partum reduces mother-to-child
  transmission rates to 10%
- Without treatment, transmission rate was 27%

From Food & Drug Administration (FDA), (2002 & 2004):
- OraQuick sensitivity with whole blood: 99.6%
- OraQuick specificity with whole blood: 100%

From the National Center for Health Statistics
- AIDS is the 5th leading cause of death of people age 25-44 in the U.S.
- AIDS is the 7th leading cause of death of people age 15-24 in the U.S.

From Mrus JM, Tsevat J. Cost Effectiveness of Interventions to Reduce Vertical HIV
Transmission from Pregnant Women Who Have Not Received Prenatal Care. Medical
- Cost of treating a person born with HIV: $185,000
- Based on life expectancy of 15 years

From the Third International AIDS Society Conference on HIV Pathogenesis and
Treatment (2005)
- Cost of treating a person in the U.S. for HIV who was diagnosed as an adult:
  $370,000-$648,000
- Life expectancy: 22.4-24.1 year
Background of Rapid HIV Testing in Labor & Delivery
Since the first case of pediatric HIV infection was documented in 1984, there have been tremendous medical and public health achievements in preventing mother-to-child transmission of HIV. When the recommended antiretroviral and obstetric interventions are used, a woman who knows of her HIV infection early in pregnancy now has a less than 2% chance of delivering an HIV-infected infant. Without intervention, this risk is approximately 25% in the United States. CDC’s revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings, released in 2006, further recommend that

- HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women;
- HIV screening should be offered after the patient is notified that testing will be performed unless the patient declines (opt-out screening);
- Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing;
- Repeat screening in the third-trimester should be conducted in certain jurisdictions with elevated rates of HIV infection among pregnant women.

The Problems

Before effective therapy, nearly 26% of infants of HIV-infected women were born with HIV infection. Through the use of HIV screening and appropriate medical care, the number of infants born with HIV infection decreased from a high of 1,650 HIV-infected infants born in 1991 to estimated 144–236 infants born in 2002.
Preventive antiviral therapy is most effective when it is initiated early in pregnancy. However, starting antiretroviral treatment during labor and delivery, or even providing it to the newborn within hours after birth can reduce mother-to-child transmission by half (Wade 1998; Kourtis 2001; Guay 1999). To maximize the benefit, it is important to obtain HIV test results for women in labor quickly in order to start antiretroviral therapy as soon as possible.

For those women whose HIV status is unknown at labor, CDC recommends routine, rapid HIV testing. When the mother’s HIV status is unknown prior to the onset of labor and rapid HIV testing is not done during labor, CDC recommends rapid HIV testing of the infant immediately post-partum, so that antiretroviral prophylaxis can be offered to HIV-exposed infants. When intervention begins at the intrapartum (during labor or delivery) or neonatal periods, 9% to 13% HIV transmission rates are achievable based on clinical trial and observational data. This represents a 50% reduction in HIV transmission from rates that would be expected without intervention.

Rapid HIV tests that can be performed right in labor and delivery can yield results in less than 45 minutes. Such timely knowledge of the mother’s HIV status also provides opportunities for other interventions that reduce transmission, such as elective cesarean section, avoiding artificial rupture of membranes, and avoiding breastfeeding (U.S. 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. http://www.aidsinfo.nih.gov/guidelines/). CDC’s Mother-Infant Rapid Intervention at Delivery (MIRIAD) study proved rapid testing is feasible and effective.
Streamlined Protocols and Procedures
Streamlined Protocol for Rapid HIV Testing in Hospital Labor & Delivery

1. When a patient presents to labor and delivery and may possibly deliver, the first provider to see the patient (physician, certified nurse midwife, or nurse) will ascertain if the patient has previously had a test of HIV infection during the current pregnancy.

2. If the patient has had a previous test, the result is available and negative, and is not at risk for contracting HIV during the pregnancy, the patient will not be offered any further HIV testing.

3. If the patient has not had an HIV test during the current pregnancy, the result is not available, or if the patient is at risk for contracting HIV since the last HIV test, the physician will offer the patient a rapid test for HIV infection while in labor. The provider will counsel the patient:
   a. The test is being offered since she does not have a result available or is at risk of contracting HIV since the last negative test
   b. That if she were positive, there would be a risk that her baby could acquire the infection during delivery
   c. That if she had an HIV infection the risk of her baby becoming infected could be reduced if she were to receive medication while in labor
   d. That the test is a preliminary result and that confirmatory testing will also be done if the preliminary test is positive
   e. That she will be treated with antiretroviral therapy if the preliminary test is positive to reduce the risk that her baby is affected during delivery
   f. That her baby will also receive antiretroviral therapy until such time as definitive HIV tests are available

4. The patient will complete the consent form for HIV testing. The attending physician will assess the patient for HIV risk factors.

5. The test will be ordered as “Rapid HIV Test.”

6. The blood will be drawn by the nurse in a purple top and labeled appropriately

7. The nurse will call the lab and alert them that the specimen is coming.

8. The nurse will transport the specimen to the lab the fastest way possible, either tubing it down or hand-delivering the specimen with a hard copy of the order attached which will indicate that the patient signed the consent form.

9. The lab will call the charge nurse with the result as soon as it is available, no longer than 1 hour after receiving the specimen. If negative, the charge nurse will deliver the result. If positive, the attending physician will inform the patient.

10. A patient who is positive will be treated with Zidovudine (AZT) immediately at a loading dose of 2 mg/kg for 1 hour and a maintained dose of 1 mg/kg/hr for the duration of her labor.

11. The nursery and social worker will be notified that the mother has had a preliminary positive test.

Maricopa Medical Center
Guidelines for Rapid HIV Testing
In Labor andDelivery at Maricopa Medical Center

Introduction

All pregnant women should be screened for HIV during prenatal care. Unfortunately, there are women who cannot or do not seek prenatal treatment or refuse the HIV test when it is offered. The Center for Disease Control and Prevention (CDC) recommends rapid HIV testing from women in Labor and Delivery (L&D) units who do not have a documented HIV test in their prenatal history or who are at high-risk for contracting HIV during their pregnancy. This provides an opportunity to prevent MTCT of HIV when ARV prophylaxis is administered. The OraQuick Rapid HIV Test is an excellent mechanism to determine the HIV status of a woman in labor. It supplies accurate results in as little as 20 minutes with turnaround times from lab to L & D under 45 minutes.

Process for Rapid HIV Testing In L&D

I. Testing for women without a documented HIV test

When a woman presents in L&D in active or imminent labor, she will be assessed to see if a rapid HIV test is appropriate. At admission, the admitting resident will review the patient’s prenatal history. If there is no documented HIV test on file, the admitting resident will provide pre-test counseling and assist the patient to complete the required consent form for the HIV test so that the test can be performed as soon as possible. The CDC recommends that pre-testing counseling include the following components:

1. HIV can be transmitted from mother to infant during pregnancy, labor and delivery, and through breastfeeding. If the mother has HIV there are interventions that can be performed during labor and delivery to reduce the chance that the baby will become infected.
2. A rapid test can be performed to screen her for HIV.
3. If the test is negative, she probably does not have HIV unless she was recently infected. If the test is positive, a second test will be performed to confirm the result.
4. If the preliminary OraQuick test is positive, there are medications that can be given to her and her baby to reduce the risk of the baby becoming infected.

Confidentiality must be maintained throughout this process. When evaluating a patient’s need for testing and discussing one’s status and risk factors, it is important to do in a setting where there is privacy so the patient feels safe and can honestly share her history. An interpreter rather than a family member should be used if one is needed.
II. Assess for HIV risk during the pregnancy for women with a prenatal HIV-negative test

When the admitting resident is taking the patient’s medical history, he/she will assess for HIV risk factors during the pregnancy. If the patient has a negative HIV result in her file but has engaged in a high-risk behavior, the physician will recommend that a rapid test be performed. High-risk behaviors for HIV are:

- Multiple sex partners
- Sex w/ a man who has sex with men (MSM)
- Sex w/ a person who has HIV
- Having sex in exchange for drugs or money
- IV drug use or sex with an IV drug user
- Having an STD infection during the pregnancy
- Sexual contact with anyone while under the influence of illegal drugs or sex with someone who uses illegal drugs

If the patient is considered high-risk for HIV, the physician will perform pre-test counseling, have the client complete the consent form, and order the test stat.

III. OraQuick Rapid Test performed to determine HIV status

OraQuick Rapid HIV Tests will only be available for patients in L&D. No other departments will have access to this technology, therefore the OraQuick test will not be on the STAR system. The nurse will draw blood for the rapid test in a purple top. The specimen will be delivered to the lab via the fastest means possible, either tubing it to the lab or carrying it down by hand. A hard copy of the order, which needs to indicate that the patient has signed the consent form, will need to be attached to the specimen. The nurse will also call the lab to inform them that the specimen is coming. The lab will complete the rapid test and will contact the charge nurse with the results in less than an hour after receiving the specimen.

If the OraQuick test is preliminary positive, the MMC lab will immediately call MCDPH HIV Counseling and Testing. Two additional vials of blood will need to be drawn and sent to the ADHS lab for a confirmatory test and a complementary Hepatitis C test. At the beginning of this program an HIV counselor from MCDPH will be sent ASAP to meet with the patient postpartum until the MMC social workers can be trained to provide post-test counseling and referrals.

IV. Delivering the results to the patient

It is critical to maintain patient confidentiality when delivering the results. Only the patient should be in the room, unless she has specifically requested that someone else be there.
a. **Negative results**

If the result is negative, the charge nurse may inform the patient. A negative result means that no further testing is needed, unless the patient was very recently exposed to HIV. In that situation, the patient should be referred to MCDPH or the patient’s doctor for future testing.

b. **Positive results**

If the MMC lab informs the charge nurse that the rapid test result is positive, the nurse should inform the attending physician ASAP so the patient can be offered ARV for herself and the baby. The attending physician will inform the patient that the rapid test result was preliminary positive and that confirmatory testing is being sent out to the lab (e.g. state or reference lab.) Along with the confirmatory test, the ADHS will also test the patient for hepatitis C, free of charge. The lab will send two yellow tops to ADHS lab with forms provided by MCDPH for these tests. The physician will also inform the patient that specially trained personnel will be coming to meet with her to provide additional counseling and referrals.

V. **Peripartum management of patients with a positive rapid test**

The physician will recommend ARV for any patient in labor who tests positive using a rapid test and will refrain from unnecessary procedures that put the baby at increased risk of contracting HIV. These procedures include fetal scalp monitoring, internal labor monitoring, internal fetal monitoring, and prolonged rupture of membranes. The nursery will also be notified of the positive result so they can provide appropriate care when the baby is born.

VI. **Postpartum management of patients with a positive rapid test**

a. **Mother**

It is critical that any patient with a preliminary positive rapid HIV test receive appropriate referrals and a follow-up appointment to receive the results of the confirmatory test. Until MMC social workers are trained in HIV post-test counseling, MCDPH will send an HIV Counselor to meet with any patients with positive test results to provide support and referrals, answer questions, gather additional information required by ADHS, and setup a follow-up appointment. Because ADHS needs specific information on each positive patient, the HIV Counselor will be given access to the patient’s chart. When the MMC social workers become responsible for these tasks, they will submit the necessary information and documentation to MCDPH.
b. Infant

The CDC recommends that infants born to women with a positive HIV rapid test should receive ARV within 8-12 hours of birth. All infants should be referred to Phoenix Children’s Hospital for follow-up care where they will be followed for HIV testing until 18 months of age. Phoenix Children’s Hospital, following the Public Health Service Task Force recommendations, prefers that all infants born to mothers with HIV to receive a birth HIV DNA PCR Qualitative test as a baseline for future testing.

VII. Reporting confirmatory results

Because MCDPH is paying for the OraQuick HIV test kits, they will be sent the confirmatory results. When MCDPH receives the confirmatory result, they will submit a copy of it to MMC lab for the client’s file. MCDPH is also required to submit a copy of the confirmatory results to ADHS for all preliminary positives identified with an OraQuick rapid test.

The patient will have a follow-up appointment with an HIV Counselor at MCDPH to receive the results of the confirmatory test. At that time, the HIV Counselor will inquire about the patient’s and infant’s care to ensure that they are receiving the services they need and give additional referrals if needed.

References


Purpose:
To provide rapid HIV testing for women in Labor and Delivery (L&D) who do not have a documented HIV test in their prenatal history or who are at high-risk for contracting HIV during their pregnancy. This provides an opportunity to prevent MTCT of HIV when ARV prophylaxis is administered.

Definitions:
HIV- Human Immune Deficiency Virus
MTCT- Maternal to child transmission
ARV- Antiretroviral

Policy:
Patients presenting to the Labor and Delivery Unit in active or imminent labor, who do not have a documented HIV test in their prenatal history will receive pre HIV consent counseling and will have a rapid HIV test ordered upon receiving their consent. Patients with a negative HIV test in pregnancy but at high risk for contracting HIV in their pregnancy will receive pre HIV consent counseling and will have a rapid HIV test ordered upon their consent at the discretion of the admitting physician.
Procedure:

1. When a patient presents to labor and delivery and may possibly deliver, the first provider to see the patient (physician, certified nurse midwife, or nurse) will ascertain if the patient has previously had a test for HIV infection during the current pregnancy.
2. If the patient has had a previous test and the result is available and the result is negative, a rapid HIV test will not be ordered.
3. A rapid HIV test may be ordered at the discretion of the LIP on patients with negative HIV tests in pregnancy that are assessed to be at high risk for contracting HIV in their pregnancy.
4. If the patient has not had an HIV test during the current pregnancy or the result is not available, the LIP will offer the patient a rapid test for HIV infection while in labor.
5. The LIP will provide pre consent counseling to include the following:
   a. The test is being offered since she does not have a result available.
   b. If she were positive, there would be a risk that her fetus could acquire HIV infection during delivery.
   c. If she had HIV infection the risk of her fetus becoming infected could be reduced if she were to receive medication while in labor.
   d. The test is a preliminary result and that definitive testing will also be done if the preliminary test is positive.
   e. She will be treated with antiretroviral therapy if her preliminary test is positive to reduce the risk that her baby is affected during delivery.
   f. Her baby will also receive antiretroviral therapy until such time as definitive HIV tests results are available.
6. The test will be ordered as “Rapid HIV test”
7. The blood will be drawn by the nurse in a purple top tube and labeled appropriately. The specimen will be sent with the hard copy lab slip. The slip will specify that consent has been obtained.
8. The nurse will assure that the lab is called to alert them that the specimen is arriving.
9. The specimen will be transported to the lab by L&D personnel when possible, when personnel is not available to transport the specimen the specimen will be sent to the lab via tube system and lab will be notified. Transportation personnel will not be used.
10. The lab will call the result as soon as it is available to the charge nurse on the L&D unit.
11. The patient will be notified of negative results by the nurse or LIP in charge of their care.
12. If the rapid HIV is positive, the charge nurse will immediately notify the attending physician. The attending physician will inform the patient, assuring that confidentiality is maintained, and will order an ARV- Zidovudine at a loading dose of 2mg/kg for 1 hour and a maintenance dose of 1mg/kg/hour until the completion of delivery.
13. The nursery and social services will be notified of the mother’s positive HIV status.
References:


Consult the *OraQuick* Rapid HIV-1 Antibody Test Manual for detailed instructions and procedures. The information listed below provides complete parameters necessary for performing this test, specific to this institution, not included in the manufacturer’s manual.

**PURPOSE**

To provide the Medical Technology staff with the procedure for performing and resulting Rapid HIV testing.

**PRINCIPLE**

Please consult the *OraQuick* Rapid HIV-1 Antibody Test Manual for a detailed description of the principles of this test.

**BLOOD COLLECTION AND STORAGE**

1. The test is approved by the FDA for use with whole blood specimens only. EDTA is the preferred anticoagulant.
2. There are no special instructions for collection.
3. Test must be performed within 30 hrs of collection whether refrigerated (2° - 8° C) or not.
4. Specimen must be at room temperature for testing.

**CALIBRATION**

N/A
QUALITY CONTROL

External controls do not need to be performed every day. The Internal Procedural Control (IPC) is a built-in control that demonstrates assay validity and is used to meet the daily QC requirements. The first test performed for the day must have the IPC recorded in a log made visible to all testing personnel. If no tests have been requested in the last 24-hour period, the IPC must be recorded with the next test received.

External quality controls consisting of a NEGATIVE and a POSITIVE HIV-1 will be run under the following circumstances:

- Every four weeks by the day shift staff.
- If the temperature of the test kit storage/testing area falls outside of 15°-27° C.
- Whenever a new box of test kits is opened, regardless of lot number.
- Whenever a test result is invalid on repeat.
- Each new trainee performing testing on patient specimens.

This protocol follows the Fixed Limit Guideline set in CLIA '88. If any control is not acceptable, refer to the Out-of-Range Flowchart/Policy that is posted at all workstations or in the Chemistry Policy Manual. Controls should be refrigerated immediately after use.

For sensitivity and specificity studies performed on this assay, please see the OraQuick Rapid HIV-1 Antibody Test Manual for a detailed explanation.

TESTING PROCEDURE

Materials needed but not provided:
- Protective Face Shield
- Absorbent Bench Protector
- Timer

See the OraQuick Rapid HIV-1 Antibody Package Insert for step-by-step instructions of testing procedure.

REPORTING RESULTS

1. Results are reported out as NON-REACTIVE, REACTIVE, or INVALID.

   Reference Range = NON-REACTIVE

2. All results (whether NON-REACTIVE or REACTIVE) must be called to the charge nurse of the floor where patient is located. Do not give results to a unit clerk. Enter the charge nurse’s name as a footnote in the computer using the “CALL” template.
3. REACTIVE results will automatically reflex to HIV-1 Western Blot (send out) and HIV EIA tests for confirmation. Immunochemistry must be notified in this case to continue test processing.

4. **All** REACTIVE results must also be called to an HIV counselor (MARICOPA COUNTY PUBLIC HEALTH) at office phone # 602 506 5038 or cell phone # 602 826 1155. If after hours, leave a message on the counselor’s cell phone. Please provide the following information when leaving a voice message:
   - Let them know result is REACTIVE and will be sent out for Western Blot.
   - Give patient name, PID #, and collection date and time.

   Record the time and date voice mail was left in logbook.

**MANUAL CALCULATIONS**

None.

**PROCEDURE NOTES**

1. Store reagent kits unopened at room temperature. Kit must be at room temperature for testing.

2. To print a work list use RAP under the RQW program in Cerner.

3. This test is considered a **STAT** test regardless of order priority.

4. This test can only be ordered in the lab. The ordering pneumonic is **RAPID HIV**. Specimen should arrive from the floor with a requisition form ordering RAPID HIV and stating that the HIV Consent was signed.

5. The HIV Consent Form must be signed by the patient before the test can be performed. If there is no designation that the consent was signed, call the floor. Verbal confirmation that the consent was signed is acceptable, but document the initials of the person giving the confirmation.

6. Nurses are allowed to add-on tests, but must have the PAS # of attending physician and the consent form must be signed. Document the nurse’s initials in the logbook.

7. **Only** physicians may call the lab requesting HIV results. They must state their name and PAS # and this information should be entered in the logbook along with the patient’s name and PID #.

8. HIV results must NEVER be faxed. The results may be expedited to a printer interfaced with Cerner however.

9. **IF THE HIV TEST IS POSITIVE, LAB PERSONNEL MUST CALL THE CHARGE NURSE/ATTENDING PHYSICIAN STAT SO THEY MAY INITIATE TREATMENT.**

10. Turn around time for this test is 1 hour from the time received in lab.

**COMPUTER ENTRY**

1. This procedure resides in the Bench section of Chemistry (Work Center 140 and Test Site 145).
2. Results may be entered using the **TSA** program. Select the correct response and press \[ENTER\] in the **INTERP** line.

3. If the result is acceptable and if the information is correct, further involvement is unnecessary and results may be verified.

**SERVICE COVERAGE**

Any problems with this system that are not be readily corrected should be referred to OraSure Technologies Customer Service at phone # 1 800 672 7873.

**LIMITATIONS**

Please see the *OraQuick Rapid HIV-1 Antibody Test Package Insert* for a complete list of limitations.

**REFERENCES**


**Yearly Review:**

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WORD-Chem SOP folder
HIV Testing Forms
EXHIBIT A. CONSENT FOR HIV-RELATED TESTING

Consent for HIV-related Testing

Information on HIV
The Human Immunodeficiency Virus (HIV) is the virus that causes Acquired Immunodeficiency Syndrome (AIDS). HIV is spread through the exchange of blood (including transfusion) or sexual fluids (semen and vaginal secretions) and sometimes through breast milk. HIV can be transmitted from mother to baby during pregnancy or childbirth.

HIV-related Testing
There are several laboratory tests for HIV. The most common is the antibody test, which is a blood test that detects antibodies produced by the body in response to infection with HIV. A positive antibody test consists of a repeatedly reactive (the same specimen testing positive twice) enzyme immunoassay (EIA) and a reactive Western blot or other confirmatory test. A positive antibody test means that an individual is infected with HIV; however, this does not always mean that the individual has AIDS. Research indicates that early and regular medical care is important to the health of an individual with HIV. Certain treatments are now available to treat HIV-associated illnesses.

A negative antibody test indicates that no detectable antibodies are present in the blood. An individual may not have antibodies because the individual is not infected with HIV or because detectable antibodies have not yet been made in response to infection. The production of these antibodies could take 3 months or longer. Therefore, in certain cases, an individual may be infected with HIV and yet test negative. Individuals with a history of HIV risk behaviors within the past 3 to 6 months should consider retesting.

Like any test, HIV-related testing is not accurate 100% of the time and may occasionally produce both false positive and false negative results.

Means to Reduce Risk for Contracting or Spreading HIV
Risk of contracting or spreading HIV can be reduced by avoiding or decreasing contact with blood and sexual fluids (sperm and vaginal secretions). Some methods of decreasing the risk of contracting or spreading HIV include abstaining from sexual intercourse, using methods that limit exposure to body fluids during intercourse (such as the proper use of condoms), not engaging in injecting drug use, not sharing needles, or using bleach and water to clean needles and syringes. The use of certain medications by an HIV-infected woman during pregnancy may reduce the chances of HIV transmission from mother to child.

Disclosure of Test Results
I understand that if the HIV test results are positive, the physician or facility representative conducting the test will make reasonable efforts to notify me of the results at the address or phone number I have provided, and will provide or arrange for counseling as required by Arizona state laws and regulations regarding (1) HIV, (2) AIDS, and (3) appropriate precautions to reduce the likelihood of transmission of the virus to others. I agree to assume all risks that may result if I cannot be contacted.

I understand that Arizona law and regulations require that if my test results are positive, they will be submitted to local and state health departments. Information received by these health departments may only be released: (1) if there is written authorization from the individual being tested, (2) for statistical purposes without individual identifying information, or (3) as otherwise required or allowed by law.

Disclosure of Test Results

Name:
Sex:
Race/Ethnicity:
Date of Birth:
Address:
Phone:

Identifying Information
I also understand that the physician or facility may report to the Arizona Department of Health Services identifiable 3rd parties such as a spouse or sex partner who may be at risk of contracting the virus if I do not release this information. Finally, I understand that the test results may be placed in a medical record kept by the facility or person administering the test and that persons involved in providing or paying for my health care may have access to that information.

Additional Sources of Information on HIV
Additional information regarding testing for HIV is available through your county health department and, in the Phoenix metropolitan area, (602) 234-2752, the Tucson metropolitan area, (520) 791-7676, or outside the Phoenix area, 1-800-334-1540. National Hotline: English, 1-800-342-2437; Spanish, 1-800-344-7432; TTY/TDD, 1-800-243-7012.

Consent
I have been given the opportunity to ask questions regarding this information and have had my questions answered to my satisfaction. I understand that this test can be performed anonymously at a public health agency. I also understand that I may withdraw my consent at any time before a blood sample is taken in order to conduct a test, and that I may be asked to put my decision to withdraw my consent in writing if I have signed this consent. I also understand that this is a voluntary test and that I have a right to refuse to be tested.

My signature below indicates that I have received and understand the information I have been given and voluntarily consent to and request HIV-related testing.

Patient/Subject Name (Printed)

Patient/Subject or Legal Representative Signature

Date

Witness

NOTICE
The Arizona Department of Health Services does not discriminate on the basis of disability in the administration of its programs and services as prescribed by Title II of the Americans with Disabilities Act of 1990 and Section 504 of the Rehabilitation Act of 1973. If you need this publication in an alternative format, please contact the ADHS Office of HIV/STD Services at (602) 364-3610 or 1-800-367-8939 (state TDD/TTY Relay).
Información sobre el VIH
El virus de Inmunodeficiencia Humana (VIH) es el virus que causa el Síndrome de Inmunodeficiencia Adquirida (SIDA). VIH se transmite a través del contacto con sangre (incluyendo la transfusión) o fluidos sexuales (semen y secreciones vaginales) y en algunas ocasiones a través de la leche materna. VIH puede ser transmitido de la madre al bebé durante el embarazo o al momento del parto.

Maneras de reducir el riesgo de infección o transmisión del VIH
El riesgo de contraer o transmitir el VIH se puede reducir al evitar contacto con la sangre y fluidos sexuales (semen y secreciones vaginales). Algunos métodos para disminuir el riesgo de infección o transmisión del VIH incluyen: abstinencia sexual, usar métodos que limitan el contacto de fluidos corporales durante las relaciones sexuales (como el uso correcto de condones), no usar drogas intravenosas, no compartir agujas, y usar "cloro" (blanqueador) y agua para limpiar las jeringas y las agujas. En mujeres infectadas con VIH, el uso de ciertos medicamentos durante el embarazo, puede reducir el riesgo de transmisión del VIH de madre a hijo.

El resultado de la prueba
Entiendo que si el resultado de la prueba del VIH es positivo, el doctor o el representante de la institución que hizo el examen va a hacer esfuerzos suficientes para notificarme del resultado a la dirección (domicilio) o al teléfono que he proporcionado y que me dará información, cumpliendo con los requisitos de la ley estatal de Arizona, sobre (1) el VIH, (2) el SIDA, y (3) las precauciones necesarias para reducir la posibilidad de transmisión del virus a otras personas. Estoy de acuerdo en asumir todos los riesgos que resultarán de no poder contactarme. Entiendo que la ley estatal de Arizona exige que si el resultado de mi prueba es positivo, éste se reportará a los departamentos de salud local y estatal. La información que estos departamentos reciben solamente puede ser revelada a otras personas: (1) si hay una autorización por escrito de la persona que se ha hecho la prueba, (2) por razones de estudios estadísticos sin revelar la identidad del individuo, o (3) por cualquier otra razón que la ley permita. También entiendo que el doctor o la institución puede reportar al Departamento de Salud del Estado de Arizona, la identidad de terceras personas como: los esposos(as) o los compañeros(as) sexuales que pueden estar en riesgo de contraer con el virus si decidó no darles esta información. por último, entiendo que el resultado de la prueba puede guardarse con el resto de mi información médica en la agencia o por la persona que hizo el examen; y que las personas encargadas de proveer o pagar por el cuidado de mi salud pueden tener acceso a esta información.

Otras fuentes de información sobre el VIH
Información adicional sobre el examen del VIH está disponible a través del departamento de salud de su condado. En el área metropolitana de Phoenix llame al (602) 234-2752, en el área metropolitana de Tucson (520) 791-7676, y en el resto de Arizona 1-800-334-1540. Líneas telefónicas a nivel nacional son: en inglés 1-800-344-2437; en español 1-800-344-7432. (TTY/TDD) Transmisión de voz 1-800-243-7012.

Consentimiento
Se me ha dado la oportunidad de hacer preguntas respecto a esta información y me han sido contestadas satisfactoriamente. Entiendo que este examen se puede hacer de forma anónima en una agencia de salud pública. También entiendo que puedo retirar mi consentimiento en cualquier momento antes de que me saquen la sangre para hacer la prueba y que me pueden pedir que ponga por escrito mi decisión de retirar mi consentimiento si ya había firmado este permiso. Entiendo también que este examen es voluntario y que tengo el derecho a negarme a que se me haga la prueba.

Mi firma indica que he recibido y he entendido la información que se me ha proporcionado y que voluntariamente autorizo y solicito la prueba del VIH.

Identifying Information/Datos de Identidad

Nombre:
Sexo:
Raza:
Fecha de nacimiento:
Dirección:
Teléfono:

Entiendo que el doctor o la institución puede reportar al Departamento de Salud del Estado de Arizona, la identidad de terceras personas como: los esposos(as) o los compañeros(as) sexuales que pueden estar en riesgo de contraer con el virus si decidio no darles esta información. Por último, entiendo que el resultado de la prueba puede guardarse con el resto de mi información médica en la agencia o por la persona que hizo el examen; y que las personas encargadas de proveer o pagar por el cuidado de mi salud pueden tener acceso a esta información.
1. Have you ever tested for HIV? When was your last negative test? __________________________
   a. Have you tested for HIV during this pregnancy? If so, when? __________________________
   b. Where was this test conducted? __________________________
      □ Doctor □ Maricopa County Dept. of Public Health
      □ Other: __________________________

2. Have you been sexually active with anyone other than the father of the baby during this pregnancy? If so, how many other partners? __________________________
   a. To your knowledge, is the father of the baby sexually active with anyone else? _________
   b. Have you or the father of the baby ever been sexually active with a man who has sex with other men? __________________________

3. Do you or any of your partners engage in sexual activity while under the influence of any illegal drugs or alcohol? __________________________
   If so, which substances? __________________________
   When was the last time? __________________________
   Are any of these drugs used intravenously? __________________________

4. Have you or any of your sexual partners ever had sex in exchange for money or drugs? _____

5. Have you ever had sex with someone who is HIV positive? If so, when? _________________

6. Have you ever been diagnosed with a STD (Sexually Transmitted Disease)? _______________
   If so, when? __________________________
   Which STD? __________________________
Identificación del Paciente

1. ¿Se ha hecho alguna vez una prueba del VIH? ¿Cuándo se hizo la última prueba con resultado negativo? ____________________________________________
a. ¿Se ha hecho una prueba del VIH durante este embarazo? De ser así, ¿Cuándo? ________________
b. ¿Dónde se realizó esta prueba? __________________________________________________
   □ Doctor □ Departamento de Salud Pública del Condado Maricopa □ Otro: ____________________________

2. ¿Ha tenido relaciones sexuales con alguien, además del padre del bebé, durante este embarazo? De ser así, ¿Con cuántas otras personas? ____________________________________________
a. Hasta donde usted sabe, ¿ha tenido el padre del bebé relaciones sexuales con alguien más? __
b. ¿Ha tenido usted o el padre del bebé relaciones sexuales con un hombre que tiene relaciones sexuales con otros hombres? ___________________________________________________

3. ¿Participa usted o (alguna de) su(s) pareja(s) en relaciones sexuales mientras se encuentra bajo la influencia de drogas ilegales o alcohol? ____________________________________________
   De ser así, ¿Qué sustancias? ____________________________________________________________
   ¿Cuándo fue la última vez? ____________________________________________________________
   ¿Es alguna de estas drogas usada de forma intravenosa?____________________________________

4. ¿Ha tenido usted o alguna de sus parejas sexuales relaciones sexuales a cambio de dinero o drogas? ____________________________________________________________

5. ¿Ha tenido alguna vez relaciones sexuales con alguien que es VIH positivo? De ser así, ¿cuándo? ____________________________________________________________

6. ¿Ha sido diagnosticada alguna vez con una ETS (Enfermedad de Transmisión Sexual)? _____
   De ser así, ¿cuándo? ____________________________________________________________
   ¿Cuál ETS? ____________________________________________________________

___________________________________    ______________________________________
Firma      Nombre en Letra Imprenta              Fecha
Opt-Out Approach
Routine Prenatal Testing
The Opt-Out Approach

Since the first case of pediatric HIV infection was documented in 1984, there have been tremendous medical and public health achievements in preventing mother-to-child transmission of HIV. A first step in prevention is knowledge of each pregnant woman’s HIV status, preferably early in her pregnancy. With this knowledge and with appropriate interventions, the risk of mother-to-child HIV transmission can be reduced from 25 percent to 2 percent or less.

Approximately 6,000 to 7,000 HIV-infected women gave birth in the United States in 2000, and an estimated 280 to 370 HIV-infected infants were born. An estimated 40 percent of the mothers of these HIV-infected infants had not been diagnosed with HIV before labor and delivery.

Prevention of perinatal HIV transmission depends on two factors: routine testing of pregnant women for HIV and the use of appropriate antiretroviral and obstetrical interventions, ideally begun during the pregnancy of a woman who is HIV-positive. The Centers for Disease Control and Prevention’s (CDC’s) “Revised Recommendations for HIV Screening of Pregnant Women” emphasize:

- Routine voluntary testing for all pregnant women,
- Simplification of the testing process,
- Flexibility in obtaining consent, and
- Exploration of reasons for refusal.

However, recent data show that, even with these guidelines in place, a large proportion of pregnant women in some states are untested.

**CDC Research**

In the November 15, 2002 *Morbidity and Mortality Weekly Report*, CDC published information on the most recent available prenatal HIV testing rates in the United States and Canada. The report looked at HIV prenatal testing rates associated with different testing approaches:

- **Opt-in**, in which each pregnant woman is provided with pre-HIV test counseling and must specifically consent to an HIV test, usually in writing.
- **Opt-out**, in which each pregnant woman is notified that an HIV test will be included in the standard battery of prenatal tests (e.g., tests performed on all pregnant women), and that she may refuse the HIV test.

Among eight states using the opt-in approach where data were collected from medical records from 1998-1999, testing rates ranged from 25 to 69 percent. Population-based data from Canada showed testing rates in three opt-in provinces of 54 to 83 percent. In contrast, medical record data from Tennessee, which uses an opt-out approach, indicated a testing rate of 85 percent. Canadian data from provinces using opt-out approaches showed a 98 percent testing rate in Alberta and a 94 percent testing rate in Newfoundland and Labrador.

**A Closer Look**

The opt-out testing approach agrees with CDC’s current voluntary prenatal testing guidelines. It is expected to substantially increase testing rates among pregnant women, increase the proportion of HIV-infected women who are offered appropriate interventions, reduce perinatal HIV transmission, and improve the health of HIV-infected women who become pregnant.

Data indicate that women are more likely to accept testing when it is offered and recommended by their prenatal care providers. But some providers find requirements for extensive pre-test counseling and consent documentation to be barriers to offering the test. The opt-out approach is designed to reduce...
those barriers while preserving the voluntary nature of testing and increasing the opportunity for all pregnant women to have HIV screening.

**Implementing Opt-Out**

Among practices and recommendations for routine prenatal HIV testing or opt-out, the simplest approach is to notify all pregnant women that an HIV test is performed as part of the standard battery of prenatal tests, and that they can refuse this test. As part of this approach, CDC recommends that pregnant women be provided information on prevention of perinatal HIV transmission and treatment of maternal HIV.

Among practices and recommendations for test documentation, the simplest approach requires documentation of refusal in the medical chart. Another approach might include documentation of the woman’s written consent for routine prenatal testing including HIV screening, and, if she refuses HIV testing, documentation of her refusal.

**Rapid HIV Testing in Labor and Delivery**

Early identification of HIV infection clearly affords the best opportunity for perinatal HIV prevention. Even when intervention does not begin until the intrapartum or neonatal periods, transmission rates of 9 to 13 percent have been achieved.

CDC recommends routine, rapid HIV testing, with patient notification and right of refusal for women who arrive at labor and delivery without a documented prenatal HIV test. Rapid HIV test kits have been approved by the U.S. Food and Drug Administration and can be used at delivery. When rapid tests are positive, antiretroviral interventions can be offered to the mother during the intrapartum period, and to her infant based on the preliminary results. Confirmatory testing should occur as soon as possible.

For more detailed information on the “Revised Recommendations for HIV Screening of Pregnant Women,” please refer to *Morbidity and Mortality Weekly Report (MMWR)* of November 9, 2001, at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a2.htm or request a copy from the National Prevention Information Network at (800) 458-5231.
HIV Rapid Testing in L&D
A Clinician’s Guide with “Scripts”

Eligibility

- Women in labor without a documented HIV test result in their records or with no history of prenatal care
- Women in labor who had a documented HIV test but who have been at risk of contracting HIV during the current pregnancy
- HIV test results are confidential. The law protects people with HIV from discrimination.

Pre-test Counseling

Scenario: No documented HIV test in the prenatal record
Script:

- “It is important for you and your baby that we offer you a “rapid” HIV test. HIV is the virus that causes AIDS. HIV can be spread through unprotected sex, therefore all pregnant women need to be tested.
- This test gives accurate results quickly.
- It is voluntary and your consent is required before we can do the test.
- If you have HIV, we can give you medications that can reduce the chance of you giving it to your baby. Your baby will also receive medication after birth.
- Without treatment the chance of your baby being infected is 25%. With treatment, the chance drops by more than half.”

Scenario: Documented negative HIV test result in the prenatal record
Script:

- “You had an HIV test during your pregnancy, which was negative. We want to see if there’s any reason to test you again. It can take up to 3 months after someone is infected to detect that they’ve been infected with HIV.”

Instead of asking these questions, tell the patient the ways in which HIV can be transmitted, let them know that if any of these apply to them they should be retested, but don’t require them to tell you which ones apply or how they apply. (There may be fear that their baby will be taken from them, or they may get in trouble if they actually admit to these specifically.) Offer the test.

Script:

- “If any of the following situations applies to you, we should re-test you. If you do have HIV, there are medications we can give you and your baby to reduce the risk of the baby being infected too. Some of these questions may be very personal and seem invasive, but we ask everyone because we want every baby to be healthy.
  o Have you been sexually active with anyone other than the baby’s father during the pregnancy?
  o Has the baby’s father had other partners during the pregnancy?
  o Have you or your partner(s) been sexually active while under the influence of drugs or alcohol? Have you or your partner(s) used any intravenous drugs?”
Have you or your partners exchanged sex for drugs or money?
Have you ever been diagnosed with a sexually transmitted infection?”

Then:
“HIV can be transmitted through unprotected sex or through sharing needles or other injection equipment. If you or your partner have had sex with other partners or have used injection drugs since your last HIV test, then another HIV test would be necessary to give you and your baby the best care.”

If the patient answers “yes” to any of these questions, a rapid test is recommended. If the patient declines the test, recommend that she have another test completed during her post-partum visit.

Post-Test Counseling

If the HIV rapid test result is negative:
Script:
• “No further testing is needed at this time. It most likely means that you do not have HIV. However, this test will not show a recent infection.
• It is OK to breast feed your baby.”

If the HIV rapid result is preliminary positive:
Script:
• “You may be infected with HIV which means your baby may have been exposed to HIV.
• The test is a screening test and it is not perfect. We always do a second test to confirm positive rapid tests.
• It is best to start treatment to reduce the chance of you giving HIV to your baby while we wait for the confirmatory result. We need your permission to start the medication for this treatment.
• After your baby is born, he/she will take medication too. There are no serious side effects for you or your baby.
• You should not breast feed.”

If the confirmatory test is negative:
Script:
• “Your baby will immediately be taken off the medication that was started.
• Your doctor will tell you if it’s OK to breast-feed.”

If the confirmatory test is positive
Script:
• “Your baby will continue to take the medication that was started.
• Your baby will need more testing for HIV infection.
• You will be referred to a health care provider who will take care of your baby’s medical needs. This health care provider specializes in working with babies exposed to HIV. The first time they will see you will be when your child is two weeks
old. They will give you more information on the medication and testing at that time. Do not stop medication unless instructed to do so by this physician.

- You will be referred to a physician for your ongoing medical care. You will also be referred for other follow-up such as case management or partner counseling and referral services. A staff member from the County Health Department will be contacting you to discuss other referrals and information with you.
- Also, your HIV test results are confidential. The law protects people with HIV from discrimination.”
Rapid HIV Test Information
Rapid HIV Test Kits Comparison Grid

The U.S. Food and Drug Administration has approved 4 rapid tests for use in the United States (Table 1). Federal regulations under the Clinical Laboratory Improvement Amendments (CLIA) program categorize tests as waived, moderate complexity, or high complexity. Two rapid tests are approved as CLIA-waived tests, meaning that they may be done at the point of care after appropriate staff training and with procedures in place to insure quality control. These tests use whole blood or oral fluid and require a few simple steps to perform. Other rapid tests are "nonwaived" tests and must be performed in laboratories. Results for rapid tests done at the point of care are available in less than 30 minutes; results for those done in a laboratory should be available within 1 hour.

Table 1. FDA-Approved Rapid HIV Antibody Screening Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Specimen Type</th>
<th>CLIA Category</th>
<th>Sensitivity (95% CI*)</th>
<th>Specificity (95% CI)</th>
<th>Manufacturer</th>
<th>Approved for HIV-2 Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OraQuick Advance Rapid HIV-1/2 Antibody Test</strong></td>
<td>Whole blood (finger stick or venipuncture)</td>
<td>Waived</td>
<td>99.6% (98.5-99.9)</td>
<td>100% (99.7-100)</td>
<td>OraSure Technologies <a href="http://www.orasure.com">www.orasure.com</a></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Oral fluid</td>
<td>Waived</td>
<td>99.3% (98.4-99.7)</td>
<td>99.8% (99.6-99.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>Moderate complexity</td>
<td>99.6% (98.9-99.8)</td>
<td>99.9% (99.6-99.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uni-Gold Recombigen HIV</strong></td>
<td>Whole blood (finger stick or venipuncture)</td>
<td>Waived</td>
<td>100% (99.5-100)</td>
<td>99.7% (99.0-100)</td>
<td>Trinity Biotech <a href="http://www.unigoldhiv.com">www.unigoldhiv.com</a></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Serum/plasma</td>
<td>Moderate complexity</td>
<td>100% (99.5-100)</td>
<td>99.8% (99.3-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>Moderate complexity</td>
<td>99.8% (99.2-100)</td>
<td>99.1% (98.8-99.4)</td>
<td>MedMira <a href="http://www.medmira.com">www.medmira.com</a></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>Moderate complexity</td>
<td>99.8% (99.0-100)</td>
<td>98.6% (98.4-98.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reveal G2</strong></td>
<td>Serum/plasma</td>
<td>Moderate complexity</td>
<td>100% (99.9-100)</td>
<td>99.9% (99.8-100)</td>
<td>BioRad Laboratories <a href="http://www.biorad.com">www.biorad.com</a></td>
<td>Yes, differentiates HIV-1 from HIV-2</td>
</tr>
<tr>
<td></td>
<td>HIV-2</td>
<td>Moderate complexity</td>
<td>100% (99.7-100)</td>
<td>99.9% (99.8-100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interpreting Rapid Test Results

All of the rapid tests are highly sensitive and specific. The negative predictive value of all rapid HIV tests is close to 100%. This means that a client who receives a negative rapid test result is almost assuredly not infected, barring recent exposures (sexual contact or needle sharing with an infected person within 3 months). A client with a history of recent HIV risk behaviors or possible exposures should repeat the HIV test in the near future because it may take up to 3 months for HIV antibodies to be detectable after infection with HIV.

The positive predictive value of a single positive rapid HIV test depends on the specificity of the test and the HIV prevalence in the community. Given the high specificity of the rapid tests (Table 1), this means that if the rapid test result is positive, the likelihood that a client is truly HIV infected depends on the local HIV prevalence. In a population with a high HIV prevalence, a positive rapid test result is likely to be a true positive, but in a population with a low HIV prevalence, that result may be a false positive. For this reason, every positive rapid HIV test is considered a preliminary result and must be confirmed by either Western blot or immunofluorescence assay (IFA).
# FDA-Approved Rapid HIV Antibody Screening Tests – Purchasing Details

March 3, 2005

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Price Per Device*</th>
<th>External Controls</th>
<th># of Tests per Case</th>
<th>Catalog numbers</th>
<th>Storage Temperature</th>
<th>Operating Temperature</th>
<th>Shelf life of Test**</th>
<th>Shelf Life of Control**</th>
<th>Total Time Required to Conduct Test***</th>
<th>Window Period for Result Validity****</th>
</tr>
</thead>
<tbody>
<tr>
<td>OraQuick Rapid HIV-1 Antibody Test</td>
<td>$14.50</td>
<td>Sold Separately ($20)</td>
<td>25 or 100</td>
<td>#1001-0052 (25 tests) #1001-0051 (100 tests) #1001-0049 (controls)</td>
<td>2-27°C (tests)</td>
<td>15-27°C</td>
<td>8 months</td>
<td>8 months</td>
<td>&lt;5 minutes</td>
<td>20-40 min</td>
</tr>
<tr>
<td>OraQuick ADVANCE Rapid HIV-1/2 Antibody Test</td>
<td>$17.50</td>
<td>Sold Separately ($25)</td>
<td>25 or 100</td>
<td>#1001-0079 (25 tests) #1001-0076 (100 tests) #1001-0077 (controls)</td>
<td>2-27°C (tests)</td>
<td>15-37°C</td>
<td>8 months</td>
<td>8 months</td>
<td>&lt;5 minutes</td>
<td>20-40 min</td>
</tr>
<tr>
<td>Uni-Gold Recombigen HIV</td>
<td>$15.75</td>
<td>Sold Separately ($26.25)</td>
<td>20</td>
<td>#1206503 (tests) #1206630 (controls)</td>
<td>2-27 °C (tests)</td>
<td>15-27°C</td>
<td>12 months</td>
<td>12 months</td>
<td>&lt;5 minutes</td>
<td>10-12 min</td>
</tr>
<tr>
<td>Reveal G-2 Rapid HIV-1 Antibody Test</td>
<td>$14.00</td>
<td>Included</td>
<td>20 or 60</td>
<td>B1057-6 (20 test kits) B1057-7 (60 test kits)</td>
<td>2-30°C (tests)</td>
<td>15-27°C</td>
<td>12 months</td>
<td>12 months</td>
<td>3-6 minutes</td>
<td>Result must be read immediately</td>
</tr>
<tr>
<td>MultiSpot Rapid HIV-1/HIV-2 Rapid Test</td>
<td>$25.00</td>
<td>Included</td>
<td>50</td>
<td>#72269 (test kits)</td>
<td>2-8 °C Or 20-30 °C</td>
<td>20-30°C</td>
<td>6-7 months</td>
<td>6-7 months</td>
<td>10-15 minutes</td>
<td>Can be read immediately or anytime up to 24 hours</td>
</tr>
</tbody>
</table>

*Actual price may vary by purchasing agreements with manufacturers

** From date of manufacture, unless otherwise noted

***First time listed is estimated time required to set up test. The second time is the required wait time before reading results. Times listed exclude time needed to draw/obtain sample

****As measured from last step of testing process

Note. Trade names are for identification purposes only and do not imply endorsement.

This information was compiled from package inserts and direct calls to manufacturers.
A Rapid Review of Rapid HIV Antibody Tests

Jeffrey L. Greenwald, MD, Gale R. Burstein, MD, MPH, FAAP, Jonathan Pincus, MD, and Bernard Branson, MD

Introduction

Despite ongoing prevention and education efforts, an estimated 40,000 new HIV infections have occurred annually in the United States since the early 1990s. Of the estimated 1,039,000 to 1,185,000 persons living with HIV, approximately 252,000 to 312,000 (25%) persons are unaware they are infected [1]. Available evidence suggests that many new infections are caused by persons unaware of their HIV infection [2,3].

HIV Testing

Many persons with HIV do not get tested until late in their infection. Approximately 40% to 50% of patients with HIV infection are diagnosed with AIDS within 1 year of first testing HIV-positive [2,4-6].

Many persons who are tested do not return to learn their test results. The National Health Interview Survey found that 12.5% of persons tested in 1994 and 13.3% in 1995 did not receive their results [7], and the Centers for Disease Control and Prevention (CDC) estimates that in 2000, 31% of patients who tested HIV-positive at public-sector testing sites did not return to receive their results [8].

To reduce barriers to early diagnosis of HIV infection and increase access to treatment and prevention services, the CDC announced a new initiative, "Advancing HIV Prevention: New Strategies for a Changing Epidemic" (AHP) [8]. This multifaceted program stresses the importance of routinely offering HIV testing as part of the medical visit and expands on the 1993 recommendations for testing inpatients and outpatients in acute-care hospital settings [9]. Additionally, AHP stresses the importance of using rapid HIV tests to facilitate access to early diagnosis in high prevalence areas, for high-risk individuals, and for women during labor and delivery who have not previously been tested and in nontraditional testing settings.

Rapid HIV tests can play an important role in HIV prevention activities and expand access to testing in both clinical and nonclinical settings. They can help overcome some of the barriers to early diagnosis and improve linkage to care of infected persons. This paper will review the operating and performance characteristics, quality assurance (QA) and laboratory requirements for currently available rapid HIV tests, and counseling implications.

The Tests

Four rapid HIV tests have been approved by the US Food and Drug Administration (FDA): OraQuick® (and its newer version OraQuick® Advance) Rapid HIV-1/2 Antibody Test (OraSure Technologies, Inc., Bethlehem, PA); Reveal™ (and its newer version Reveal™ G2) Rapid HIV-1 Antibody Test (MedMira, Halifax, Nova Scotia); Uni-Gold Recombigen® HIV Test (Trinity BioTech, Bray, Ireland); and Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories, Redmond, WA). Like conventional HIV enzyme immunoassays (EIAs), rapid HIV tests are screening tests that require confirmation if reactive. Though each of these rapid HIV tests has unique characteristics, they share many common features, including how the tests work, the use of external controls, and other requirements such as the product information sheets that are provided to patients.
Table 1. US Food and Drug Administration–approved rapid HIV antibody tests for HIV-1 detection

<table>
<thead>
<tr>
<th>Rapid HIV test*</th>
<th>Specimen type</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>CLIA category</th>
</tr>
</thead>
<tbody>
<tr>
<td>OraQuick® Advance Rapid HIV-1/2 Antibody test</td>
<td>Oral fluid</td>
<td>99.3% (98.4-99.7)</td>
<td>99.8% (99.6-99.9)</td>
<td>Waived</td>
</tr>
<tr>
<td></td>
<td>Whole blood (fingerstick or venipuncture)</td>
<td>99.6% (98.5-99.9)</td>
<td>100% (99.7-100)</td>
<td>Waived</td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>99.6% (98.9-99.8)</td>
<td>99.9% (99.6-99.9)</td>
<td>Moderate complexity</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>99.8% (99.5-100)</td>
<td>99.1% (98.8-99.4)</td>
<td>Moderate complexity</td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>99.8% (99.5-100)</td>
<td>98.6% (98.4-98.8)</td>
<td>Moderate complexity</td>
</tr>
<tr>
<td></td>
<td>Whole blood (fingerstick or venipuncture)</td>
<td>100% (99.5-100)</td>
<td>99.7% (99.0-100)</td>
<td>Waived</td>
</tr>
<tr>
<td>Uni-Gold Recombigen® HIV test</td>
<td>Serum and plasma</td>
<td>100% (99.5-100)</td>
<td>99.8% (99.3-100)</td>
<td>Moderate complexity</td>
</tr>
<tr>
<td>Multispot HIV-1/HIV-2 Rapid test</td>
<td>Plasma</td>
<td>100% (99.94-100)</td>
<td>99.93% (99.79-100)</td>
<td>Moderate complexity</td>
</tr>
</tbody>
</table>

*Trade names are for identification purposes only and do not imply endorsement by the US Department of Health and Human Services or the Centers for Disease Control and Prevention.

CLIA—the Clinical Laboratory Improvement Amendments of 1998.


All four tests are interpreted visually and require no instrumentation. HIV antigens are affixed to the test strip or membrane. If HIV antibodies are present in the specimen being tested, they bind to the affixed antigen. The test kit's colorimetric reagent binds to these immunoglobulins creating an indicator that is visually detectable.

External controls
All four rapid HIV tests require the periodic use of external controls (known HIV-positive and -negative specimens). External controls must be run 1) by each new operator prior to performing the test on patients, 2) when a new lot of test kits is used, 3) upon receipt of a new shipment of test kits, 4) when the temperature of the storage or testing area falls outside the recommended range, and 5) at periodic intervals determined by the testing facility, usually based on their volume of testing.

Subject information sheets
The FDA requires that persons who undergo rapid testing receive a subject information sheet. This sheet, provided by each manufacturer with its rapid HIV test kits, includes basic information about HIV/AIDS, HIV testing, how the test works, what the test results mean, and specifies that reactive rapid test results need to be confirmed.

The Clinical Laboratory Improvement Amendments of 1988
All laboratory testing is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which classifies tests according to their complexity. To receive a CLIA waiver, tests must use direct, unprocessed specimens (such as whole blood or oral fluid) and be easy to perform with a negligible chance of error. Waived tests can be performed by persons without formal laboratory training outside traditional laboratories. Waived tests, suitable for use at the point-of-care, make it easier for nonclinical testing sites to offer rapid HIV tests. In order to purchase CLIA-waived rapid HIV tests, a facility must register as a laboratory with the CLIA program and adhere to the manufacturer's instructions for performing the tests.

OraQuick® and Uni-Gold are CLIA-waived; Reveal™ and Multispot are categorized as moderate complexity (Table 1). Laboratories that perform moderate complexity testing must meet more stringent standards for personnel, supervision, quality assurance, and proficiency testing than laboratories that perform waived testing.

OraQuick® Advance Rapid HIV-1/2 Antibody Test
On November 7, 2002, the FDA approved the OraQuick® Rapid HIV-1 Antibody Test for use on fingerstick blood samples. It received its CLIA waiver in January 2003. Subsequently, OraQuick® received approval for use with venipuncture whole blood and plasma (though OraQuick® used with plasma is classified as moderate complexity under CLIA). In 2004, OraQuick® Advance received FDA approval for use with oral fluid and for detection of both HIV-1 and HIV-2.

The OraQuick® test device is shown in Figure 1. The paddle-shaped device contains a nitrocellulose strip, upon which a stripe of synthetic gp41 peptides represent-
A Rapid Review of Rapid HIV Antibody Tests

Greenwald et al

Reactive

Non-Reactive

Figure 1. OraQuick* Advance Rapid HIV Antibody test.

ing the HIV-1 envelope and the gp36 region of the HIV-2 envelope have been applied in the "T" (test) location, and a stripe of goat antihuman IgG in the "C" (control) location. The specimen of blood or plasma is added directly to the developer vial. For oral fluid testing, the oral fluid sample is collected by swabbing the gums with the paddle-shaped device. The test device is then added to the developer vial. If HIV antibodies are present in the specimen, they bind to the peptides causing a red line to appear in the test location. As the solution migrates further, it encounters the antihuman IgG control, and if an adequate specimen was added, a red line appears in the control location.

The test result should be read no sooner than 20 minutes and no later than 40 minutes after the test device is inserted into the developer vial. A red line at both the test and control location indicates a valid reactive test result; a red line only in the control location indicates a valid negative test result. The test is invalid and should be repeated with a new device if no line appears at the control location or if lines appear outside the areas indicated by the triangles [10].

Designed as a point-of-care HIV test, OraQuick* has been used in numerous settings including labor and delivery [11*], ambulatory clinical sites [12], emergency departments [13,14], hospital inpatient services [15] (Greenwald JL, unpublished data), correctional facilities [16], and for occupational exposures [17-19]. Additionally, OraQuick* has also been used by the military in battlefield operations [20].

Reveal™ G2 Rapid HIV-1 Antibody Test

On April 17, 2003, the FDA approved the Reveal™ Rapid HIV-1 Antibody Test to detect HIV antibodies in serum or plasma. In June 2004, it was superseded by the second generation Reveal™ G2 test, which incorporates an internal control [21]. Reveal™ G2 consists of a test cartridge and a proprietary colorimetric detection agent. Positive and negative external controls, which must also be reconstituted, are supplied with the kit.

Reveal™ is considered reactive if both the red control line and central red test dot appear, negative if only the control line appears, and invalid if the control line does not appear (Fig. 2). The Reveal™ G2 only takes 3 minutes to run [22]. However, because it requires serum or plasma from centrifuged blood samples and several reagent steps, it is classified as a moderate complexity test under CLIA and is usually performed in a clinical laboratory.

Uni-Gold Recombigen* HIV Test

The Uni-Gold Recombigen* HIV Test received FDA approval in December 2003 for testing whole blood, serum, and plasma for antibodies to HIV-1. It was waived under CLIA in 2004 for use with venipuncture and fingerstick whole blood specimens [23]. The device consists of a rectangular plastic test cartridge and a dropper bottle of buffer solution (Fig. 3). Peptides from the immunodominant region of the HIV-1 envelope are immobilized on a nitrocellulose strip in the test region. Reagents are also bound at the control region to indicate whether the test is functioning correctly, but these do not detect IgG and thus appearance of the control line does not validate that adequate patient specimen has been added. One drop of specimen is added to the specimen well on the test cartridge followed by four drops of wash buffer. The specimen combines with the colorimetric reagent and migrates along the nitrocellulose strip past the test and control regions. The test is read 10 to 12 minutes after specimen is added. A line in both the test and control regions indicates a reactive test; a line in only the control region indicates a negative test. When used with whole blood, the test is valid only if the control line is present and the sample well is red, indicating that an adequate blood sample has been added [24].
Multispot HIV-1/HIV-2 Rapid Test
The Multispot HIV-1/HIV-2 Rapid Test received FDA approval in November, 2004 [25]. Multispot is classified as a moderate complexity under CLIA, approved for use on fresh or frozen serum and plasma to both detect and distinguish HIV-1 from HIV-2.

Multispot consists of a test cartridge and five reagents: specimen diluent, wash solution, conjugate, development reagent, and stop solution. The cartridge contains a membrane on which microparticles have been immobilized in four spots. Two of the spots consist of recombinant and synthetic gp41 peptides to detect HIV-1 antibodies; one consists of synthetic gp36 peptides to detect antibodies to HIV-2; and the fourth spot consists of goat antihuman IgG as the internal control.

The test is considered positive for HIV-1 if the control spot and either or both of the HIV-1 spots turn purple, and positive for HIV-2 if the control and HIV-2 spots appear (Fig. 4). If purple appears in the control spot, the HIV-2 spot, and one or both of the HIV-1 spots, the test is considered HIV reactive (undifferentiated). In this case, the specimen may be tested by additional methods which allow differentiation between HIV-1 and HIV-2. The test is negative when only the control spot appears. The absence of the control spot indicates an invalid result, regardless of any other spot pattern.

Quality Assurance for CLIA-waived Rapid HIV Antibody Tests
Although CLIA-waived rapid HIV test devices are easy to use and can provide reliable results when the manufacturer's directions are followed, mistakes can occur at any point in the testing process, including storage and testing area temperature, test kit shelf-life, specimen collection, test performance and results interpretation, referring specimens for confirmatory testing, managing confirmatory test results, etc. To reduce mistakes and to ensure that the FDA restrictions for sale of the test are followed, a site that performs rapid HIV tests must have a QA program in place before offering these tests. In January 2003, the CDC convened a panel of experts including laboratory scientists and individuals from the FDA and the Centers for Medicare and Medicaid Services to develop guidelines that outline the basic parts of a rapid HIV test QA program [32*]. The Quality
Assurance Guidelines for Testing Using the OraQuick* Rapid HIV-1 Antibody Test are intended to assist a range of providers in developing policies, processes and procedures to ensure high quality HIV testing services. These guidelines include 1) the basics of a QA program for testing using OraQuick*, 2) an overview of government rules that apply to using this test, and 3) examples of forms/checklists that can be used to keep track of QA outcomes.

Counseling with Rapid HIV Antibody Tests

Counseling for patients choosing rapid HIV testing involves some differences compared with conventional testing, including assessing preparedness for clients to receive test results in the same session and explaining the meaning of preliminary positive results. Information can be provided either face-to-face or in a pamphlet, brochure, or video [34].

Patients with reactive rapid test results must be counseled in simple terms about the meaning of a reactive test. The provider must emphasize the need for a confirmatory test and schedule a return visit for results. Providers offering rapid HIV testing should be able to collect blood or oral fluid specimens on-site for confirmatory testing. All patients with reactive tests should be counseled on risk-reduction behaviors while awaiting the results of confirmatory testing. A simple message to convey this information could be "Your preliminary test result is positive, but we won't know for sure if you are infected with HIV until we get the results from your confirmatory test. In the meantime, you should take precautions to avoid transmitting the virus" [34]. The New York State Department of Health AIDS Institute has also created guidelines for how to discuss reactive results stratifying the language based on the patient's level of risk for HIV infection. For clients at high risk, the guidelines suggest saying "Based on your risk factors, it is highly likely that the preliminary test result is correct and that you have HIV" (emphasis added). For those at low risk, the phrase "quite likely" is recommended, and for those with no admitted risk factors, they advise informing them "There is a chance that this result could be a false positive" [35].

Physicians and counseling staff may be apprehensive about rapid testing specifically with regards to the ability to handle preliminary positive test results at any time. Data from RESPECT-2, a large, randomized, controlled trial that compared different forms of HIV testing and risk-reduction counseling in clients at sexually transmitted disease (STD) clinics in the United States, found that after gaining experience in the field, the majority of counselors preferred rapid testing, felt that rapid HIV testing sessions resulted in enhanced counseling, and felt that it was more convenient for both clients and counseling staff [36]. Although some have expressed concern about how counselors and clients will deal with discussing and understanding reactive results [37], others have noted that providers have extensive experience managing preliminary positive test results (eg, abnormal mammograms that require biopsies and abnormal pap smears that require colposcopy) [38] and studies of rapid testing have demonstrated good client understanding of results [39].

Providing HIV counseling and testing may be challenging in some health care settings. Because the average primary care office visit in the United States is less than 18 minutes long [40], even the "brief" counseling protocol of RESPECT-2 could take up an entire office visit. In these situations, alternative procedures for HIV counseling with rapid testing should be considered, eg, providing information either in a face-to-face meeting with a counselor or in a pamphlet, brochure, or video [34].

Outcomes of Rapid HIV Testing—Receipt of Test Results

Compared with the standard two-session counseling and testing protocol, single-session, rapid HIV testing has the potential advantages of decreasing costs and increasing the number of patients who receive their results [41]. In anonymous testing and STD clinics in Dallas, the use of rapid testing with the Single Use Diagnostic System (SUDS) HIV-1 test (Murex, Norcross, GA) was associated with an increase in the number of patients learning their serostatus, lower costs, and improved patient satisfaction [39]. A randomized, controlled trial at a needle exchange and two bathhouses compared SUDS HIV-1 testing to other conventional HIV testing. This study found that more clients received their test results after rapid testing than with traditional testing: at the needle exchange, 66 (83%) of 80 versus 27 (56%) of 48 (odds ratio [OR] = 3.7; P = 0.002), and at the bathhouses, 102 (99%) of 103 versus 82 (74%) of 111 [OR = 36.1; P < 0.001] [38].

Patients failing to return for their confirmatory HIV test results remain a challenge [42]. Patients who do not return for confirmatory test results may choose to seek care at another clinic.
locations, already know their status, or seek retesting elsewhere. However, with rapid HIV testing, patients with reactive test results leave the initial testing visit with information that there is a high likelihood that they are seropositive compared with receiving no test result information at the end of a visit where a conventional HIV test specimen was collected. Because rapid HIV testing is likely to increase in the coming years, validation of an algorithm using a combination of point-of-care rapid HIV tests would enhance opportunities for individuals to get a confirmed HIV status.

Patient Satisfaction
Overwhelmingly, both patients and providers prefer rapid HIV tests to conventional EIAs [43,44-45]. Ninety percent (1038/1148) of persons seeking HIV testing at 24 clinical and nonclinical settings that offered the OraQuick® HIV test and an oral or serum EIA in New York, Utah, and Wisconsin preferred the rapid test; 13% of the clients in New York and Utah said they would not have tested that day if the rapid test had not been available [43].

Financial Considerations
The price for the FDA-approved rapid HIV test kits, as of July 2005, range from $14 to $25. Costs for multidose external control vials range from $20 to $26.25 [29]. According to the Centers for Medicare and Medicaid Services 2005 Clinical Laboratory Fee Schedule, average reimbursement for a CLIA-waived rapid HIV-1 antibody test (Current Procedural Terminology [CPT] code 86701QW) is $12.41/test and for a CLIA-waived rapid HIV-1/2 antibody test (CPT code 86703QW) is $19.17 [46-48]. Providers offering point-of-care, rapid HIV testing may be challenged by reimbursement not keeping pace with the list prices of the tests. In addition, comparable with counseling for other health issues, HIV counseling by a nonphysician is not reimbursable. Physicians performing HIV counseling may attempt to collect reimbursement for it by billing for prolonged services.

Conclusions
Rapid testing overcomes major barriers to individuals with HIV infection knowing their status: 1) HIV testing opportunities can be expanded to both medical and nonmedical settings and 2) rapid testing facilitates patients receiving their test results the same day, usually at the encounter where the test specimen was collected. Providing greater access to testing, prevention, and care services for persons living with HIV can reduce the number of new infections and lead to reductions in HIV-associated morbidity and mortality [49,50].

Disclaimer
Use of trade names and commercial sources is for identification only and does not imply endorsement by the US Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to this manuscript's readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the US Department of Health and Human Services. CDC is not responsible for the content of these sites. URL addresses listed in this manuscript were current as of the date of publication.

References and Recommended Reading
Papers of particular interest, published recently, have been highlighted as:
• Of importance
** Of major importance


The authors demonstrate that rapid HIV testing is feasible and delivers accurate and timely test results for women in hospital-based labor and delivery wards.
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This document provides guidance on quality assurance practices for sites using or planning to use the OraQuick Rapid HIV-1 Antibody test to detect antibodies to HIV.
What should I know before I get tested?

Your healthcare provider is the best person to answer your questions about HIV, the OraQuick® ADVANCE™ Rapid HIV-1/2 Antibody Test, and other testing options.

You have a choice of the type of test to use. When you are tested for HIV, a specimen will be collected and checked for HIV antibodies. The presence of HIV antibodies in your blood means that you have been infected with the virus that causes AIDS.

You should be aware that the presence of HIV antibodies can be detected in many ways. Ask your healthcare provider for the information you need to make good choices. Some questions answered in this pamphlet are:

- How does someone get HIV?
- What does a preliminary positive result mean?
- What are HIV and AIDS?
- What is the OraQuick® ADVANCE™ Rapid HIV-1/2 Antibody Test and how is it done?
- What does a negative result mean?
- Where can I get more information?
- What is the OraQuick® ADVANCE™ Rapid HIV-1/2 Antibody Test, and other testing options.

The OraQuick® ADVANCE™ Rapid HIV-1/2 Antibody Test is manufactured by:

The OraQuick® ADVANCE™ Rapid HIV-1/2 Antibody Test is manufactured by:

OraSure Technologies, Inc.

Bethlehem, PA 18015 USA

www.orasure.com

What are HIV and AIDS?

HIV is the human immunodeficiency virus. AIDS is the virus that causes AIDS (acquired immunodeficiency syndrome). It is possible for a person to have HIV in their body for months or years before any signs of illness appear. The virus weakens the body's ability to fight off infections. As a result, people with AIDS develop serious infections and cancers. These illnesses make them very sick and can eventually kill them.

How do people get HIV?

HIV spreads through contact with blood, semen, vaginal fluids, or breast milk from infected people. Contact can come from unsafe sex. It can also come from sharing used needles and syringes. Infected women can pass the virus to their babies during pregnancy, childbirth, and breast feeding. It is also possible to become infected with HIV through blood transfusions, although this is now very rare.

People do not become infected with HIV through everyday casual contact with people at school, work, home, or anywhere else. The virus is not spread from contact with sweat, saliva, or a casual kiss from an infected person (even an "French" kissing is not advised). Nor can people become infected from contact with foods prepared by an HIV-infected person. People have not been infected with HIV through insect bites.

What are HIV antibodies?

HIV antibodies are the proteins in the blood that help fight off the HIV virus. They are present in the blood of people who have been infected with HIV. OraQuick® ADVANCE™ Rapid HIV-1/2 Antibody Test measures the presence of these antibodies in your blood.

Rapid HIV-1/2 Anticorps Rapid HIV-1/2

Prueba de detección de anticuerpos Rapid HIV-1/2

Prior to Being Tested

¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?

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¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?

¿Qué debo saber antes de que me hagan la prueba?
¿Cómo puedo evitar contagiarme?

La mejor manera de prevenir el contagio es evitar cualquier actividad que permita el paso del virus. Es recomendable evitar el contacto directo con personas infectadas, especialmente si no sabes si están enfermos. Si tienes contacto con alguien que podría estar infectado, debes informarte lo antes posible.

Si se detecta que estás infectado, puedes recibir tratamiento antiviral que puede ayudarte a mantener el sistema inmunológico adelante y atrasar el avance de la enfermedad. Sin embargo, debes tener en cuenta que la eficacia de este tratamiento puede variar dependiendo de varios factores, incluyendo el estado de tu sistema inmunológico y el tipo de infección.

Si se te detecta que estás infectado, debes saber que el VIH es un virus que puede ser transmitido a través del contacto sexual, la sangre o el sistema inmunológico, pero no a través del aire o del agua. Es importante que te hagas pruebas periódicas para determinar si estás infectado y recibir el tratamiento adecuado.

¿Qué significa un resultado PRELIMINAR POSITIVO?

Un resultado PRELIMINAR POSITIVO sugiere que posiblemente haya anticuerpos contra el VIH en tu sangre. Sin embargo, es importante tener en cuenta que este tipo de pruebas puede dañar los resultados falsos positivos, por lo que no es recomendable confiar en ellos por completo. Para confirmar un resultado positivo, es necesario realizar otro tipo de prueba.

¿Qué significa un resultado NEGATIVO?

Un resultado NEGATIVO significa que tu sangre no contiene anticuerpos contra el VIH. Sin embargo, es importante mencionar que este resultado no garantiza que no estás infectado, ya que existen casos raros en los que el cuerpo no produce anticuerpos en respuesta a la infección.

¿Qué es la prueba de detección del VIH?

La prueba de detección del VIH se realiza con sangre, orina o líquido corporal. En algunos casos, se puede realizar con saliva o material de la boca y el cuello. La prueba se realiza en el laboratorio y se puede obtener un resultado en pocas horas o días, dependiendo del método utilizado.

En cuanto a la prueba de detección del VIH, es importante mencionar que no existe una prueba 100% precisa. Por lo tanto, es posible que se obtengan resultados falsos negativos o falsos positivos. Es por esto que es importante que consultes a un profesional de la salud para interpretar los resultados de la prueba.

¿Qué es un análisis de anticuerpos contra el VIH?

Un análisis de anticuerpos contra el VIH es una prueba que se realiza con sangre, orina o líquido corporal. En algunos casos, se puede realizar con saliva o material de la boca y el cuello. La prueba se realiza en el laboratorio y se puede obtener un resultado en pocas horas o días, dependiendo del método utilizado.

En cuanto a la prueba de detección del VIH, es importante mencionar que no existe una prueba 100% precisa. Por lo tanto, es posible que se obtengan resultados falsos negativos o falsos positivos. Es por esto que es importante que consultes a un profesional de la salud para interpretar los resultados de la prueba.
Appendix: Quality Assurance Guidelines for Testing Using the OraQuick Rapid HIV-1 Antibody Test

Overview
This appendix includes several items to facilitate conducting testing and performing quality assurance using the OraQuick Rapid HIV-1 Antibody test. The forms provided are examples and templates that can be adapted for local use, adding or deleting fields, as needed. The appendix includes the following:

A. Government regulations
B. Example training checklist for the OraQuick Rapid HIV-1 Antibody Test
C. Example of a temperature log
D. Example log of quality control results
E. Example log of test results
F. Example specimen transfer log
G. External assessment: proficiency testing and other mailed evaluation programs
Appendix A  
Government Regulations

<table>
<thead>
<tr>
<th>Food and Drug Administration (FDA) sales restrictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>To help ensure the quality of testing with the OraQuick test, the FDA approved the test kit it with specific restrictions for its sale. These restrictions apply to the waived test kit. By purchasing the test, the customer agrees to follow these restrictions. The restrictions are outlined below (for the specific FDA language, refer to the OraQuick package insert). The kit purchaser must:</td>
</tr>
<tr>
<td>▪ Be a clinical laboratory, i.e., holds a certificate from the Federal government (Clinical Laboratory Improvement Act of 1988 (CLIA) certificate – see below for details) and any state or other certification that is required.</td>
</tr>
<tr>
<td>▪ Have an established quality assurance program.</td>
</tr>
<tr>
<td>▪ Provide training for testing personnel (operators) using the instructional materials provided by the manufacturer.</td>
</tr>
<tr>
<td>▪ Provide information to persons being tested by giving each a copy of the manufacturer’s “Subject Information” pamphlet prior to specimen collection and appropriate information when providing the test results.</td>
</tr>
<tr>
<td>▪ Not use the kit to screen blood or tissue donors.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Laboratory Improvement Amendment (CLIA) regulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>The OraQuick test is a waived test under Federal regulations—the regulations for the Clinical Laboratory Improvement Amendments of 1988 (CLIA regulations). As a waived test, Federal requirements for the OraQuick test are minimal. The CLIA requirements for sites wishing to offer testing using the OraQuick test are listed below and can be found at <a href="http://www.phppo.cdc.gov/clia/regs/toc.asp">http://www.phppo.cdc.gov/clia/regs/toc.asp</a>. Each site must:</td>
</tr>
<tr>
<td>▪ Have a valid CLIA certificate of waiver, certificate of compliance or certificate of accreditation.</td>
</tr>
<tr>
<td>▪ Follow the manufacturer’s instructions for performing the test, and</td>
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<td>▪ Permit announced or unannounced inspections by representatives of the Centers for Medicare &amp; Medicaid Services (CMS) under certain circumstances (see §493.35(d) in the regulations at the Web site listed above).</td>
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<tr>
<td>▪ Perform only waived tests if holding a certificate of waiver.</td>
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</tbody>
</table>
### Government Regulations (continued)

| How to obtain a CLIA certificate | All sites planning to offer only the OraQuick test that are not already CLIA certified, must obtain a Certificate of Waiver or be included under a multiple site exception, such as limited public health testing or mobile testing. To obtain a Certificate of Waiver, complete Form CMS-116, found at the following CMS Internet address: http://www.cms.gov/clia/cliaapp.asp. This form asks for information on the facility type (select from a list), hours of operation, estimated annual number of waived tests to be performed, the type of control (nonprofit, for profit or government control) and the total number of individuals involved in performing testing. The facility owner or laboratory director must sign the form. Mail the completed form to the State agency in which your site is located. To find your State agency contact, refer to the information provided at the following Internet address http://www.cms.gov/clia/ssa-map.asp. After the completed form is processed by the State agency, a fee of $150 will be assessed for a Certificate of Waiver. The certificate is valid for two years. |
| State regulations | In addition to CLIA, some States have specific regulatory requirements for HIV testing. Contact your State agency for information on State requirements. State agency contacts are listed at http://www.cms.gov/clia/ssa-map.asp. |
| Occupational safety and health regulations | Employers with employees who have an occupational exposure to blood or other potentially infectious materials must meet the U.S. Department of Labor Occupational Health and Safety Administration (OSHA) standards for bloodborne pathogens. Individuals collecting blood specimens or performing the OraQuick test have exposure to blood or other potentially infectious materials resulting from the performance of their duties. Therefore, sites offering the OraQuick test must meet OSHA standards that include, but are not limited to, the following requirements:  
- Have a written Exposure Control Plan.  
- Provide personal protective equipment, such as gloves.  
- Make available the hepatitis B vaccine and vaccination series to all employees who have occupational exposure.  
- Provide post-exposure evaluation and follow-up to all employees who have had an exposure incident.  
- Provide training for all employees with occupational exposure.  
- Contain and dispose of biohazard waste following applicable regulations (includes blood and items contaminated with blood or other potentially infectious materials). Refer to state and local regulations regarding disposal of biohazardous materials.  

**NOTE:** This is an overview of OSHA requirements and is not a complete list. For specific information, visit the OSHA Web site at http://www.osha.gov/SLTC/bloodbornepathogens/index.html. |
Appendix B

Providing Information to Women in Labor with Unknown HIV Status Regarding Routine, Rapid HIV-1 Antibody Testing (Using an OPT-OUT Approach)

and

Sample Consent for Rapid HIV-1 Antibody Testing in Labor and Delivery Settings for Women with Unknown HIV Status (Using an OPT-IN Approach)
Appendix B
Example Training Checklist for the OraQuick Rapid HIV-1 Antibody Test

Employee: Name________________________

Instructions: Fill in dates when the trainee observes and performs each objective or procedural step, as applicable. (If a trainee will not perform a specific task, enter N/A for not applicable.) The trainee should initial when he/she feels the objective/procedure has been mastered and the trainer when he/she thinks the trainee has met the objective or performs the specific procedure competently.

<table>
<thead>
<tr>
<th>Objective/Procedural Step</th>
<th>Date Observed</th>
<th>Date Performed</th>
<th>Trainee’s initial and date</th>
<th>Trainer’s initial and date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read OraQuick procedure</td>
<td>N/A</td>
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<tr>
<td>Read Biohazard Exposure Control Plan</td>
<td>N/A</td>
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<td>Determine if requirements for acceptable testing environment are met (e.g., temperature, lighting, level work space)</td>
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<td>Practice test with negative and positive external controls</td>
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<td>Give person getting tested the “Subject Information” brochure</td>
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<td>Label test device components and appropriate paperwork</td>
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<td>Collect finger-stick specimen, put loop into vial and mix correctly</td>
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<td>Insert test device, time test, read result</td>
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<td>Dispose of lancet and other biohazardous waste appropriately</td>
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<td>Record results on report form and log sheet</td>
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<tr>
<td>Record internal and external quality control (QC) results in QC log</td>
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<td>Evaluate a new OraQuick test kit lot number and record results in QC log</td>
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<td>Report test result to the person being tested (one negative and one preliminary positive)</td>
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<td>Refer person or collect specimen for confirmatory testing</td>
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<td>Send confirmatory test specimen to referral laboratory and document submission</td>
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<td>Receive referral laboratory results and record results</td>
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<td>Explain what to do if QC results show a problem</td>
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</table>
Appendix C
Example Temperature Log

Thermometer location ________________________________

Acceptable temperature range* ___________________________

Month/Year ___________________

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<thead>
<tr>
<th>Day</th>
<th>Temperature</th>
<th>Initials</th>
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*The acceptable range for test kit storage is 2° to 27° C or 35° to 80° F; the acceptable range for control kit storage is 2° to 8°C or 35° to 46° F; the acceptable range for the testing area is 15° to 27° C or 59° to 80° F.

NOTE: Periodically (e.g., every six months) check thermometer performance and document.

Corrective Action

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Reviewed by and date ________________________________________
### Appendix D

**Example Log of Control Results**

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<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Test Kit Lot #</th>
<th>Test Kit Exp. Date*</th>
<th>New Lot #, shipment?</th>
<th>Control Kit Lot #</th>
<th>Control Kit Exp. Date</th>
<th>Date controls opened</th>
<th>Negative Control Result</th>
<th>Positive Control Result</th>
<th>Results Acceptable?</th>
<th>Performed by</th>
<th>Reviewed by and Date</th>
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*Exp. = Expiration

**Corrective Action** (use reverse side, if needed)

<table>
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<tr>
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<th>Action Taken</th>
<th>Initials</th>
<th>Reviewed by and date</th>
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*Appendix to the QA Guidelines for OraQuick*
Appendix E
Example Log of Test Results

<table>
<thead>
<tr>
<th>Test Subject ID*</th>
<th>Date and Time Specimen Collected</th>
<th>Kit Lot Number</th>
<th>Kit Expiration Date</th>
<th>Actual Test Incubation Time</th>
<th>Test result N=non-reactive R=reactive I=invalid</th>
<th>Tester</th>
<th>Result and Time Reported to Subject</th>
<th>Confirmatory Testing</th>
<th>Reviewed by and Date</th>
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*ID = Identification
Appendix F
Example Specimen Transfer Log

[Put Referring Facility Name, Address and Phone Number here]

Date:______________________

Referral Laboratory ________________________________

<table>
<thead>
<tr>
<th>Specimen Tracking Number</th>
<th>Test Subject ID*</th>
<th>OraQuick Test Result</th>
<th>Date Specimen Collected</th>
<th>Time Specimen Collected</th>
<th>Collected by</th>
<th>Referral Lab Req† Completed (✓)</th>
<th>Date Conf Result Received</th>
<th>Confirm Test Result</th>
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*ID = Identification
†Lab Req = Laboratory Requisition

(NOTE: If you use more than one referral laboratory, add a column to record each one.)
Appendix G
External Assessment: Proficiency Testing and Other Mailed Evaluation Programs

**Background and overview**

Some States may require participation in a State or Centers for Medicare & Medicaid Services (CMS)-approved proficiency testing program, even though this program is not required by CLIA for waived tests. Participating in proficiency testing or an external evaluation program is a relatively easy way to obtain an external assessment of the quality of waived testing. There are several programs in which a site may choose to enroll. Test samples will be received by mail on a periodic basis, usually two to three times per year. These samples include a combination of several (typically five) HIV antibody positive and negative specimens with results known to the program provider, but not to the participants. The participants test the samples as if they were client/patient specimens and send results back to the program provider.

**Evaluation reports**

In proficiency testing programs, the results from the individual participant sites are compared to the expected values. Each site receives a graded individualized report and summary report showing their performance and the performance of all the participants. In some evaluation programs, such as the Model Performance Evaluation Program (MPEP) offered by the Centers for Disease Control and Prevention (CDC), individual participant results are not graded; instead a summary report is provided with a compilation of results from all participants and a commentary on overall performance.

**For more information**

For more information, refer to the following Internet sites:

- The CDC MPEP for rapid HIV testing can accommodate a limited number of additional sites. For more information and to enroll on-line go to the following Web sites: [http://www.phppo.cdc.gov/mpep/default.asp](http://www.phppo.cdc.gov/mpep/default.asp), [http://www.phppo.cdc.gov/mpep/enrollment.asp](http://www.phppo.cdc.gov/mpep/enrollment.asp). There is currently no fee to enroll in the MPEP program.

- For a list of CLIA approved proficiency testing programs (several of which include HIV testing) go to [http://www.cms.gov/clia/ptlist.pdf](http://www.cms.gov/clia/ptlist.pdf). This list includes contact information for each program and the tests offered. These programs charge an enrollment fee.
Consumer Education
CONGRATULATIONS ON YOUR NEW BABY!

When you leave the hospital:

1. Follow-up with the Maricopa County Department of Public Health. They will call you for follow-up lab work. If you don't hear from them within 7-10 days, call 602-506-5052.

2. See your medical care provider within 7 days. If you don't have a medical care provider, make an appointment at McDowell Healthcare Center at 1144 E. McDowell Road, phone #: 602-344-6550.

3. Keep your appointment at Phoenix Children’s Hospital for your baby. The outpatient clinic, Bill Holt Clinic, is located at 1919 E. Thomas, Building B, phone #: (602) 546-0955.

4. If you would like to join a women’s group, call Lorraine Brown at (602) 344-2627.
CUIDADO MÉDICO DE SEGUIMIENTO- MIHS

¡FELICITACIONES POR SU NUEVO BEBÉ!

Cuando se vaya del hospital:

1. Vaya a una cita de seguimiento con el Departamento de Salud Pública del Condado Maricopa. Ellos la van a llamar para hacer pruebas de laboratorio de seguimiento, Si no sabe nada de ellos dentro de 7 a 10 días, llame al 602-506-5052.

5. Vea a su proveedor de cuidado médico dentro de 7 días. Si usted no cuenta con un proveedor de cuidado médico, haga una cita en el Centro de Salud McDowell en 1144 E. McDowell Road, teléfono 602-344-6550.

6. Asista a la cita en el Phoenix Children's Hospital hecha para su bebé. La Clínica Bill Holt queda ubicada en 1919 E. Thomas, Edificio B, teléfono (602) 546-0955.

7. Si a usted le gustaría ser parte de un grupo de apoyo para mujeres, llame a Lorraine al (602) 344-2627.
HIV During Pregnancy, Labor and Delivery, and After Birth

Health Information for HIV Positive Pregnant Women

August 2006

Fact Sheets

P.O. Box 6303, Rockville, MD 20849-6303
Telephone: 1-800-448-0440
International: 301-519-0459
Fax: 301-519-6616
TTY/TTD: 888-480-3739

Live Help: http://aidsinfo.nih.gov/LiveHelp
E-mail: ContactUs@aidsinfo.nih.gov
Web: http://aidsinfo.nih.gov
HIV During Pregnancy, Labor and Delivery, and After Birth

This series of fact sheets is intended for women who are HIV positive and pregnant or have recently given birth. These fact sheets describe the steps an HIV positive pregnant woman can take to preserve her health and prevent transmission of HIV to her baby.

These fact sheets are designed as a series, but can also be used as stand-alone documents. The information in these fact sheets is based on the U.S. Public Health Service's 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 and Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (available at http://aidsinfo.nih.gov/guidelines).

Table of Contents

- HIV Testing and Pregnancy
- Treatment Regimens for HIV Positive Pregnant Women
- Safety and Toxicity of Anti-HIV Medications During Pregnancy
- Delivery Options for HIV Positive Pregnant Women
- HIV Positive Women and Their Babies After Birth

This information is based on the U.S. Public Health Service's 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 and Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (available at http://aidsinfo.nih.gov).
HIV and Pregnancy — Perinatal Testing

HIV Testing and Pregnancy

I am pregnant, and I may have HIV. Will I be tested for HIV when I visit a doctor?
In most cases, health care providers cannot test you for HIV without your permission. However, the U.S. Public Health Service recommends that all pregnant women be tested. If you are thinking about being tested, it is important to understand the different ways perinatal HIV testing is done. There are two main approaches to HIV testing in pregnant women: opt-in and opt-out testing.

In opt-in testing, a woman cannot be given an HIV test unless she specifically requests to be tested. Often, she must put this request in writing.

In opt-out testing, health care providers must inform pregnant women that an HIV test will be included in the standard group of tests pregnant women receive. A woman will receive that HIV test unless she specifically refuses. The CDC currently recommends that health care providers adopt an opt-out approach to perinatal HIV testing.

What are the benefits of being tested?
By knowing your HIV status, you and your doctor can decide on the best treatment for you and your baby and can take steps to prevent mother-to-child transmission of HIV (see HIV and Pregnancy Fact Sheet). It is also important to know your HIV status so that you can take the appropriate steps to avoid infecting others (see Understanding HIV Prevention Fact Sheet).

What happens if I agree to be tested?
If you agree to be tested, your doctor should counsel you before the test about the way your life may change after you receive the test results. If the test indicates that you have HIV, you should be given a second test to confirm the results. If your second test is positive for HIV, you and your doctor will decide which treatment options are best for you and your baby (see Treatment Regimens for HIV Positive Pregnant Women Fact Sheet). If the test indicates that you do not have HIV, you may receive counseling on HIV prevention.

What happens if I refuse to be tested?
If you decide that you do not want to be tested for HIV, your doctor may offer you counseling about the way HIV is transmitted and the importance of taking steps to prevent HIV transmission. He or she may also talk to you about the importance of finding out your HIV status so that you can take steps to prevent your baby from becoming infected.

Will my baby be tested for HIV?
Health care providers recommend that all babies born to HIV positive mothers be tested for HIV. However, states differ in the ways they approach HIV testing for babies.
- some states require that babies receive a mandatory HIV test if the status of the mother is unknown
- some states require that health care providers test babies for HIV unless the mother refuses
- some states are only required to offer an HIV test to pregnant women (not their babies), which they can either accept or refuse

How can I find out the testing policies of my state?
The U.S. Department of Health and Human Services (HHS) can provide you with HIV testing information for your state. Contact HHS at 1–877–696–6775 or 202–619–0257.

For more information:
Contact your doctor or an AIDSinfo Health Information Specialist at 1–800–448–0440 or http://aidsinfo.nih.gov.

Terms Used in This Fact Sheet:
Mother-to-child transmission: the passage of HIV from an HIV positive mother to her infant. The infant may become infected while in the womb, during labor and delivery, or through breastfeeding. Also known as perinatal transmission.
Perinatal HIV testing: testing for HIV during pregnancy or during labor and delivery.

This information is based on the U.S. Public Health Service's 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 (available at http://aidsinfo.nih.gov). Reviewed August 2006
I am HIV positive and pregnant. Should I take anti-HIV medications?

You should take anti-HIV medications if:

• you are experiencing severe symptoms of HIV or have been diagnosed with AIDS
• your CD4 count is 200 cells/mm³ or less (treatment should be considered at 350 cells/mm³ or less)
• your viral load is greater than 1,000 copies/mL

You should also take anti-HIV medications to prevent your baby from becoming infected with HIV. Specific treatment to prevent mother-to-child transmission of HIV is discussed below.

How do I find out what HIV treatment regimen is best for me?

HIV treatment is an important part of maintaining your health and preventing your baby from becoming infected with HIV. Decisions about when to start HIV treatment and which medications to take should be based on many of the same factors that women who are not pregnant must consider. These factors include:

• risk that the HIV infection may become worse
• risks and benefits of delaying treatment (see Starting Anti-HIV Medications Fact Sheet)
• potential drug toxicities and interactions with other drugs you are taking (see Safety and Toxicity of Anti-HIV Medications During Pregnancy Fact Sheet)
• the need to adhere to a treatment regimen closely (see What is Treatment Adherence Fact Sheet)
• the results of drug resistance testing

In addition to these factors, pregnant women must consider the following issues:

• benefit of lowering viral load and reducing the risk of mother-to-child transmission of HIV
• unknown long-term effects on your baby if you take anti-HIV medications during your pregnancy
• information available about the use of anti-HIV medications during pregnancy

What treatment regimen should I follow during my pregnancy if I have never taken anti-HIV medications?

Your best treatment options depend on when you were diagnosed with HIV, when you found out you were pregnant, and at what point you sought medical treatment during your pregnancy. Women who are in the first trimester of pregnancy and who do not have symptoms of HIV disease may consider delaying treatment until after the first trimester, pregnant women with HIV should receive at least AZT (Retrovir, zidovudine, or ZDV); your doctor may recommend additional medications depending on your CD4 count, viral load, and drug resistance testing.

Terms Used in This Fact Sheet:

CD4 count: CD4 cells, also called T cells or CD4+ T cells, are white blood cells that fight infection. HIV destroys CD4 cells, making it harder for your body to fight infections. A CD4 count is the number of CD4 cells in a sample of blood.

Drug resistance testing: A laboratory test to determine if an individual's HIV strain is resistant to any anti-HIV medications. HIV can mutate (change form), resulting in HIV that cannot be controlled with certain medications.

Intravenous (IV): the administration of fluid or medicine into a vein.

Mother-to-child transmission: the passage of HIV from an HIV positive mother to her infant. The infant may become infected while in the womb, during labor and delivery, or through breastfeeding. Also known as perinatal transmission.

Viral load: the amount of HIV in a sample of blood.
Treatment Regimens for HIV Positive Pregnant Women (continued)

I am currently taking anti-HIV medications, and I just learned that I am pregnant. Should I stop taking my medications?

Do not stop taking any of your medications without consulting your doctor first. Stopping HIV treatment could lead to problems for you and your baby. If you are taking anti-HIV medications and your pregnancy is identified during the first trimester, talk with your doctor about the risks and benefits of continuing your current regimen. He or she may recommend that you stop your anti-HIV medications or change the medications you take. If your pregnancy is identified after the first trimester, it is recommended that you continue with your current treatment. No matter what HIV treatment regimen you were on before your pregnancy, it is generally recommended that AZT become part of your regimen.

Will I need treatment during labor and delivery?

Most mother-to-child transmission of HIV occurs around the time of labor and delivery. Therefore, HIV treatment during this time is very important for protecting your baby from HIV infection. Several treatment regimens are available to reduce the risk of transmission to your baby. The most common regimen is the three-part AZT regimen:

1. HIV infected pregnant women should take AZT starting at 14 to 34 weeks of pregnancy. You can take either 100 mg five times a day, 200 mg three times a day, or 300 mg twice a day.
2. During labor and delivery, you should receive intravenous (IV) AZT.
3. Your baby should take AZT (in liquid form) every 6 hours for 6 weeks after he or she is born.

If you have been taking any other anti-HIV medications during your pregnancy, your doctor will probably recommend that you continue to take them on schedule during labor.

Better understanding of HIV transmission has contributed to dramatically reduced rates of mother-to-child transmission of HIV. Discuss the benefits of HIV treatment during pregnancy with your doctor; these benefits should be weighed against the risks to you and to your baby.

For more information:

Contact your doctor or an AIDSinfo Health Information Specialist at 1–800–448–0440 or http://aidsinfo.nih.gov.
Safety and Toxicity of Anti-HIV Medications During Pregnancy

I am HIV positive and pregnant. Are there any anti-HIV medications that may be dangerous to me or my baby during my pregnancy?

Although information on anti-HIV medications in pregnant women is limited compared to information for non-pregnant adults, enough is known to make recommendations about which medications are appropriate for you and your baby. However, the long-term consequences of babies' exposure to anti-HIV medications in utero are unknown. Talk to your doctor about which medications may be harmful during your pregnancy and what medication substitutions and dose changes are possible.

The non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (Viramune or NVP) may be part of your HIV treatment regimen. Long-term use of NVP may cause negative side effects, such as exhaustion or weakness; nausea or lack of appetite; yellowing of eyes or skin; or signs of liver toxicity, such as liver tenderness or enlargement or elevated liver enzyme levels (see Hepatotoxicity Fact Sheet). These negative side effects have not been observed with short-term use (one or two doses) of NVP during pregnancy. However, because pregnancy can mimic some of the early symptoms of liver toxicity, your doctor should monitor your condition closely while you are taking NVP. Also, NVP should be used with caution in women who have never received HIV treatment and who have CD4 counts greater than 250 cells/mm³. Liver toxicity has occurred more frequently in these patients.

Delavirdine (Rescriptor or DLV) and efavirenz (Sustiva or EFV), the two other FDA-approved NNRTIs, are not recommended for the treatment of HIV positive pregnant women. Use of these medications during pregnancy may lead to birth defects.

Nucleoside reverse transcriptase inhibitors (NRTIs) may cause mitochondrial toxicity, which may lead to a buildup of lactic acid in the blood. This buildup is known as hyperlactatemia or lactic acidosis (see Lactic Acidosis Fact Sheet). This toxicity may be of particular concern for pregnant women and babies exposed to NRTIs in utero.

Protease inhibitors (PIs) are associated with increased levels of blood sugar (hyperglycemia), development of diabetes mellitus or a worsening of diabetes mellitus symptoms (see Hyperglycemia Fact Sheet), and diabetic ketoacidosis. Pregnancy is also a risk factor for hyperglycemia, but it is not known whether PI use increases the risk for pregnancy-associated hyperglycemia or gestational diabetes.

Enfuvirtide (Fuzeon or T-20) is the only FDA-approved fusion inhibitor; very little is known about use of this drug during pregnancy.

For more information:
Contact your doctor or an AIDSinfo Health Information Specialist at 1–800–448–0440 or http://aidsinfo.nih.gov.

Terms Used in This Fact Sheet:

Diabetic ketoacidosis: a complication of diabetes in which sugar is not broken down for energy and fat is broken down instead. This leads to an unhealthy buildup of ketones (fat by-products).

Fusion inhibitor: class of anti-HIV medication. A fusion inhibitor works by preventing HIV from entering a cell. The fusion inhibitor approved by the FDA is Fuzeon.

In utero: the time an unborn baby is in its mother's uterus.

Mitochondrial toxicity: damage to the mitochondria (rod-like structures that serve as a cell's powerhouse) that can cause problems in the heart, nerves, muscles, pancreas, kidneys, and liver.

Non-nucleoside reverse transcriptase inhibitor (NNRTI): class of anti-HIV medication. NNRTIs work by blocking reverse transcriptase, a protein that HIV needs to make copies of itself. The NNRTIs approved by the FDA are Rescriptor, Sustiva (also a part of Atripla), and Viramune.

Nucleoside reverse transcriptase inhibitor (NRTI): class of anti-HIV medication. NRTIs are faulty versions of the building blocks (nucleosides) used by reverse transcriptase, a protein that HIV needs to make copies of itself. The NRTIs approved by the FDA are Combivir, Emtriva, Epivir, Epzicom, Hivid, Retrovir, Trizivir, Truvada (also a part of Atripla), Viread, Zerit, and Ziagen.

Protease inhibitor (PI): class of anti-HIV medication. PIs work by blocking protease, a protein that HIV needs to make copies of itself. The PIs approved by the FDA are Agenerase, Aptivus, Crixivan, Fortovase, Invirase, Kaletra, Lexiva, Norvir, Prezista, Reyataz, and Viracept.

This information is based on the U.S. Public Health Service's 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 (available at http://aidsinfo.nih.gov).
Delivery Options for HIV Positive Pregnant Women

I am HIV positive and pregnant. What delivery options are available to me when I give birth?

Depending on your health and treatment status, you may plan to have either a cesarean (also called c-section) or a vaginal delivery. The decision of whether to have a cesarean or a vaginal delivery is something that you should discuss with your doctor during your pregnancy.

How do I decide which delivery option is best for my baby and me?

It is important that you discuss your delivery options with your doctor as early as possible in your pregnancy so that he or she can help you decide which delivery method is most appropriate for you.

Cesarean delivery is recommended for an HIV positive mother when:

- her viral load is unknown or is greater than 1,000 copies/mL at 36 weeks of pregnancy
- she has not taken any anti-HIV medications or has only taken AZT (Retrovir, zidovudine, or ZDV) during her pregnancy
- she has not received prenatal care until 36 weeks into her pregnancy or later

To be most effective in preventing transmission, the cesarean should be scheduled at 38 weeks or should be done before the rupture of membranes (also called water breaking).

Vaginal delivery is an option for an HIV positive mother when:

- she has been receiving prenatal care throughout her pregnancy
- she has a viral load less than 1,000 copies/mL at 36 weeks, and
- she is taking AZT with or without other anti-HIV medications

Vaginal delivery may also be recommended if a mother has ruptured membranes and labor is progressing rapidly.

What are the risks involved with these delivery options?

All deliveries have risks. The risk of mother-to-child transmission of HIV may be higher for vaginal delivery than for a scheduled cesarean. For the mother, cesarean delivery has an increased risk of infection, anesthesia-related problems, and other risks associated with any type of surgery. For the infant, cesarean delivery has an increased risk of infant respiratory distress.

Is there anything else I should know about labor and delivery?

Intravenous (IV) AZT should be started 3 hours before a scheduled cesarean delivery and should be continued until delivery. IV AZT should be given throughout labor and delivery for a vaginal delivery. It is also important to minimize the baby's exposure to the mother's blood. This can be done by avoiding any invasive monitoring and forceps- or vacuum-assisted delivery.

All babies born to HIV positive mothers should receive anti-HIV medication to prevent mother-to-child transmission of HIV. The usual treatment for infants is 6 weeks of AZT; sometimes, additional medications are also given (see the After Birth Fact Sheet).

For more information:

Contact your doctor or an AIDSinfo Health Information Specialist at 1–800–448–0440 or http://aidsinfo.nih.gov.

Terms Used in This Fact Sheet:

- Intravenous (IV): the administration of fluid or medicine into a vein.
- Mother-to-child transmission: the passage of HIV from an HIV positive mother to her infant. The infant may become infected while in the womb, during labor and delivery, or through breastfeeding. Also known as perinatal transmission.
- Prenatal: the time before birth.
- Rupture of membranes: when the sac containing the unborn baby bursts or develops a hole. Also called water breaking.
HIV Positive Women and Their Babies After Birth

I am an HIV positive pregnant woman, and I am currently on an HIV regimen. Will my regimen change after I give birth?

Many women who are on an HIV treatment regimen during pregnancy decide to stop or change their regimens after they give birth. You and your doctor should discuss your postpartum treatment options during your pregnancy or shortly after delivery. Don't stop taking any of your medications without consulting your doctor first. Stopping HIV treatment could lead to problems.

How will I know if my baby is infected with HIV?

Babies born to HIV positive mothers are tested for HIV differently than adults. Adults are tested by looking for antibodies to HIV in their blood. A baby keeps antibodies from its mother, including antibodies to HIV, for many months after birth. Therefore, an antibody test given before the baby is 1 year old may be positive even if the baby does NOT have HIV infection. For the first year, babies are tested for HIV directly, and not by looking for antibodies to HIV. When babies are more than 1 year old, they no longer have their mother's antibodies and can be tested for HIV using the antibody test.

Preliminary HIV tests for babies are usually performed at three time points:

- within 48 hours of birth
- at 1 to 2 months of age
- at 3 to 6 months of age

Babies are considered HIV positive if they test positive on two of these preliminary HIV tests.

At 12 months, babies who test positive to the preliminary tests should have an HIV antibody test to confirm infection. Babies who test negative for HIV antibodies at this time are not HIV infected. Babies who test positive for HIV antibodies will need to be retested at 15 to 18 months. A positive HIV antibody test given after 18 months of age confirms HIV infection in children.

Terms Used in this Fact Sheet:

**Adherence**: how closely you follow, or adhere to, your treatment regimen. This includes taking the correct dose at the correct time as prescribed by your doctor.

**Anemia**: a condition in which there are too few red blood cells in the blood. Without enough red blood cells, not enough oxygen gets to tissues and organs. Symptoms of anemia include fatigue, chest pain, and shortness of breath.

**CDC (Centers for Disease Control and Prevention)**: an agency of the U.S. Federal government that focuses on disease prevention and control, environmental health, and health promotion and education. [http://www.cdc.gov](http://www.cdc.gov).

**Complete blood count (CBC)**: a routine blood test that measures white and red blood cell counts, platelets (cells involved in blood clotting), hematocrit (amount of iron in the blood), and hemoglobin (an iron-containing substance in red blood cells). Changes in the amounts of each of these may indicate infection, anemia, or other problems.

**Mother-to-child transmission**: the passage of HIV from an HIV positive mother to her infant. The infant may become infected while in the womb, during labor and delivery, or through breastfeeding. Also known as perinatal transmission.

**Oral**: to be taken by mouth.

**P. carinii/jiroveci pneumonia (PCP)**: a common opportunistic infection in which fluid develops in the lungs. It is caused by the fungus Pneumocystis carinii/jiroveci. PCP is considered an AIDS-defining illness by the CDC.

**Postpartum**: the time after giving birth.

Are there any other tests my baby will receive after birth?

Babies born to HIV positive mothers should have a complete blood count (CBC) after birth. They should also be monitored for signs of anemia, which is the main negative side effect caused by the 6-week AZT (also known as Retrovir, zidovudine, or ZDV) regimen infants should take to reduce the risk of HIV infection. They may also undergo other routine blood tests and vaccinations for babies.
Will my baby receive anti-HIV medication?

It is recommended that all babies born to HIV positive mothers receive a 6-week course of oral AZT to help prevent mother-to-child transmission of HIV. This oral AZT regimen should begin within 6 to 12 hours after your baby is born. Some doctors may recommend that AZT be given in combination with other anti-HIV medications. You and your doctor should discuss the options to decide which treatment is best for your baby.

In addition to HIV treatment, your baby should also receive treatment to prevent P. carinii/jiroveci pneumonia (PCP). The recommended treatment is a combination of the medications sulfamethoxazole and trimethoprim. This treatment should be started when your baby is 4 to 6 weeks old and should continue until your baby is confirmed to be HIV negative. If your baby is HIV positive, he or she will need to take this treatment indefinitely.

What type of medical follow-up should I consider for my baby and me after I give birth?

Seeking the right medical and supportive care services is important for your and your baby's health. These services may include:

- routine medical care
- HIV specialty care
- family planning services
- mental health services
- substance abuse treatment
- case management

Talk to your doctor about these services and any others you may need. He or she should be able to help you locate appropriate resources.

What else should I think about after I give birth?

The CDC recommends that in areas where safe drinking water and infant formula are available (such as the United States), women should not breastfeed in order to avoid transmission of HIV to their infants through breast milk.

Physical and emotional changes during the postpartum period, along with the stresses and demands of caring for a new baby, can make it difficult to follow your HIV treatment regimen. Adherence to your regimen is important for you to stay healthy (see What is Treatment Adherence Fact Sheet). Other issues you may want to discuss with your doctor include:

- concerns you may have about your regimen and treatment adherence
- feelings of depression (many women have these feelings after giving birth)
- long-term plans for continuing medical care and HIV treatment for you and your baby

For more information about HIV and pregnancy, your doctor can contact the National HIV Telephone Consultation Service (Warmline), a service that provides health care professionals with HIV information. The number is 1–800–933–3413.

If you are interested in joining a pregnancy registry that monitors HIV positive women during their pregnancies and after giving birth, please visit the Food and Drug Administration's Guide to Pregnancy Registries at http://www.fda.gov/womens/registries. Researchers are especially interested in learning more about the effects of anti-HIV drugs during pregnancy. HIV positive pregnant women are therefore encouraged to register with the Antiretroviral Pregnancy Registry at 1–800–258–4263 or http://www.APRegistry.com.

For more information:
Contact your doctor or an AIDSinfo Health Information Specialist at 1–800–448–0440 or http://aidsinfo.nih.gov.

This information is based on the U.S. Public Health Service's 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 and Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (available at http://aidsinfo.nih.gov).
Appendix
Rapid HIV Antibody Testing During Labor and Delivery for Women of Unknown HIV Status
A Practical Guide and Model Protocol
Rapid HIV-1 Antibody Testing During Labor and Delivery for Women of Unknown HIV Status

A Practical Guide and Model Protocol

January 30, 2004

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Introduction

Effective interventions are available to reduce the rate of perinatal HIV transmission when women are identified as HIV infected early in pregnancy. Pregnant women who are HIV infected but who do not receive prenatal care or do not receive an HIV test during prenatal care are not identified as HIV infected and therefore miss opportunities to reduce the risk of transmission to their infants and to receive life-saving treatments for themselves. With the implementation of screening programs using rapid HIV testing in labor and delivery settings, women with unknown HIV test results during prenatal care (results not documented in the prenatal medical record) can learn their HIV status quickly and receive short-course antiretroviral (ARV) prophylaxis to dramatically reduce the risk of transmitting HIV to their infants. The Centers for Disease Control and Prevention (CDC) recommends routine rapid HIV testing using an opt-out approach for women in labor whose HIV status is unknown (see Dear Colleague Letter, Appendix A).

As a result of a congressional mandate contained in the Ryan White CARE Act Amendments of 2000 that a study should be conducted of perinatal HIV transmission in the United States, the Office of the Inspector General (OIG) issued a 2002 report entitled “Reducing Obstetrician Barriers to HIV Testing.” One of the recommendations in the report is that “CDC should facilitate the development and states’ implementation of protocols for HIV testing during labor and delivery in order to promote testing in this setting as the standard of care.” Implementing rapid testing and short-course ARV prophylaxis in labor and delivery settings is feasible, but as is true when implementing any new screening program and clinical intervention, there are challenges. CDC has established a working group of 10 persons with expertise in obstetrics, pediatrics, public health practice, nursing, health education and training, blood screening and laboratory science, epidemiology, and rapid HIV testing technology to develop this model protocol for rapid HIV screening for women in labor. The working group represents academic institutions and university hospitals, a peer advocacy and support organization for women living with HIV infection, state and federal health agencies, as well as an internationally recognized HIV training and education organization. Each member of the group brings diverse experiences with rapid HIV testing to this document. The committee recognizes that as rapid HIV testing is more routinely implemented in labor and delivery settings, more knowledge will be gained. This guide will therefore be maintained as a “living document” and will be regularly updated and maintained on the CDC Web sites; it can be viewed on the perinatal HIV prevention site (www.cdc.gov/hiv/projects/perinatal/) and the rapid HIV testing site (www.cdc.gov/hiv/rapid_testing).
I. Background on Rapid Testing During Labor and Delivery

Tremendous medical and public health achievements have been made in the prevention of mother-to-child transmission (MTCT) of HIV-1. The risk for infant infection has been reduced from approximately 25% to less than 2% by the use of currently recommended prenatal ARV and obstetric interventions for a woman who is aware of her HIV infection early in pregnancy.

Ideally, all women should be screened for HIV before delivery, during an initial prenatal care visit so that potent combination antiretroviral treatment can be given to women who are HIV-infected. However, according to the CDC, approximately 40% of the mothers of the estimated 280–370 HIV-infected infants born in 2000 were not known to have HIV infection before delivery. It is critical to greatly reduce these missed opportunities for identifying HIV-infected pregnant women during the prenatal period, when the most effective interventions can be delivered.

According to clinical trial data, ARV prophylaxis, even when begun during labor and delivery and then given to the neonate, can reduce MTCT of HIV as much as 50%. To maximize this benefit, it is of utmost importance to obtain HIV test results for women in labor as soon as possible. Timely rapid HIV test results may allow providers to avoid some common obstetric practices that may increase the risk of transmission (e.g., artificial rupture of membranes, amniocentesis, or sampling of blood from the fetus’s scalp), and they can also advise the mother not to breastfeed.

Routinely offering rapid HIV testing to women whose HIV status is unknown during labor and delivery provides the opportunity to reduce transmission even among women who do not seek care until labor begins. The rapid HIV test kits now licensed in the United States allow test results to be available in 20 minutes or less. Results from the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Inc., Bethlehem, Pennsylvania) can be read within 20–40 minutes, and results from the Reveal Rapid HIV-1 Antibody Test (MedMira Laboratories, Inc., Halifax, Nova Scotia) can be read in approximately 5–10 minutes after test procedures are begun. Findings from the CDC-sponsored Mother-Infant Rapid Intervention at Delivery (MIRIAD) study indicate that offering voluntary HIV testing during labor is feasible in obstetric settings and that the OraQuick Rapid HIV-1 Antibody Test, used on whole blood specimens, delivers accurate and timely test results.

The purpose of this document is to offer guidance and practical tips to clinicians, laboratorians, hospital administrators, and policymakers who are planning and implementing a program for HIV rapid testing during labor and delivery for women of unknown HIV status and to provide the general structure of a model rapid HIV testing protocol that can be adapted by staff at facilities that seek to implement rapid testing during labor and delivery. For additional background on perinatal HIV prevention, see References, Other Suggested Reading, and Resources.
II. Planning and Implementing a Rapid HIV Testing Program for Women in Labor: Points to Consider in Preparing to Develop a Rapid HIV Testing Protocol

A. Location of Testing: in the Laboratory or in the Labor and Delivery Unit?

The U.S. Food and Drug Administration (FDA) recently approved a 1-step rapid HIV test that can be performed with whole blood either in the laboratory or at the point of care, that is, in the labor and delivery unit.\textsuperscript{9} With this test, it is possible to obtain results in as little as 20 minutes from the time the specimen is collected. In practice, based on data from the MIRIAD study at 1 site, median turnaround time for test results was 45 minutes in hospitals where testing was performed in the labor and delivery unit, and 3 1/2 hours when specimens were sent to the laboratory.\textsuperscript{10}

Deciding where to conduct rapid HIV testing depends on a number of factors, including logistics in the labor and delivery unit, availability of trained staff, the capacity of the laboratory to consistently convey rapid HIV test results quickly (optimally in less than 60 minutes),\textsuperscript{10} and the Clinical Laboratory Improvement Act (CLIA) categorization of the test device. The OraQuick Rapid HIV-1 Antibody Test is designated by CLIA as waived and can be performed in the labor and delivery unit; the Reveal Rapid HIV-1 Antibody Test is designated under CLIA as moderate-complexity and must therefore be performed in a laboratory.

Point-of-care testing requires training and continual supervision to ensure competent and proficient testing. This requirement can pose a challenge, especially if staff turnover is high. When rapid testing is performed in the laboratory, attaining consistently prompt results requires the availability of 24-hour staff responsive to the urgent need for immediate HIV test results. Choosing the location for rapid testing may be best accomplished after a needs assessment during labor and delivery and consultation with the hospital’s point-of-care testing committee. (See section IV for the training essentials for point-of-care testing.) The College of American Pathologists Commission on Laboratory Accreditation has published a point-of-care testing checklist, which is used as part of its accreditation process. The checklist, which may help to guide the point-of-care testing process in labor and delivery settings, is available at www.cap.org/apps/docs/laboratory_accreditation/checklists/checklistftp.html.

B. Interpretation of Test Results: What Does a Positive Rapid HIV Test Result Mean?

The accuracy of diagnostic tests is expressed in terms of sensitivity and specificity, as well as the positive and negative predictive value of the test result. No test is both 100% sensitive (no false-negative test results) and 100% specific (no false-positive test results). Screening tests are designed to be highly sensitive to ensure that no infected person is missed. The price for this high sensitivity is a slightly reduced specificity, that is, some women who are not infected with HIV will have false-positive HIV screening test results. In addition, the positive predictive value of a test depends on the prevalence of the condition in the group being screened. In a setting where prevalence is high, a positive result from a screening test is much more likely to reflect the person’s true status than is a positive result in an area of low prevalence, where a higher percentage of positive results will be false-positives. In all settings, a positive rapid HIV test result is a preliminary positive result that requires confirmation.
Provisions, therefore, must be made to confirm all preliminary positive rapid HIV test results, as soon as possible, with a supplemental test such as the Western blot or immunofluorescent assay (IFA). However, such testing can take several days or more and does not satisfy the need for timely HIV test results for women in labor. Thus, even in optimal rapid testing programs, some women who are not infected will receive ARV prophylaxis on the basis of a false-positive result from a rapid HIV test. The seriousness of the psychological effect of such a result is self-evident. However, a short course of the ARV prophylaxis currently recommended by the US Public Health Service has no known long-term safety effects for women and infants who are not infected.11 Observational studies and clinical trials have shown that when ARV prophylaxis is administered during labor or within the first 12 hours after birth, the risk of perinatal HIV transmission is reduced from 25% to 9%–13%.2-6 In addition, diagnosing HIV infection during labor and delivery provides a window of opportunity to offer infected women referral and treatment for their own care.

C. Importance of System to Ensure Labor Staff Access to Prenatal HIV Test Results

Experience at several hospitals has shown that HIV testing has often been done during the prenatal period but that results have not been available to labor and delivery staff. The lack of access to prenatal test results thus leads to unnecessary rapid testing and increases the potential for false-positive results and unnecessary ARV prophylaxis. During planning for the implementation of a protocol for rapid testing during labor, it is critical to ensure that all results of HIV testing during pregnancy are documented in the woman’s prenatal record and readily available to labor and delivery staff. Ensuring the availability of prenatal results may require coordination with other antenatal health care facilities to make sure that the pregnant woman signs a medical release and that her prenatal records are routinely and promptly transferred to the delivery facility before the woman’s due date.

D. Choosing the Type of Rapid HIV Testing to Use

Four rapid tests approved by the U.S. Food and Drug Administration (FDA) can provide rapid results during labor and delivery: the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Inc., Bethlehem, Pennsylvania), the Reveal Rapid HIV-1 Antibody Test (MedMira Laboratories, Inc., Halifax, Nova Scotia), the Uni-Gold Recombigen HIV Test (Trinity Biotech Plc., Co Wicklow, Ireland) and the Murex-SUDS-Single Use Diagnostic System HIV-1 Antibody Test (Abbott Laboratories, Abbott Park, Illinois). The SUDS test is no longer available because manufacture was discontinued in 2003.

When selecting a rapid HIV test for use during labor and delivery, it is important to consider the accuracy of the test and the location within the institution at which testing will be performed. Tests that require serum or plasma (i.e., Reveal and SUDS) are more suitable for use in the laboratory because of the need to centrifuge the blood specimen, whereas tests that can be performed with whole blood (e.g., OraQuick, Uni-Gold) without specimen processing are more easily performed in the labor and delivery unit. The sensitivities and specificities, according to clinical licensure data submitted to the FDA, are shown in Table 1.
Because HIV prevalence among pregnant women is low in many parts of the United States, a test with high specificity will minimize the number of false-positive results. Comparisons of the positive predictive values of several FDA-approved HIV-1 antibody tests in populations with differing HIV prevalence rates are shown in Table 2.

Table 1. FDA-approved Test Performance, by Specimen Type*

<table>
<thead>
<tr>
<th>Test</th>
<th>Specimen Type</th>
<th>Sensitivity, % (95% C.I.)</th>
<th>Specificity, % (95% C.I.)</th>
<th>CLIA complexity</th>
</tr>
</thead>
<tbody>
<tr>
<td>OraQuick</td>
<td>Whole blood**</td>
<td>99.6 (98.5-99.9)</td>
<td>100 (99.7-100)</td>
<td>Waived</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral Fluid</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Reveal</td>
<td>Whole blood</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>99.8 (99.2-100)</td>
<td>99.1 (98.8-99.4)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>99.8 (99.0-100)</td>
<td>98.6 (98.4-98.8)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Uni-Gold</td>
<td>Whole blood^</td>
<td>100 (99.5-100)</td>
<td>99.7 (99.0-100)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>100 (99.5-100)</td>
<td>99.8 (99.3-100)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>100 (99.5-100)</td>
<td>99.8 (99.3-100)</td>
<td>Moderate</td>
</tr>
<tr>
<td>SUDS</td>
<td>Whole blood</td>
<td>—</td>
<td>—</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Serum</td>
<td>99.9 (—)</td>
<td>99.6 (—)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>99.9 (—)</td>
<td>99.6 (—)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

* Data from FDA summary basis of approval
** Fingerstick and venipuncture
^ Venipuncture only

Note: SUDS has not been available since August 2003.

Based on the specificity observed in clinical licensure trials, the number of false-positive results would be substantially fewer with OraQuick than with either a single enzyme immunoassay, Uni-Gold or the Reveal rapid test. In fifteen hospitals participating in the MIRIAD study, the prevalence of HIV ranged from 0.3% to 3% among women with unknown HIV status who consented to HIV testing in labor and delivery.

Table 2. Positive Predictive Value of a Single Screening Test for HIV in Populations with Differing HIV Prevalence*

<table>
<thead>
<tr>
<th>HIV Prevalence, %</th>
<th>Estimated Positive Predictive Value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OraQuick (blood)</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>0.3</td>
<td>100</td>
</tr>
<tr>
<td>0.1</td>
<td>100</td>
</tr>
</tbody>
</table>

*Based on point estimate for specificity from FDA summary basis of approval. In practice, the specificity and actual PPV may differ from these estimates.

Note. Trade names are for identification purposes only and do not imply endorsement by the US Department of Health and Human Services or the Centers for Disease Control and Prevention. EIA, enzyme immunoassay; SUDS, Single Use Diagnostic System.
E. Training Labor and Delivery Staff in Rapid Testing

Whether or not point-of-care testing is performed, labor and delivery staff will be called upon to provide women in labor whose HIV status is unknown with information on the availability of rapid HIV testing and perinatal HIV prevention and also to inform them that they will be tested unless they decline. (See section IV. for training essentials for persons performing the test.)

III. Key Elements of a Model Protocol for Rapid Testing during Labor and Delivery

A. Determining Eligibility for Rapid HIV Testing

The prenatal records of all women presenting to the labor and delivery unit should be reviewed for documentation of an HIV test result during the current pregnancy. Any woman without documentation of an HIV test result during the current pregnancy should be routinely screened for HIV by the use of a rapid HIV test and an opt-out approach (see section III. C). Including a standing order (e.g., “provide routine rapid HIV testing if there is no documentation of prenatal HIV test results unless the woman declines”) as part of the admission orders for women in labor may also save valuable time. Clinicians may use an opt-out approach to rapid HIV testing to re-screen women with documented negative HIV test results during the current pregnancy if there are indications that the woman is at continued risk for HIV infection (e.g., a history of sexually transmitted diseases [STDs], exchange of sex for money or drugs, multiple sex partners during the current pregnancy, use of illicit drugs, sex partner[s] known to be HIV-positive or at high risk, or signs and symptoms of seroconversion). This approach is similar to that used for syphilis screening, in which retesting for syphilis during the third trimester and again at delivery is recommended for pregnant women at high risk. Some states mandate syphilis screening at delivery for all pregnant women. Routine universal retesting for HIV by the use of an opt-out approach should be considered in health care facilities in areas with high HIV seroprevalence among women of childbearing age.

B. Ensuring Confidentiality of Pregnant Women

Protecting the confidentiality of the pregnant woman who receives HIV testing during labor is required both by ethical standards and legal requirements. However, in the busy and complex labor and delivery unit, maintaining confidentiality requires that staff members be knowledgeable and vigilant. The following are practical tips to help protect the confidentiality of women who receive rapid HIV testing during labor and delivery:

- Discuss HIV testing when the woman is alone and feels safe to answer honestly: spouses, partners, and other family members may not know her sexual, reproductive or HIV testing history and this information should not be disclosed to them.
- Set up services as part of the rapid testing protocol to make available a professional interpreter, rather than family members, to protect the confidentiality of women who do not speak English.
- Ask the woman in labor ahead of time whom, if anyone, she would like present when the results of the HIV test are provided. Confidentiality should be maintained when giving results, and only the persons the woman has indicated should be present when the test results are provided.
- Ensure confidentiality when discussing ARV prophylaxis if the test result is positive.
- Label intravenous ARV medications in a way that protects confidentiality.
• Develop and implement procedures to ensure the confidentiality of HIV test results received in the labor and delivery unit. Some hospitals maintain a logbook in which to record the following information: the patient’s medical record number, date and time that the HIV test is done in the unit or sent to the laboratory, date and time the test results are received, and notation that the test results have been documented in the chart or communicated to the postpartum unit if the patient has given birth and been transferred. The system should both maintain confidentiality and ensure that results are communicated promptly to clinical staff.

C. Suggested Approaches to Routine Rapid HIV Testing during Labor and Delivery for Women of Unknown HIV Status: Considerations in Implementing the Opt-out Approach

CDC recommends routine rapid HIV testing for women in labor whose HIV status is unknown (women with no documentation of a prenatal HIV test in their medical records) unless they decline testing, that is, unless they opt out (Appendix A, CDC, Dear Colleague Letter, April 22, 2003; also available at: http://www.cdc.gov/hiv/PROJECTS/perinatal/2003/letter.htm). CDC also recognizes that regulations, laws, and policies regarding the HIV screening of pregnant women and neonates are not standardized throughout US states and territories. Health care providers and other hospital staff developing a rapid testing protocol for their facility should be familiar with, and adhere to, state and local laws, regulations, and policies concerning the HIV screening of pregnant women and neonates. They should document in the medical chart the results of all tests, both the rapid and the confirmatory. If a woman in labor and of unknown HIV status refuses rapid HIV screening, her refusal should likewise be noted in the medical chart.

The following information should be given to a woman in labor whose HIV status is unknown so that she has sufficient information to make an informed decision about screening:

1. She should be informed that the HIV virus can be transmitted from a mother to her infant during pregnancy, during labor and delivery, and through breastfeeding and that effective interventions during labor and after birth can substantially reduce the risk that her baby will become infected.
2. She should be informed that rapid HIV testing will be done routinely to help protect her infant’s health unless she declines testing.
3. She should be informed that a negative rapid HIV test result means that she is most probably not HIV infected, but that the test cannot detect very recent infection or recent exposure. A positive rapid test result is preliminary and a confirmatory test will need to be done.
4. She will be offered medicines right away for both her and her baby to reduce the chance that her baby will become infected. If the confirmatory test is also positive, she will be offered medical care for her own health.

All efforts should be made to determine a mother’s HIV status as soon as possible during labor. If the mother’s HIV status remains unknown at delivery, she or the infant or both should have rapid HIV testing as soon as possible postpartum. Some states mandate HIV screening of the neonate in this circumstance; however no states mandate screening of mothers.

Providing information about HIV infection to women in labor whose HIV status is unknown and routinely conducting rapid HIV testing are challenging, but the obstacles can generally be overcome with a thoughtful and systematic approach.
CDC recommends routine rapid HIV testing by the use of an opt-out approach, in which women are informed that HIV testing will be routinely done if her HIV status is unknown during labor and delivery but that she may decline testing (Appendix A, CDC, Dear Colleague Letter, April 22, 2003, available also at: http://www.cdc.gov/hiv/PROJECTS/perinatal/2003/letter.htm). (For an example of a script for an opt-out approach, see Appendix B.) Recognizing that some jurisdictions may still require written, signed informed consent for HIV testing, a sample written informed consent document (opt-in; also included in Appendix B) may be useful during the transition to routine HIV testing during labor and delivery.

The François-Xavier Bagnoud Center (FXBC), of the University of Medicine and Dentistry of New Jersey is an internationally recognized organization dedicated to improving the lives families infected and affected by HIV infection. FXBC has developed a formula for offering routine rapid testing. (For an adaptation of this forumla, see Appendix C, which incorporates both the content that must be covered and the process still required by some state laws.)

D. Currently Approved Rapid HIV Test Kits

Two of the 4 rapid HIV antibody tests currently approved by the FDA are available for clinical use: the OraQuick Rapid HIV-1 Antibody Test and the Reveal HIV-1 Antibody Test. The Uni-Gold Recombigen HIV Test is expected to become available shortly. The availability of rapid HIV tests will change as new devices are developed and approved by the FDA and marketed by manufacturers. Information on the availability of rapid HIV tests is routinely updated on the CDC Web site, at www.cdc.gov/hiv/rapid_testing/ and is also available on the FDA Web site, at http://www.fda.gov/cber/products/testkits.htm. The manufacturer’s instructions for rapid HIV tests should be strictly followed.15,16

E. Interpreting Preliminary and Confirmatory Testing Results

Test results from rapid HIV tests are interpreted the same as other HIV screening test results.

- A negative result from a single test is considered negative. However, if the person being tested may have been exposed to HIV within the past 3 months, a repeat test at a later time is recommended because the rapid antibody test may not show very recent infection.
- A positive (or reactive) result from a rapid HIV test is considered a preliminary positive and must be followed up with a confirmatory test, either a Western blot or an immunofluorescence assay (IFA). Confirmatory testing should be done as soon as possible.
- When the results of a rapid test and a confirmatory test are discrepant, both the rapid and confirmatory test should be repeated, and consultation with an infectious disease specialist is recommended.

F. Providing Results

When the rapid HIV test is discussed, the woman should be told how soon to expect the results. Usually, test results will be available before delivery and are given to the woman during labor, at which time she is asked to consent to antiretroviral prophylaxis if the preliminary result is positive. A woman may state that she doesn’t want to be told the result of the rapid HIV test until after the baby’s birth. In such an instance, consent for the initiation of prophylaxis should be obtained when testing is discussed. If possible, the clinician who discussed the HIV test should give the results.
Privacy during the discussion of test results is essential to ensure confidentiality. The woman’s physical comfort should be assessed and monitored while she is being given test results.

**Providing NEGATIVE rapid HIV test results**

If the rapid test result is negative, no further medical intervention is necessary. The woman should be told that she is most likely not infected with HIV but that the test may not show recent infection. The clinician should ask whether she is concerned about any recent specific risk of exposure; if she is concerned, the clinician should recommend retesting after 3 months if indicated. More extensive HIV counseling should be set up for her during the postpartum period, and she should be told of these arrangements.

**Providing POSITIVE rapid HIV test results**

If the rapid HIV test result is positive, the clinician should tell the woman that she is likely to have HIV infection and that the baby may be exposed to HIV. She should be assured that a second test is being done right away to confirm the rapid test result but that the results will not likely be available before delivery. The clinician should explain that the rapid test result is preliminary and that false-positive results are possible but that it would be best to start ARV prophylaxis as soon as possible to reduce the risk of HIV transmission to the baby. The medication regimen that will be offered to the woman and her baby should be explained, including the known effects and possible adverse effects, and she should be given the opportunity to ask questions before accepting it. She should also be told to postpone breastfeeding until the confirmatory results are available because she should not breastfeed if she is HIV infected. The clinician should explain that all ARV prophylaxis will be stopped if the confirmatory test result is negative.

Preliminary results may not be available before delivery if labor is rapid or the woman is admitted to the unit late in labor. If the preliminary HIV test result is positive, ARV prophylaxis for the neonate should be initiated as soon as possible. (See Section G, for information on peripartum clinical management, scenario 4)

If the confirmatory HIV test result is positive, antiretroviral prophylaxis for the infant, to help prevent perinatal transmission, will be continued.

If the rapid HIV test result is positive, complicated and sensitive information needs to be explained privately to the woman during labor, a very vulnerable time. The clinician should allow time for questions and assure her that with her permission, every measure will be taken to reduce the infant’s risk of acquiring HIV. She should also be reassured that effective treatment is available to help keep her healthy while she is raising her child.

In some settings, the results of the confirmatory Western blot or IFA will be available after the mother and her infant are discharged from the hospital. As part of discharge planning, the woman should be informed of the importance of returning to discuss her confirmatory test result so that both she and her infant can receive appropriate medical care. A system for contacting women who miss appointments to receive their confirmatory test results is important, especially for women who did not receive prenatal care. Involving family members or other support persons in discharge planning...
can be helpful if the woman agrees to their participation and has disclosed her rapid HIV test results to them.

**G. Peripartum Clinical Management of Women with Positive Rapid HIV Test Results**

The US Public Health Service Perinatal HIV Guidelines Working Group publishes Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1–Infected Women for Maternal Health and to Reduce Perinatal HIV-1 Transmission in the United States. The recommendations are available as a living document (frequently updated) at [www.aidsinfo.nih.gov/guidelines/](http://www.aidsinfo.nih.gov/guidelines/). Given the potential complexity of the clinical management decisions, it is strongly encouraged that local protocols for peripartum intervention for women whose HIV infection is diagnosed during labor be developed in consultation with HIV/infectious disease experts.

The current recommendations (version dated November 26, 2003) present 4 clinical scenarios and ARV treatment recommendations to reduce perinatal transmission. Scenarios 3 and 4 (summarized in the following sections) apply to women who arrive in a labor and delivery with undocumented HIV status and who have positive rapid HIV test results. In initiating rapid HIV testing and treatment protocols, hospital staff should access [www.aidsinfo.nih.gov/guidelines/](http://www.aidsinfo.nih.gov/guidelines/) to ensure that they follow the most recently updated recommendations. When hospital policy is being developed, input from clinicians with expertise in perinatal HIV management is encouraged.

**HIV-infected women in labor with no prior treatment**

(The following is a summary of scenario 3 from the USPHS guidelines.)

Several effective ARV treatment regimens are available, including (1) zidovudine (ZDV) monotherapy, (2) ZDV plus lamivudine (3TC), (3) nevirapine (NVP) monotherapy, and (4) ZDV plus NVP. Dosing is described in Table 3.

**Table 3. Antiretroviral regimens for HIV-infected women in labor with no prior therapy.**

<table>
<thead>
<tr>
<th>Medication(s)</th>
<th>Woman</th>
<th>Neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>Intrapartum IV ZDV (loading dose [2 mg/kg] for 1 hour, followed by continuous infusion [1mg/kg/hr] until delivery)</td>
<td>ZDV syrup (2 mg/kg) orally every 6 hours for 6 weeks, beginning 8–12 hours after birth&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ZDV + 3TC</td>
<td>ZDV (600mg) po and 3TC (150 mg) orally at onset of labor, followed by ZDV (300 mg) orally every 3 hours and 3TC (150 mg) orally every 12 hours until delivery</td>
<td>ZDV syrup (4 mg/kg) and 3TC (2 mg/kg) orally every 12 hours for 7 days</td>
</tr>
<tr>
<td>NVP</td>
<td>Single dose of NVP (200 mg) orally at onset of labor&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Single dose of NVP 2 mg/kg 48–72 hours after birth</td>
</tr>
<tr>
<td>NVP+ZDV</td>
<td>Intrapartum IV ZDV (loading dose [2 mg/kg] for 1 hour, followed by [1 mg/kg/hr.] until delivery) and single dose of NVP (200 mg) orally at onset of labor&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ZDV syrup (2 mg/kg) orally every 6 hours for 6 weeks, beginning 8–12 hrs after birth and single dose of NVP (2 mg/kg) orally 48–72 hours after birth</td>
</tr>
</tbody>
</table>

<sup>a</sup> ZDV dosing for infants of <35 weeks gestation at birth is 1.5 mg/kg/dose orally, every 12 hours, increasing to every 8 hours at 2 weeks of age if >30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth.17

<sup>b</sup> If the mother received NVP less than 1 hour before delivery, the neonate should be given 2 mg/kg of oral NVP as soon as possible after birth and again at 48–72 hours.
During the immediate postpartum period, the woman should have appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine whether ARV treatment is recommended for her own health.

A description of recommended intrapartum and postpartum treatment regimens for women identified in labor (USPHS guidelines, scenario 3) is available at www.aidsinfo.nih.gov/guidelines/ and includes data on transmission and the advantages and disadvantages of each regimen. The selection of a specific abbreviated ARV prophylaxis regimen may be based on the resources of the institution or the facility and an individualized clinical assessment of the patient. Clinicians should also weigh the potential for future NVP resistance when considering treatment options.

Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum (Summary of scenario 4 of the USPHS guidelines)

- The 6-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and recommended for the neonate.
- ZDV for the neonate should be initiated as soon as possible after birth—preferably within 6–12 hours.
- Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for the prevention of transmission is unknown, and appropriate dosages for neonates are incompletely defined.
- During the immediate postpartum period, the woman should undergo appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine whether ARV treatment is required for her health. The neonate should undergo early diagnostic testing so that if the neonate is HIV infected, treatment can be initiated as soon as possible.

Note: Discussion of treatment options and recommendations should not be coercive, and the final decision about the use of ARV prophylaxis is the mother’s. The selection of a specific, abbreviated course of ARV prophylaxis may be based on the resources and policies of the institution or the facility, as well as an individualized clinical assessment of the patient.

Intrapartum care
If labor progresses and membranes are intact, artificial rupture of membranes and invasive monitoring should be avoided. Labor should be managed with spontaneous rupture of membranes (SROM). Episiotomy should be avoided if clinically appropriate. Breastfeeding should also be avoided.

Cesarean section
Women diagnosed with HIV infection through rapid testing at the time of presentation for delivery will frequently present in active labor and/or with ruptured membranes. In such circumstances, information regarding maternal viral load will likely not be available to guide the management of delivery. Data are insufficient to indicate whether cesarean section (C-section) will add any benefit in reducing the risk of MTCT. In the only published randomized controlled trial of c-section in HIV-infected women, rates of perinatal HIV transmission between mother-infant pairs with emergency C-section (after active labor or rupture of membranes) and mother-infant pairs with vaginal delivery did not differ. However, for women whose HIV infection was diagnosed late in pregnancy and who have no evidence of labor or rupture of membranes but who have clinical indications for delivery (e.g. preeclampsia, vaginal bleeding, fetal heart rate abnormalities, intrauterine growth retardation,
oligohydramnios), c-section may help to prevent HIV transmission. Management in such circumstances should be individualized, and accepted principles should be taken into consideration:

1. The greatest benefit in preventing transmission is associated with cesarean delivery performed before the rupture of membranes or to the onset of labor in conjunction with the administration of ARV prophylaxis.
2. ARV prophylaxis should be administered to the woman before cesarean delivery whenever possible (ideally, 2–4 hours).

A more comprehensive discussion of the role of C-section in the prevention of perinatal HIV transmission is available in the U.S. 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 (www.aidsinfo.nih.gov/guidelines/).

Neonatal care
- The neonate should be bathed promptly after birth and before injections (e.g., vaccines or vitamin K).
- A baseline complete blood count (CBC) with differential AND serum chemistries should be performed before initiating ARV prophylaxis. A CBC should be repeated at 6 and 12 weeks of age.
- Polymerase chain reaction (PCR) testing for HIV-1 should be done at birth (before 48 hours of age) and repeated at ages 1–2 months and 3–6 months. Additional testing at 14 days of age might allow the early detection of infection.20

*HIV-exposed infants should be evaluated by, or in consultation with, a specialist in HIV infection in pediatric patients. Regular updates of the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection are available at www.aidsinfo.nih.gov/guidelines.

H. Communication with Pediatricians

It is crucial that the obstetric provider communicate with the pediatric provider when a neonate has been exposed to HIV. The medical care of an HIV-exposed infant is different than that of an infant who has not been exposed to HIV. In some states, regulations ensure that the obstetric provider’s communication of the mother’s HIV status to the pediatric provider is not considered a breach of confidentiality.

I. Referral for Follow-up of HIV-infected Mother and HIV-exposed Infant

Both mother and infant need to be referred for ongoing care to providers with experience and expertise in HIV care. Services for families affected by HIV infection are available in many communities through Title IV or Title III of the Ryan White CARE Act. HIV-infected mothers who are just learning their HIV status or who have not been in care need a thorough evaluation of their immune and clinical status and assessment of their need for ARV treatment or other care. Infants need diagnostic testing and clinical monitoring to determine their HIV status. All infants exposed to HIV should be placed on an antibiotic for prophylaxis against *Pneumocystis carinii* pneumonia (PCP) at 6 weeks of age, and should continue to receive it until it has been confirmed that they are not infected with HIV.20 Families need access to case management and psychosocial support services, ideally through a comprehensive, family-centered HIV program. In some communities, a case manager from the family HIV care program will visit the mother in the hospital if notified of the referral.
Before discharge, the mother should be educated about the ARV prophylaxis and why it is important that the infant complete the full course of medication. Teaching should emphasize that (1) the infant must complete the ARV prophylaxis, (2) the infant should begin taking antibiotic prophylaxis for PCP at 6 weeks of age, (3) the infant will need further testing during the first few months of life to determine HIV status, and (4) the mother should return to receive confirmatory HIV test results (if not received before discharge). If the mother has disclosed her HIV status to a family member or other support person, it is beneficial to involve the support person in instructions about the necessary follow-up care of both mother and infant.

J. Reporting HIV/AIDS

If Western blot or IFA test results confirm HIV infection, the facility must follow all applicable local and state requirements regarding the reporting of HIV infection or AIDS. If personnel are uncertain about the HIV/AIDS reporting requirements in their area, they should contact their state health department HIV/AIDS surveillance unit.

IV. Management Considerations in Developing and Implementing a Facility-based Rapid HIV Testing Protocol for Women in Labor: Preparation and Training

A. Key Players

Training is essential when introducing a new procedure to labor and delivery care. The entire patient care team should be educated about rapid HIV testing during labor. The hospital laboratory staff should be involved in developing and maintaining a quality assurance program.

B. Training of Labor and Delivery Staff--Rapid HIV Testing for Women in Labor

It is essential to provide ongoing training for labor and delivery staff in providing information about HIV infection and rapid testing for women in labor whose HIV status is unknown. Without such training, many nurses, obstetricians, nurse-midwives, residents, and house staff may not have up-to-date information about perinatal HIV transmission or the experience, comfort, or skill to use sensitivity when providing women with accurate information about rapid HIV testing or to perform rapid HIV testing during labor and delivery.

Who should be trained

Training in rapid HIV testing and intrapartum or neonatal ARV prophylaxis to reduce perinatal HIV transmission should be available for all staff who provide care for pregnant women, women in labor, and neonates. These staff members include obstetricians, residents and house staff, family practice physicians, nurse-midwives, labor and delivery nurses, perinatal nurse educators and managers, nurse practitioners, pediatricians, and infection control practitioners.

In nonteaching hospitals, the labor and delivery nurse is the person most likely to assess the woman’s medical record for documentation of HIV testing and to provide the woman with information about rapid HIV testing. In teaching hospitals, medical residents, house staff, obstetricians, or nurse-
midwives are most likely to have the responsibility for offering rapid testing. However, the labor and delivery nurse plays an important role in admission assessment, patient teaching, and support.

**Content**
The training should include the following:
- The failure of risk-based HIV testing to identify HIV-infected pregnant women
- Local, regional, and national HIV/AIDS statistics for women
- CDC guidelines for HIV testing for women in labor
- Factors that influence perinatal HIV transmission
- Interventions to reduce transmission during labor and postpartum
- Short-course ARV prophylaxis for mother and infant
- Strategies to ensure confidentiality
- Approaches to providing information during labor
- Methods for interpreting rapid test results
- Local referrals and follow-up care for the HIV-infected woman and her infant

Training in ARV prophylaxis should include the options for preventing MTCT, strategies for ensuring the availability of medication, specifics of medication administration for mother and infant, and teaching and follow-up for mother and infant.

**Teaching strategies and methods for staff:** Didactic or independent learning (computer-based or Web-based) works well for HIV statistics, factors that influence perinatal transmission, current research, treatment to reduce perinatal transmission, and specifics about the rapid test.

**Case-study discussion** in small groups can be the best approach for skill building and problem solving and for exploring attitudes. One or two cases can be discussed in approximately 30 minutes.

**Role-playing** can be used separately or with case-study discussion to practice discussions about rapid testing of the mother during labor or rapid testing of the infant during the postpartum period. One session of role-playing can usually be completed and discussed in 30?–45 minutes.

**Opportunities to provide training**
The busy labor and delivery suite does not offer many opportunities for formal in-service training. Thought is needed to present content and make it available at times that are convenient for obstetric staff and providers. Motivation for learning can be increased if CME (continuing medical education) credit and nursing CE (continuing education) contact hours are provided.

In the fall of 2003, CDC funded the Health Research Education Trust, the research and education affiliate of the American Hospital Association ([www.hret.org](http://www.hret.org)) and the François-Xavier Bagnoud Center ([www.fxbcenter.org](http://www.fxbcenter.org)) to develop model policies, tools, and training materials to assist hospitals and birthing centers implement rapid HIV testing programs in labor and delivery units.
C. Training Essentials for Persons Performing Point-of-Care Rapid HIV Testing

The OraQuick rapid HIV test is used as an illustration of a test that can be performed in the labor and delivery unit. The laboratory, medical, or nursing staff may lead the training session. Including the following suggested points will allow trainees to:

- Review the OraQuick package insert along with the facility’s standard operating procedure.
- View the OraQuick rapid HIV antibody testing video
- Observe a demonstration of setting up the OraQuick Rapid HIV Antibody Test
- Perform a panel of 5 known specimens and obtain 100% accuracy
- Take a competency test on the OraQuick rapid HIV test—100% accuracy or counseling documented for incorrect answers

The following points should be emphasized as part of training staff to carry out rapid HIV testing:

- Handle requests for rapid HIV testing stat.
- Verify that appropriate positive and negative controls have been performed on the lot number in use and match expected results before setting up a patient’s specimen.
- Read the OraQuick Test 20 minutes after setup. Do not exceed 40 minutes. A timer can be clipped onto one’s uniform to ensure that the test is read within time limit.
- Report results as soon as possible (no longer than 60 minutes after receipt of specimen).
- Document all rapid HIV test results and inform the patient’s health care provider according to protocol.
- Refer all specimens that test preliminary positive to the appropriate laboratory for confirmatory testing.

In October 2003, CDC began to offer a training course called Fundamentals of HIV Testing Using the OraQuick Rapid HIV-1 Antibody Test in various locations throughout the United States. Information about the training and a regularly updated list of the cities can be found at [http://www.cdc.gov/hiv/rapid_testing/](http://www.cdc.gov/hiv/rapid_testing/). In early 2004, CDC will partner with the François-Xavier Bagnoud Center to offer regional training specific to perinatal HIV prevention, with emphasis on rapid HIV testing in labor and delivery settings. In addition, to assist with local training, OraSure, for example, offers a short training video about performing the OraQuick HIV-1 antibody test.

D. Ensuring Staff Proficiency and Competency to Carry Out Rapid HIV Testing in Labor and Delivery Settings

Implementation of a rapid HIV testing program is essential to effect the quick (no longer than 60 minutes) turnaround time of results, which is needed to offer timely prophylaxis to women in labor whose HIV status is undocumented but whose specimens are reactive (positive) to the rapid HIV test. All laboratories and testing sites must adhere to the minimum requirements of the Clinical Laboratory Improvement Act of 1988 (CLIA88). Because of the critical clinical implications of this test result, it is of the utmost importance to ensure accurate testing and the reporting of all results. CDC has developed quality assurance guidelines for performing rapid HIV testing, which are available at [www.cdc.gov/hiv/rapid_testing/](http://www.cdc.gov/hiv/rapid_testing/).
The keys to successful performance of rapid HIV testing and reporting are

- Clear and concise procedures
- Training of personnel
- Verification of competence of personnel
- Proper performance of quality control procedures
- Recognition of when the testing does not comply with procedures

In a laboratory, these duties would be managed by a Quality Control or Quality Assurance Compliance Officer. In a point-of-care testing (POCT) setting, it is important to establish a POCT coordinator (typically a laboratorian) who is responsible for training, quality control, and quality assurance issues.

One way to assess the capacity of the laboratory or testing site to accurately test and report rapid HIV results is through proficiency testing, “an external program in which samples are periodically sent . . . for analysis.” The results from the individual participants are compared to the expected values. Each site receives a graded individualized report and a summary report showing their performance and the performance of all the participants. Proficiency testing is desirable, even for the CLIA-waived OraQuick test, because the decision to administer ARV prophylaxis will be based initially on a single, preliminary positive result. CLIA-certified laboratories and testing sites are required to participate in a proficiency testing program that is approved by the Center for Medicare and Medicaid Services for any test that is not certified by CLIA as waived (e.g., Reveal).

Another mechanism for ensuring the accuracy of test results is continued competency testing of personnel. Competency testing refers to the periodic evaluation of a person’s ability to “perform a test and use the testing device.” CLIA88 requires each person who is authorized to perform rapid HIV testing that has not been waived by CLIA (e.g., Reveal) and report results to perform competency testing semiannually the first year and at least annually thereafter. Competency testing can take many forms, including performance of the test on known specimens, direct observation, a written examination on the test, and a Web-based competency test. Although this testing is not explicitly required for CLIA-waived tests (e.g., OraQuick), it is recommended to ensure competency, and it is desirable because the decision to administer ARV prophylaxis will be based on 1 preliminary positive result of a rapid HIV test.

For testing done in the labor and delivery unit, the POCT coordinator would keep records of all training and competency verification of personnel, quality control, patient testing, and proficiency testing.

V. Conclusion

Until all HIV-infected pregnant women are tested for HIV infection during prenatal care, the promise of the findings of AIDS Clinical Trials Group Protocol 076, the first study to demonstrate the efficacy of an ARV medication (i.e., AZT) to substantially reduce perinatal HIV transmission, and the findings of other important perinatal HIV prevention studies—that perinatal HIV transmission can largely be prevented and virtually eliminated—cannot be realized. Although efforts are in place to improve access to prenatal care, prenatal HIV testing, and ARV prophylaxis, opportunities to prevent perinatal HIV transmission continue to be missed, and infants acquire HIV infection. The routine use
of rapid HIV testing and medical interventions in labor and delivery settings provides a final opportunity to reduce the effect of those missed opportunities for prevention. It is recommended that **hospitals adopt a policy of routine rapid HIV testing by using an opt-out approach for women whose HIV status is unknown when presenting to the labor and delivery.** It is recognized that implementing rapid testing programs in labor and delivery settings poses challenges. However, clinicians in labor and delivery settings frequently make complex medical decisions, implement emergency life-saving interventions, and discuss sensitive and difficult personal information with patients. This document is intended to assist clinicians by adding another important tool to their repertoire of clinical screening and HIV prevention interventions.

For inquiries or comments, e-mail Margaret A. Lampe, RN, MPH (mlampe@cdc.gov).

**Acknowledgments**

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References


**Suggested Reading**


**Resources**


Includes current CDC perinatal HIV prevention programs, current CDC recommendations and studies on perinatal HIV prevention in the United States, and notices and summaries of national meetings of CDC perinatal HIV prevention grantees.


Includes frequently asked questions about rapid HIV testing, official CDC and FDA releases, and studies on rapid tests.
Women and Children with HIV Web site of François-Xavier Bagnoud Center (University of Medicine and Dentistry of New Jersey) and Center for HIV Information (University of California San Francisco). Available at: http://www.womenchildrenhiv.org/.

Includes clinical information, training resources, and best-practice recommendations regarding perinatal HIV prevention and pediatric HIV infection. Resources for U.S. and international settings.


Includes fact sheets, data sets, summary slides, a searchable database of clinical trials, a resource directory, and a physician network for expert discussion on treatment. Additionally, members will be able to participate in confidential and secure discussion boards; read about real people living with, and successfully managing, HIV; download advocacy tools; and receive a regular e-mail newsletter highlighting the most up-to-date information about women and HIV infection.
Appendix A

Letter from Dr. Julie Louise Gerberding, Director
Centers for Disease Control and Prevention

and

Dr. Harold W. Jaffee, Director
National Center for HIV, STD, and TB Prevention
Dear Colleague:

The prevention of perinatal HIV transmission requires routine HIV screening of all pregnant women and the use of appropriate antiretroviral and obstetrical interventions that begin during pregnancy. Together, these actions can reduce the rate of mother-to-child HIV transmission to 2 percent or lower. Recently, new data have emerged indicating that higher testing rates are associated with testing strategies that routinely incorporate HIV tests in the standard battery of tests for all pregnant women. In light of this information, the Centers for Disease Control and Prevention (CDC) recommends that HIV testing be a routine screening procedure. CDC also recommends implementing rapid HIV testing in postnatal settings for infants of women not tested prenatally. Considering the potential for preventing transmission, no child should be born in this country whose HIV status, or whose mother’s status, is unknown.

CDC published data on recent prenatal HIV testing rates in the United States and Canada in the Morbidity and Mortality Weekly Report (MMWR,) of November 15, 2002. This study examined HIV prenatal testing rates associated with three different prenatal testing approaches from data gathered from 16 states and 5 Canadian provinces. A brief description of the testing approaches and data findings follows:

1. **“Opt-in”:** Pregnant women receive pre-HIV test counseling and must specifically consent to an HIV antibody test, usually in writing. This is the most common prenatal HIV testing approach in the United States. Among eight states using the “opt-in” approach where data were collected from medical records for 1998—1999, testing rates ranged from 25 percent to 69 percent. Canadian testing rates in three “opt-in” provinces ranged from 54 percent to 83 percent.

2. **“Opt-out”:** Pregnant women are notified that an HIV test will be routinely included in the standard battery of prenatal tests for all pregnant women, but they can decline HIV testing. Currently, Arkansas, Michigan, Tennessee, and Texas have adopted some version of this approach. In Tennessee, where this approach was used, a testing rate of 85 percent was reported. Two Canadian provinces using this approach showed a testing rate of 98 percent and 94 percent.

3. **Mandatory newborn screening:** If the mother’s HIV status is unknown at delivery, newborns are tested for maternal HIV-antibody, with or without the mother’s consent. Results must be available within 48 hours of testing. Connecticut and New York have implemented these approaches (in combination with an opt-in approach for pregnant women). In these two states, data indicate that prenatal testing rates rose from 52 percent to 83 percent in a seven-county area of New York, and from 31 percent to 81 percent in Connecticut, during the periods just before and just after implementation of mandatory newborn testing. In 2001, New York reported a statewide prenatal HIV testing rate of 93 percent based on newborn metabolic screening of all live births.
Prenatal HIV Screening

Based on information presented in the MMWR, the available data indicate that both “opt-out” prenatal maternal screening and mandatory newborn screening achieve higher maternal screening rates than “opt-in” prenatal screening. Accordingly, CDC recommends that clinicians routinely screen all pregnant women for HIV infection, using an “opt-out” approach, and that jurisdictions with statutory barriers to such routine prenatal screening consider revising them.

Newborn HIV Screening

In addition, CDC encourages clinicians to test for HIV any newborn whose mother’s HIV status is unknown. Jurisdictions should consider whether a mandatory screening policy for these infants is the best way to achieve such routine screening. Data demonstrate that detection of HIV infection during pregnancy through HIV testing of all pregnant women affords the best opportunity to deliver interventions when they are most efficacious. When intervention does not begin until the intrapartum or neonatal periods, 9 percent to 13 percent transmission rates are achievable based on clinical trial and observational data. Recent experience from the CDC funded Mother-Infant Rapid Intervention at Delivery (MIRIAD) study indicates that HIV rapid testing of women can be done during labor, and that antiretroviral interventions can be quickly delivered to HIV-infected mothers and their infants. Therefore, for those women whose HIV status is unknown at labor, CDC recommends routine, rapid testing. When the mother’s HIV status is unknown prior to the onset of labor and rapid HIV testing is not done during labor, CDC recommends rapid testing of the infant immediately post-partum, so that antiretroviral prophylaxis can be offered to HIV-exposed infants.

The federal Food and Drug Administration has approved three rapid HIV test kits (SUDS Oraquick and Reveal which can be used at delivery. When rapid test results are positive, antiretroviral interventions can be offered to the mother intrapartum and to her infant based on the preliminary results. Confirmatory testing should occur as soon as possible after delivery.

Sincerely,

Julie Louise Gerberding, M.D., M.P.H.
Director

Harold W. Jaffe, M.D.
Director
National Center for HIV, STD, and TB Prevention
References

1 CDC. Revised recommendations for HIV screening of pregnant women. MMWR 2001; 50(RR-19):59-86.
6 CDC. Notice to readers: Approval of new rapid test for HIV antibodies. MMWR 2002; 51:1051-2.
Providing Information to Women in Labor with Unknown HIV Status Regarding Routine, Rapid HIV-1 Antibody Testing (Using an OPT-OUT Approach)

Eligibility

Pregnant women in labor and delivery settings who have no documentation of HIV testing on prenatal record or no history of prenatal care.

How to Use This Script:

- The script is meant to be a guide to help you inform women in labor. Background information/instructions are in regular type, words you can use are in italics – italics are hard to read – suggest reworking – perhaps putting them in quotation marks.]
- It is important to show empathy while you are talking with the laboring woman – through your body language and/or through holding her hand/touch.
- Tell the woman she should signal you when a contraction is happening, so you can pause until it is over.
- Pause to verify understanding. Adjust your terminology as needed.
- Tell the woman that the discussion about HIV testing will be kept confidential.

Before discussing HIV testing, ensure that the woman is between contractions, that she is fairly comfortable, and that she is alone (no family member or significant other is present in the room, or within hearing). Tell her that you are going to talk to her about HIV testing, and ask if she wants her partner or family member to be present.

Introduction

You can begin the discussion in the following way:

We recommend HIV testing to all women in labor for whom we don’t have records of an HIV test result during pregnancy. We do this because so much can be done to protect the babies of women living with HIV, and to help women live a healthier, longer life. We have no record that you had an HIV test during this pregnancy.

I have three things I am going to talk to you about:

- A special HIV/AIDS test
- Why this test is important for you and your baby, AND
- What happens when the test result comes back

A special HIV/AIDS test

- It is important for you and your baby that you have a “rapid” HIV test. HIV is the virus that causes AIDS
- This test can give us results quickly
- It is a blood test that we do for all women in labor without results from a prenatal HIV test unless they decline to have the test.
Why the test is important
- Human Immunodeficiency Virus (HIV) is the virus that causes AIDS
- HIV is a serious illness that can affect a woman’s health and her baby’s health.
- One of the ways HIV is spread is by unprotected sex. Therefore, all pregnant women may be at risk for HIV infection.
- HIV can be passed from a mother to her baby during pregnancy, at delivery, and through breastfeeding.
- If you have HIV infection, rapid testing will allow you to get medication during labor and delivery to reduce the risk of passing HIV to your baby.
- Your baby will receive the same medication after birth.
- Without treatment, the chance the baby will be infected is about 25%, or 1 in 4 babies.
- We know if women are given medication during labor and delivery and their babies get the medication right after birth, we can reduce the risk of HIV transmission to about 10%, or about 1 in 10 babies.

What happens when the rapid test result comes back?
- You will receive a preliminary result about an hour after your blood is drawn.
- If the rapid HIV test is negative, no further testing is needed at this time. It is most likely that you do not have HIV. However, the test may not show very recent infection.
- If the rapid test is negative it is OK to breast feed your baby.

If the rapid HIV test is positive
- You likely have HIV infection and your baby may have been exposed to HIV
- The test is a screening test that provides a preliminary result and a false-positive result can happen.
- We always do a second test to confirm rapid tests that are positive.
- To be safe, it is best to start medicines to help prevent transmission of HIV to your baby, while we wait for the confirmatory test result.
- Experts recommend several medicines to reduce chance your baby will get HIV. One is called AZT and it is given through your IV fluids into your vein. The other is a pill called nevirapine.
- Your doctor will decide which medicines will be best for you and your baby and will discuss them with you before starting them.
- After your baby is born, he/she will start taking AZT syrup.
- These medicines have been studied for in pregnant women and newborns and there have been no serious side effects.
- Side effects that may occur with AZT are: vomiting, headache, feeling tired, anemia (low red blood cell numbers), decreased number of white blood cells, that fight infection, loss of appetite, heartburn, trouble sleeping. Side effects of nevirapine can be skin reactions or problems with the liver.
- You should wait until we have the results of the confirmatory test before you start breastfeeding.

If the confirmatory test is negative
- You and your baby will immediately be taken off any medication that was started.

If the test is confirmed as positive
- All medication that was started to help prevent HIV transmission will continue.
- If treatment is started, a doctor or nurse will discuss again any consequences of taking the medication.
- Your baby will need more testing for HIV infection.
- You will be referred to a physician for your own medical care—there are also medications to help keep you healthy longer. You will also be referred to a health care provider who will take care of your baby’s medical needs.
- HIV test results are confidential. There are laws to protect people with HIV from discrimination.
Conduct rapid HIV testing and document the result clearly in the medical record.

If the woman declines HIV testing, probe for her reasons and help her address her concerns. If she still declines testing, document her refusal clearly in the medical record and communicate to her baby’s pediatrician that her HIV status is unknown.
Sample Consent for Rapid HIV-1 Antibody Testing in Labor and Delivery Settings for Women with Unknown HIV Status (Using an OPT-IN Approach)

This is a sample consent form (OPT-IN) from the Francois Xavier Bagnoud Center for use in New Jersey. Recognizing that a number of jurisdictions may still require written, signed informed consent for HIV testing (an OPT-IN approach), this sample informed consent document may be useful during the transition to a more routine (OPT-OUT) approach to HIV testing in labor and delivery.

Introduction

New Jersey law mandates that all pregnant women be counseled about HIV infection and be offered the HIV/AIDS test. In our hospital, we follow this recommendation because so much can be done to protect the baby.

I have four things I am going to talk to you about

- A special HIV/AIDS test
- Why this test is important for you and your baby
- How HIV is transmitted
- What happens when the test result comes back

A special HIV/AIDS test

- It is important for you and your baby that we offer you what is called a “rapid” HIV test. Human Immunodeficiency Virus (HIV) is the virus that causes AIDS.
- This test can give us results quickly.
- It is a blood test. It is voluntary, and your consent is required before the test can be done.

Why the test is important

- HIV can be passed from a mother to her baby during pregnancy, at delivery, and through breastfeeding.
- If you have HIV infection, rapid testing will allow you to get medication during labor and delivery to reduce the risk of passing HIV to your baby.
- Your baby will receive the same medication after birth.
- Without treatment, the chance the baby will be infected is about 25%, or 1 in 4 babies.
- We know if women are given medication during labor and delivery and their babies get the medication right after birth, we can reduce the risk of HIV transmission to about 10%, or about 1 in 10 babies.

What is HIV and how is it transmitted?

- HIV is the virus that causes AIDS.
- HIV is a **serious** illness that can affect a woman’s health and her baby’s health.
- One of the ways HIV is spread is by unprotected sexual intercourse. Therefore, **all** pregnant women may be at risk for HIV infection.
- HIV can be passed from a mother to her baby during pregnancy, at delivery, and through breastfeeding.

**What happens when the rapid test result comes back?**
- You will receive a **preliminary** result about an hour after your blood is drawn.
- If the rapid HIV test is **negative**, no further testing is needed at this time. It **most likely means** that you do not have HIV. However, the test may not show recent infection.
- If the rapid test is negative it is OK to breast feed your baby.

**If the rapid HIV test is positive**
- You **likely** have HIV infection and your baby **may** have been exposed to HIV.
- The test is a **screening** test that provides a preliminary result. A false-positive result can happen.
- We always do a second test to confirm rapid tests that are positive.
- **But if your test result is positive, it is be best** to start treatment to help prevent transmission of HIV to your baby, while we wait for the confirmatory test result.
- We will need your permission to start medications if the preliminary test is positive.
- Experts recommend several medicines to reduce the chance your baby will get HIV. One is called AZT. We give it to you in your IV fluids through your vein. The other is a pill called nevirapine.
- Your doctor will decide which medicines will be best for you and your baby.
- After your baby is born, he/she will start taking AZT syrup.
- These medicines have been studied in pregnant women and newborns and there have been no serious side effects.
- Side effects that may occur with AZT are vomiting, headache, feeling tired, anemia (low red blood cell numbers), decreased number of white blood cells that fight infection, loss of appetite, heartburn, trouble sleeping. Side effects of nevirapine can be skin reactions or problems with the liver.
- You should **wait** until we have the results of the confirmatory test before you start breastfeeding.

**If the confirmatory test is negative**
- **You and your baby will immediately be taken off any medication that was started.**
If the test is confirmed as positive

- All medication that was started to help prevent HIV transmission will continue.
- If treatment is started, a doctor or nurse will discuss with you again any consequences of taking the medication.
- Your baby will need more testing for HIV infection.
- You will be referred to a physician for your on-going medical care. You will also be referred to a health care provider who will take care of your baby’s medical needs.
- HIV test results are confidential. There are laws to protect the rights of people with HIV and prevent discrimination.

Sample Informed Consent Form

Please sign your name below once you have read (or have had explained to you) and understand:

1. Antiretroviral medication may reduce the risk of HIV transmission to my baby and this medication will be started if my preliminary HIV test result is positive.
2. A positive preliminary test will be confirmed with additional testing.
3. Refusing to be tested will not jeopardize my ongoing care or services.
4. I have been given written information about everything told to me.

☐ I consent to be tested for HIV infection using a rapid test

☐ If my preliminary HIV test is positive, I consent to have antiretroviral medication started during labor and for my baby after birth

☐ I decline to have rapid HIV testing at this time.

Name_________________________________________    Signature__________________________________________

(Print)

Date__________________________________________    Witness____________________________________________
Appendix C

The François-Xavier Bagnoud Center’s Formula for Offering Routine, Rapid HIV Testing to Women in Labor with Unknown HIV Status
The François-Xavier Bagnoud Center’s Formula for Offering Routine, Rapid HIV Testing to Women in Labor with Unknown HIV Status

(Based on the mnemonic “C³R³”)

The three Cs represent confidentiality, comfort, and consent. The three Rs are reasons for the rapid test, results, and “Rx” for treatment, or medications to reduce mother to child transmission.

C³

- **Confidentiality**: It is important to reassure the woman that the discussion about HIV testing will be kept confidential and that the information will not be shared with her partner or family without her permission.
- **Comfort**: The clinician should assess the woman’s stage of labor, comfort level, and need for analgesics. Providers need to show empathy while presenting information about rapid HIV testing. The content covered should be short and to the point and should be explained between contractions. The clinician should ask the woman to signal for a pause when a contraction is starting. The clinician should always consider the woman’s language and culture and, as needed, must adjust the terminology used. The clinician should make sure that the woman being counseled understands the content being covered by checking after each point is made and before beginning the next point to be sure she understands.
- **Consent** for testing and for antiretroviral treatment, if needed, in labor: Regulations, laws, and policies about HIV testing of pregnant women vary from state to state. Providers need to know and need to follow the laws and policies of their state. The minimum content that should be included in educating a pregnant woman about HIV rapid testing during labor is detailed next under *Reasons to test*.

R³

**Reasons to test**: The woman should be informed of the important reasons to get an HIV test during labor, and the crucial opportunity to prevent possible transmission of the virus to her unborn baby should be emphasized:

- HIV is the virus that causes AIDS. One of the ways HIV is spread is by unprotected sexual intercourse. Therefore, all pregnant women are at risk for HIV infection.
- A woman could be at risk for HIV and not know that she is at risk.
- The HIV virus can be passed from a mother to her baby during pregnancy, at delivery, and through breastfeeding.
- Learning that a woman has an HIV infection while she is still in labor gives her a crucial opportunity to reduce the risk of transmitting HIV to her infant; and, just as importantly, having this knowledge also ensures that both she and her baby receive the care and the treatment they need.
- HIV testing is recommended for all pregnant women. Hospital/national policy (and/or state law) recommends HIV testing for all women in labor with unknown HIV status.
- Unless the woman refuses to be tested, our hospital routinely does rapid HIV testing for all women in labor who don’t already have an HIV test result in their medical record.

**Results**

- If she is tested for HIV during labor, a woman should be told when she will receive her test results.
• A negative HIV test result means a woman almost certainly does not have HIV infection at this time. A positive HIV test result means a woman likely has HIV infection even if she is feeling well. Further testing will be done after she delivers to confirm if she has HIV infection.
• A woman should be asked who she wants to be present when she receives her rapid HIV test result.

Rx – Medications
• Medications can reduce the risk of transmission of HIV to the baby. Without medication, the chance the baby will be infected is about 25%—or about 1 baby in 4 births could be infected with HIV. With the medications given to the woman during labor and to the newborn, the risk of HIV transmission can be reduced to about 10— or to about 1 baby out of 10 births.
• If a woman is found to have HIV infection, treatment is available to help keep her well.
• Any medication will be stopped if the confirmatory HIV test result is negative.
Appendix D

Boxed Case Studies:

Development of a Statewide Standard of Care:
The New Jersey Experience

and

A Review of the Implementation of
Perinatal HIV Rapid Testing
Medical Center Of Louisiana, New Orleans
New Jersey is a high prevalence state for HIV disease, ranked fifth in the country in cumulative reported AIDS cases, third in the country in cumulative reported pediatric AIDS cases, and first in the country in the proportion of women among reported cumulative AIDS cases. Ninety-four percent of the pediatric AIDS and HIV cases are attributed to perinatal transmission.

The approach taken by the New Jersey Department of Health and Senior Services (NJDHSS) was to conduct a needs assessment to determine the major missed opportunity to reduce vertical transmission, develop a standard of care in collaboration with stakeholders with consensus facilitated by meeting with stakeholders individually (i.e. meetings with the obstetrical society), dissemination of information, and evaluation of implementation and effectiveness.

Needs Assessment
The need for a statewide standard of care for women who present in labor with the delivery team unaware of her HIV status was determined based on several factors. These include:
1) A review of missed opportunities that indicated that currently the major barrier to maximal reduction of vertical HIV transmission in New Jersey is women who present in labor with unknown HIV status;
2) Advances in HIV diagnostic testing technology and medical management that led to recent national recommendations that women who present in labor with unknown HIV status should receive counseling, be offered rapid HIV diagnostic testing, and, if HIV positive, be offered short course therapy;
3) Results of a study that was conducted in the highest risk areas in New Jersey that determined that none of the hospitals providing obstetrical care had policies, procedures, or laboratory capability to provide counseling and offer rapid testing and short course therapy; and
4) Meetings with two ad hoc advisory committees of stakeholders.

Working with Stakeholders
- Two ad hoc advisory committees were developed and met to 1) determine if a statewide approach was appropriate and 2) to develop the prototype policy and algorithm that facilities providing obstetrical care could implement for women who present in labor with unknown HIV serostatus.
- One ad hoc advisory committee consisted of stakeholders responsible for writing and implementing the Standard of Care. This ad hoc advisory committee included representatives from the New Jersey Department of Health and Senior Services (Division of AIDS Prevention and Control and the Division of Family Health Services), obstetricians, pediatricians, Title IV providers, the New Jersey Family-Centered HIV Care Network, case managers, social workers, consumers, maternal and child health consortia, infection control professionals, the Academy of Medicine of New Jersey, the AIDS Education and Training Center, and Medicaid. This committee met three times. The unanimous decision was that a statewide Standard of Care was the best approach to take in New Jersey. The committee felt that the NJDHSS should be the lead on developing, disseminating, and evaluating the Standard of Care. In the fall of 2001, the NJDHSS approved the draft of the Standard of Care for Women Who Present in Labor With Unknown HIV Status, which was written with the ad hoc advisory committee.
• The second ad hoc advisory committee consisted of stakeholders responsible for facilitating implementation of the Standard of Care. This ad hoc advisory committee included representatives from the New Jersey Department of Health and Senior Services (Division of AIDS Prevention and Control and the Division of Family Health Services), the Medical Society of New Jersey, all three hospital associations in New Jersey, the Infectious Diseases Society of New Jersey, the New Jersey Association of Osteopathic Physicians and Surgeons, New Jersey Section of the American College of Obstetrics and Gynecology, the New Jersey Obstetrical and Gynecology Society, the New Jersey Section of the American Academy of Pediatrics, the New Jersey Academy of Family Physicians, pediatric and obstetrical providers with a high-volume client load. This committee met once and provided written comments on the draft Standard of Care. They concurred with the other committee that NJDHSS should take the lead on developing, disseminating, and evaluating the Standard of Care. The unanimous decision was that a statewide Standard of Care was the best approach to take in New Jersey.

• Individual meetings were held with some key organizations such as the New Jersey Obstetrical and Gynecology Society, the Infectious Diseases Society of New Jersey, Medicaid, the NJDHSS Laboratory Task Force, and the Association for Professionals in Infection Control and Epidemiology.

• A one-on-one meeting was held with a high-volume facility in a high-prevalence area to help ascertain the potential barriers to implementing a statewide Standard of Care.

• Support for the statewide Standard of Care was obtained from the Governor’s Advisory Council on AIDS.

Identification and Overcoming Barriers
Several barriers were encountered in implementation of the standard of care. The first barrier was that the advisory committee members did not have enough information on rapid testing. To overcome this obstacle, a half-day continuing medical education conference with a didactic lecture on rapid testing by Dr. Bernard Branson from CDC and case studies of women who presented in labor with unknown HIV status preceded the advisory committee meeting. The committee then felt that they had enough information on rapid testing to proceed with development of the standard of care.

The second barrier was that providers were uncertain about the content of counseling for women in labor. To overcome this, a template counseling session was developed with assistance from focus groups composed of postpartum women. The template counseling session was disseminated statewide through five train-the-train sessions conducted in collaboration with all the local maternal-child health consortia.

The third barrier identified was that hospital laboratory directors were under the misimpression that preliminary positive rapid or expedited test results could not be given to the providers and patients. To overcome this, a fact sheet on rapid testing was sent to each hospital with other information related to the standard of care, information was provided in a series of lectures given statewide, and an article was published in New Jersey Medicine.

The fourth barrier was that some hospitals requested a template policy to use. This was provided to them.
**Dissemination of the Statewide Standard of Care**

A multimedia comprehensive approach is underway to disseminate the Standard of Care. This consists of free Internet-based continuing medical education (available at www.acadmed.org), publication of articles in New Jersey Medicine, publication of articles in AIDSLine, a laminated pocket card for providers, poster presentations, train-the-trainer sessions, and continuing medical education lectures statewide. A mailing was sent to the chair of pediatrics, the chair of obstetrics, the laboratory director, the infection control professional, the chief executive officer, the medical director, the head nurse for labor and delivery, the executive committee, the vice-president of risk management, and the emergency room director of each hospital. The information packet included a cover letter from the Deputy Commissioner, the Standard of Care, the laboratory alert, the laboratory algorithm, and information on continuing medical education and train-the-trainer sessions.

**Evaluation**

Evaluation will be conducted to look at process measures and outcome measures.

- Repeat the hospital survey to determine if the Standard of Care has been incorporated into hospital policies and procedures and identify barriers to its implementation
- Retrospective medical record review to evaluate the implementation and effectiveness of the Standard of Care
- Continuous evaluation of efforts to reduce vertical transmission through surveillance, survey for childbearing women, and special studies.

**Funding**

Funding to develop, disseminate, and evaluate the Standard of Care came from state and federal funds. These funds allowed NJDHSS to contract with the National Pediatric and Family HIV Resource Center to help develop the counseling session, conduct the train-the-trainer sessions, provide three of the continuing medical education programs, and evaluate the implementation and effectiveness of the Standard of Care.
This is a summary of the initial clinical experience with the SUDS assay, for obstetric rapid testing, at the Medical Center of Louisiana.

In October of 1998, the Medical Center of Louisiana, New Orleans (formerly Charity Hospital), initiated rapid HIV-1 screening for obstetric patients admitted to the labor and delivery unit without prior documentation of HIV status. This program was approved by the Hospital Executive Committee and was established in conjunction with the use of rapid screening for employee occupational exposures. The program was developed by the hospital’s Infection Control Division to address disease prevention and health care delivery needs of a subgroup of obstetric patients shown to have a two- to threefold greater HIV seroprevalence as compared with patients receiving obstetric prenatal care in the hospital’s clinics. As a standard of care, all obstetric patients presenting to the labor and delivery unit with an undocumented HIV serostatus are offered voluntary HIV testing. Patients at risk for delivery prior to the completion of conventional HIV testing were offered initial screening with the FDA-licensed Single-Use Diagnostic System Test (SUDS), a rapid enzyme-linked immunosorbent assay (EIA). Patient acceptance of HIV testing was documented with written informed consent based on hospital policy and standards of care and in accordance with State guidelines for HIV testing at public facilities. Request for SUDS testing are submitted via the computer laboratory entry system. Patients consenting for screening were tested concurrently with a conventional HIV EIA and the SUDS HIV-1 rapid assay. SUDS assay determinations were conducted in the hospital blood bank laboratory service. This laboratory resource was selected based on the presence of adequate technical staff on a 24-hour basis. A confirmatory Western blot was used to document a true positive HIV result. The results of the SUDS test are reported electronically via the computerized laboratory inquiry system and are read out as SUDS reactive or non-reactive, and patients are informed of their SUDS test result by their treating physician.

Patients with a positive SUDS test result were counseled by their treating physician about the implications of the presumptive HIV positive status and were counseled about options for intervention to reduce vertical transmission of HIV. Laboring patients were administered peripartum antiretroviral prophylaxis consistent with the Public Health Service (PHS) guidelines. Infants delivered to mothers with positive SUDS tests were considered HIV exposed and initiated postpartum antiretroviral prophylaxis consistent with the PHS guidelines. When conventional HIV test results were discordant with the SUDS test and failed to confirm infection, the newborn prophylaxis was discontinued. All mothers with a confirmed HIV infection and their HIV-exposed infants were referred for HIV primary care follow-up at time of hospital discharge. The results of all obstetric patients who underwent both conventional and rapid HIV testing were recorded in the Office of Hospital of Infection Control’s database.

Initial laboratory implementation and training was accomplished over several months. Blood bank technologists participated in a half-day “hands on” training session conducted by a SUDS vendor representative. Validation testing was conducted on site at the Medical Center of Louisiana, New Orleans Blood Bank Laboratory. The validation laboratory protocol required running 100
“unknown” serum samples with positive and negative controls. Compliance with accreditation guidelines required an evaluation of the new testing program with a proficiency testing survey. Subscription to the Wisconsin State Lab of Hygiene HIV Survey for HIV-1/2, formerly the Health Care Financing Administration (now called Centers for Medicare and Medicaid Services) approved and vendor recommended, was acquired to meet these requirements. The initial implementation cost of the hospital program for SUDS testing was approximately $2,000.

An examination of the Hospital’s perinatal HIV rapid testing program through the first 12 months demonstrated a SUDS test performance with a sensitivity and specificity of 100% and 99.2%, and positive and negative predictive value of 79% and 100%, respectively. The overall seroprevalence in the tested population was 2.9%. The positive predictive value of the SUDS assay was highest among laboring women with inadequate prenatal care and an undocumented HIV status, which represented the highest seroprevalence group (>5%).

An evaluation of the initial clinical experience with perinatal HIV rapid testing demonstrated that nearly 20% of the HIV exposed births at the facility were identified through rapid testing. The majority of these mothers had inadequate or absent prenatal care. All SUDS positive laboring mothers with a subsequent confirmed positive HIV status had evidence of advance labor or rupture of membranes at admission. All of these mothers had inadequate prenatal care. Of note upon review of medical records, it was determined that as many as 50% these mothers had evidence of a positive HIV test prior to the current pregnancy, but did not disclose their HIV status to their treating physician at time of presentation. Intrapartum antiretroviral prophylaxis was successfully initiated in the majority of these mothers, and newborn prophylaxis was initiated for all infants prior to hospital discharge. All infants entered HIV primary care follow-up post hospital discharge. A preliminary assessment of a small number of HIV-exposed infants identified with HIV rapid testing demonstrated significantly reduced transmission rate in contrast to that expected among HIV-exposed infants without peripartum antiretroviral prophylaxis.

This medical center’s experience highlights the capacity to effectively develop and implement targeted strategies for perinatal HIV rapid testing in a high-seroprevalence, obstetric population, and the potential impact of similar public health measures/interventions to reduce mother-to-child HIV transmission among childbearing women with an undocumented HIV status and poor prenatal care.
Effective September 2006, CDC has revised its recommendations for HIV testing in healthcare settings. The Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Healthcare Settings aim to make HIV testing a routine part of medical care in addition to expanding the gains made in diagnosing HIV infection among pregnant women. The Recommendations replace CDC’s 1993 Recommendations for HIV Testing Services for Inpatients and Outpatients in Acute-Care Settings and they update portions of CDC’s 2001 Revised Guidelines for HIV Counseling, Testing, and Referral and Revised Recommendations for HIV Screening of Pregnant Women.

**What is different about the new Recommendations?**

Key differences in the Recommendations for patients in all healthcare settings are:

- HIV screening (another term for broad-based testing) for patients ages 13 to 64 in all healthcare settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- HIV testing of people at high risk for HIV infection at least once a year.
- Screening should be incorporated into the general consent for medical care; separate written consent is not recommended.
- Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in healthcare settings.

Additional key differences in the Recommendations for pregnant women in healthcare settings are:

- Including HIV screening in the routine panel of prenatal screening tests for all pregnant women, unless the patient declines (opt-out screening).
- Repeat screening in the third trimester in certain jurisdictions with elevated rates of HIV infection among pregnant women.

The Recommendations emphasize the importance of voluntary testing. Various constituencies have expressed concern that eliminating the recommendation for separate informed consent for an HIV test could result in some patients being tested for HIV without their knowledge. Others have asserted that requiring separate, written informed consent is a barrier that makes HIV screening difficult to conduct in healthcare settings, and that removing this requirement would make widespread HIV screening feasible.

Concerns have also been expressed over the lack of HIV prevention counseling in conjunction with HIV testing. CDC continues to support prevention counseling as an intervention to help people reduce their risks for HIV, but recognizes it can become a barrier to HIV testing in busy healthcare settings.
CDC still recommends that patients receive information about HIV testing, HIV infection, and the meaning of test results.

**Why did CDC revise the Recommendations?**

There are several compelling reasons why CDC has revised the Recommendations.

- An estimated one-fourth of the approximately 1 million persons in this country who are living with HIV do not know they are infected. That’s approximately 250,000 persons who could be spreading HIV to their partners unknowingly. As HIV screening becomes a more routine aspect of medical care, more people will know they are infected with HIV.

- People living with HIV can receive effective treatment, resulting in improved health and extended life, if their HIV infection is diagnosed earlier. Currently, many people learn of their HIV infection only after they have developed symptoms (in a large study of HIV-infected persons, 65% reported they were first tested for HIV because of illness).

- Most people, after finding out they have HIV, adopt behaviors that reduce HIV transmission. Routine HIV testing may help protect the partners of persons who are living with HIV but do not know it. In theory, new sexually transmitted HIV infections could be reduced more than 30% per year if all HIV-infected persons knew of their infection and adopted changes in behavior similar to those of persons already aware of their infection.

- Routine HIV testing may reduce the stigma associated with an HIV test offered based on the healthcare provider’s perception (or knowledge) of risk. When every person gets offered an HIV test at some point in his or her health care, it should take controversy and judgment out of the test and make it a normal part of taking care of oneself.

- Providers reported that requirements for pretest counseling and written informed consent were not feasible in emergency rooms and other busy healthcare settings.

**For whom are the Recommendations intended?**

The Recommendations are intended for healthcare providers in both the public and private sectors. These include healthcare workers in hospital emergency departments, inpatient services (including labor and delivery), correctional health care facilities, clinics including substance abuse treatment, public health, community, pediatric and adolescent, prenatal, and mental health, and other primary care settings.

These Recommendations address HIV testing in healthcare settings only. They do not change existing CDC guidelines on HIV counseling, testing, and referral for persons at high risk for HIV who receive testing in nonclinical settings (e.g., at community-based organizations.)

**How did CDC develop the Recommendations?**

These Recommendations are the culmination of a lengthy and deliberate process that began in 1999 when the Institute of Medicine (IOM) recommended adopting a national policy of universal testing of pregnant women with patient notification (opt-out screening), eliminating requirements for extensive pretest counseling, and eliminating requirements for explicit written consent for HIV testing. Adoption of the IOM recommendations led to increased prenatal screening, and, combined with appropriate medical care, contributed to a dramatic 95% decline in perinatally acquired AIDS cases. CDC began exploring the feasibility of adopting a similar policy for the general public, which could bring about reductions in sexually transmitted HIV.

Between 1999 and 2006, CDC involved healthcare providers, representatives from professional associations and community organizations, researchers, public health officials, and persons living with HIV to research and refine the
Recommendations in order to expand HIV testing, especially in high-volume, high-prevalence acute-care settings. Through this process, CDC has tried to involve persons most likely to be affected by the Recommendations and ensure the resulting Recommendations are ethical and fair and would achieve their stated goals.

Conclusion
CDC believes that the adoption of voluntary, HIV screening in healthcare settings will foster the earlier detection of HIV infection, help healthcare workers identify and counsel persons with previously unrecognized HIV infection and link them to clinical and prevention services, and further reduce sexual and perinatal transmission of HIV in the United States.

For more information . . .

CDC HIV/AIDS
http://www.cdc.gov/hiv
CDC HIV/AIDS resources

CDC-INFO
1-800-232-4636
Information about personal risk and where to get an HIV test

CDC National HIV Testing Resources
http://www.hivtest.org
Location of HIV testing sites

CDC National Prevention Information Network (NPIN)
1-800-458-51
http://www.cdcnpin.org
CDC resources, technical assistance, and publications

AIDSinfo
1-800-448-0440
http://www.aidsinfo.nih.gov
Resources on HIV/AIDS treatment and clinical trials
Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings

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Summary

These recommendations for human immunodeficiency virus (HIV) testing are intended for all health-care providers in the public and private sectors, including those working in hospital emergency departments, urgent care clinics, inpatient services, substance abuse treatment clinics, public health clinics, community clinics, correctional health-care facilities, and primary care settings. The recommendations address HIV testing in health-care settings only. They do not modify existing guidelines concerning HIV counseling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans). The objectives of these recommendations are to increase HIV screening of patients, including pregnant women, in health-care settings; foster earlier detection of HIV infection; identify and counsel persons with unrecognized HIV infection and link them to clinical and prevention services; and further reduce perinatal transmission of HIV in the United States. These revised recommendations update previous recommendations for HIV testing in health-care settings and for screening of pregnant women (CDC. Recommendations for HIV testing services for inpatients and outpatients in acute-care hospital settings. MMWR 1993;42[No. RR-2]:1--10; CDC. Revised guidelines for HIV counseling, testing, and referral. MMWR 2001;50[No. RR-}
Major revisions from previously published guidelines are as follows:

**For patients in all health-care settings**

- **HIV screening is recommended for patients in all health-care settings after the patient is notified that testing will be performed unless the patient declines (opt-out screening).**
- **Persons at high risk for HIV infection should be screened for HIV at least annually.**
- **Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.**
- **Prevention counseling should not be required with HIV diagnostic testing or as part of HIV screening programs in health-care settings.**

**For pregnant women**

- **HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women.**
- **HIV screening is recommended after the patient is notified that testing will be performed unless the patient declines (opt-out screening).**
- **Separate written consent for HIV testing should not be required; general consent for medical care should be considered sufficient to encompass consent for HIV testing.**
- **Repeat screening in the third trimester is recommended in certain jurisdictions with elevated rates of HIV infection among pregnant women.**

**Introduction**

Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) remain leading causes of illness and death in the United States. As of December 2004, an estimated 944,306 persons had received a diagnosis of AIDS, and of these, 529,113 (56%) had died (1). The annual number of AIDS cases and deaths declined substantially after 1994 but stabilized during 1999--2004 (1). However, since 1994, the annual number of cases among blacks, members of other racial/ethnic minority populations, and persons exposed through heterosexual contact has increased. The number of children reported with AIDS attributed to perinatal HIV transmission peaked at 945 in 1992 and declined 95% to 48 in 2004 (1), primarily because of the identification of HIV-infected pregnant women and the effectiveness of antiretroviral prophylaxis in reducing mother-to-child transmission of HIV (2).

By 2002, an estimated 38%--44% of all adults in the United States had been tested for HIV; 16--22 million persons aged 18--64 years are tested annually for HIV (3). However, at the end of 2003, of the approximately 1.0--1.2 million persons estimated to be living with HIV in the United States, an estimated one quarter (252,000--312,000 persons) were unaware of their infection and therefore unable to benefit from clinical care to reduce morbidity and mortality (4). A number of these persons are likely to have transmitted HIV unknowingly (5). Treatment has improved survival rates dramatically, especially since the introduction of highly active antiretroviral therapy (HAART) in 1995 (6). However, progress in effecting
earlier diagnosis has been insufficient. During 1990--1992, the proportion of persons who first tested positive for HIV <1 year before receiving a diagnosis of AIDS was 51% (7); during 1993--2004, this proportion declined only modestly, to 39% in 2004 (7). Persons tested late in the course of their infection were more likely to be black or Hispanic and to have been exposed through heterosexual contact; 87% received their first positive HIV test result at an acute or referral medical care setting, and 65% were tested for HIV antibody because of illness (8).

These recommendations update previous recommendations for HIV testing in health-care settings (9,10) and for screening of pregnant women (11). The objectives of these recommendations are to increase HIV screening of patients, including pregnant women, in health-care settings; foster earlier detection of HIV infection; identify and counsel persons with unrecognized HIV infection and link them to clinical and prevention services; and further reduce perinatal transmission of HIV in the United States.

Single copies of this report are available free of charge from CDC's National Prevention Information Network, telephone 800-458-5231 (Mondays--Fridays, 9:00 a.m.--8:00 p.m. ET).

Background

Definitions
Diagnostic testing. Performing an HIV test for persons with clinical signs or symptoms consistent with HIV infection.
Screening. Performing an HIV test for all persons in a defined population (12).
Targeted testing. Performing an HIV test for subpopulations of persons at higher risk, typically defined on the basis of behavior, clinical, or demographic characteristics (9).
Informed consent. A process of communication between patient and provider through which an informed patient can choose whether to undergo HIV testing or decline to do so. Elements of informed consent typically include providing oral or written information regarding HIV, the risks and benefits of testing, the implications of HIV test results, how test results will be communicated, and the opportunity to ask questions.
Opt-out screening. Performing HIV screening after notifying the patient that 1) the test will be performed and 2) the patient may elect to decline or defer testing. Assent is inferred unless the patient declines testing.
HIV-prevention counseling. An interactive process of assessing risk, recognizing specific behaviors that increase the risk for acquiring or transmitting HIV, and developing a plan to take specific steps to reduce risks (13).

Evolution of HIV Testing Recommendations in Health-Care Settings and for Pregnant Women

In 1985, when HIV testing first became available, the main goal of such testing was to protect the blood supply. Alternative test sites were established to deter persons from using blood bank testing to learn their HIV status. At that time, professional opinion was divided regarding the value of HIV testing and whether HIV testing should be encouraged because no consensus existed regarding whether a positive test predicted transmission to sex partners or from mother to infant (14). No effective treatment existed, and counseling was designed in
part to ensure that persons tested were aware that the meaning of positive test results was uncertain.

During the next 2 years, the implications of positive HIV serology became evident, and in 1987, the United States Public Health Service (USPHS) issued guidelines making HIV counseling and testing a priority as a prevention strategy for persons most likely to be infected or who practiced high-risk behaviors and recommended routine testing of all persons seeking treatment for STDs, regardless of health-care setting (15). "Routine" was defined as a policy to provide these services to all clients after informing them that testing would be conducted (15).

In 1993, CDC recommendations for voluntary HIV counseling and testing were extended to include hospitalized patients and persons obtaining health care as outpatients in acute-care hospital settings, including emergency departments (EDs) (10). Hospitals with HIV seroprevalence rates of >1% or AIDS diagnosis rates of >1 per 1,000 discharges were encouraged to adopt a policy of offering voluntary HIV counseling and testing routinely to all patients aged 15--54 years. Health-care providers in acute-care settings were encouraged to structure counseling and testing procedures to facilitate confidential, voluntary participation and to include basic information regarding the medical implications of the test, the option to receive more information, and documentation of informed consent (10). In 1994, guidelines for counseling and testing persons with high-risk behaviors specified prevention counseling to develop specific prevention goals and strategies for each person (client-centered counseling) (16). In 1995, after perinatal transmission of HIV was demonstrated to be substantially reduced by administration of zidovudine to HIV-infected pregnant women and their newborns, USPHS recommended that all pregnant women be counseled and encouraged to undergo voluntary testing for HIV (17,18).

In 2001, CDC modified the recommendations for pregnant women to emphasize HIV screening as a routine part of prenatal care, simplification of the testing process so pretest counseling would not pose a barrier, and flexibility of the consent process to allow multiple types of informed consent (11). In addition, the 2001 recommendations for HIV testing in health-care settings were extended to include multiple additional clinical venues in both private and public health-care sectors, encouraging providers to make HIV counseling and testing more accessible and acknowledging their need for flexibility (9). CDC recommended that HIV testing be offered routinely to all patients in high HIV-prevalence health-care settings. In low prevalence settings, in which the majority of clients are at minimal risk, targeted HIV testing on the basis of risk screening was considered more feasible for identifying limited numbers of HIV-infected persons (9).

In 2003, CDC introduced the initiative Advancing HIV Prevention: New Strategies for a Changing Epidemic (19). Two key strategies of this initiative are 1) to make HIV testing a routine part of medical care on the same voluntary basis as other diagnostic and screening tests and 2) to reduce perinatal transmission of HIV further by universal testing of all pregnant women and by using rapid tests during labor and delivery or postpartum if the mother was not screened prenata lly (19). In its technical guidance, CDC acknowledged that prevention counseling is desirable for all persons at risk for HIV but recognized that such counseling might not be appropriate or feasible in all settings (20). Because time constraints or discomfort with discussing their patients' risk behaviors caused some providers to perceive requirements for prevention counseling and written informed consent as a barrier (12,21--23), the initiative advocated streamlined approaches.
In March 2004, CDC convened a meeting of health-care providers, representatives from professional associations, and local health officials to obtain advice concerning how best to expand HIV testing, especially in high-volume, high-prevalence acute-care settings. Consultants recommended simplifying the HIV screening process to make it more feasible and less costly and advocated more frequent diagnostic testing of patients with symptoms. In April 2005, CDC initiated a comprehensive review of the literature regarding HIV testing in health-care settings and, on the basis of published evidence and lessons learned from CDC-sponsored demonstration projects of HIV screening in health-care facilities, began to prepare recommendations to implement these strategies. In August 2005, CDC invited health-care providers, representatives from public health agencies and community organizations, and persons living with HIV to review an outline of proposed recommendations. In November 2005, CDC convened a meeting of researchers, representatives of professional health-care provider organizations, clinicians, persons living with HIV, and representatives from community organizations and agencies overseeing care of HIV-infected persons to review CDC’s proposed recommendations. Before final revision of these recommendations, CDC described the proposals at national meetings of researchers and health-care providers and, in March 2006, solicited peer review by health-care professionals, in compliance with requirements of the Office of Management and Budget for influential scientific assessments, and invited comment from multiple professional and community organizations. The final recommendations were further refined on the basis of comments from these constituents.

Rationale for Routine Screening for HIV Infection

Previous CDC and U.S. Preventive Services Task Force guidelines for HIV testing recommended routine counseling and testing for persons at high risk for HIV and for those in acute-care settings in which HIV prevalence was ≥1% (9,10,24). These guidelines proved difficult to implement because 1) the cost of HIV screening often is not reimbursed, 2) 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, and 3) explicit information regarding HIV prevalence typically is not available to guide selection of specific settings for screening (25--29).

These revised CDC recommendations advocate routine voluntary HIV screening as a normal part of medical practice, similar to screening for other treatable conditions. Screening is a basic public health tool used to identify unrecognized health conditions so treatment can be offered before symptoms develop and, for communicable diseases, so interventions can be implemented to reduce the likelihood of continued transmission (30).

HIV infection is consistent with all generally accepted criteria that justify screening: 1) HIV infection is a serious health disorder that can be diagnosed before symptoms develop; 2) HIV can be detected by reliable, inexpensive, and noninvasive screening tests; 3) infected patients have years of life to gain if treatment is initiated early, before symptoms develop; and 4) the costs of screening are reasonable in relation to the anticipated benefits (30). Among pregnant women, screening has proven substantially more effective than risk-based testing for detecting unsuspected maternal HIV infection and preventing perinatal transmission (31--33).

Rationale for New Recommendations
Often, persons with HIV infection visit health-care settings (e.g., hospitals, acute-care clinics, and sexually transmitted disease [STD] clinics) years before receiving a diagnosis but are not tested for HIV (34--36). Since the 1980s, the demographics of the HIV/AIDS epidemic in the United States have changed; increasing proportions of infected persons are aged <20 years, women, members of racial or ethnic minority populations, persons who reside outside metropolitan areas, and heterosexual men and women who frequently are unaware that they are at risk for HIV (37). As a result, the effectiveness of using risk-based testing to identify HIV-infected persons has diminished (34,35,38,39).

Prevention strategies that incorporate universal HIV screening have been highly effective. For example, screening blood donors for HIV has nearly eliminated transfusion-associated HIV infection in the United States (40). In addition, incidence of pediatric HIV/AIDS in the United States has declined substantially since the 1990s, when prevention strategies began to include specific recommendations for routine HIV testing of pregnant women (18,41). Perinatal transmission rates can be reduced to <2% with universal screening of pregnant women in combination with prophylactic administration of antiretroviral drugs (42,43), scheduled cesarean delivery when indicated (44,45), and avoidance of breast feeding (46). These successes contrast with a relative lack of progress in preventing sexual transmission of HIV, for which screening rarely is performed. Declines in HIV incidence observed in the early 1990s have leveled and might even have reversed in certain populations in recent years (47,48). Since 1998, the estimated number of new infections has remained stable at approximately 40,000 annually (49). In 2001, the Institute of Medicine (IOM) emphasized prevention services for HIV-infected persons and recommended policies for diagnosing HIV infections earlier to increase the number of HIV-infected persons who were aware of their infections and who were offered clinical and prevention services (37). The majority of persons who are aware of their HIV infections substantially reduce sexual behaviors that might transmit HIV after they become aware they are infected (5). In a meta-analysis of findings from eight studies, the prevalence of unprotected anal or vaginal intercourse with uninfected partners was on average 68% lower for HIV-infected persons who were aware of their status than it was for HIV-infected persons who were unaware of their status (5). To increase diagnosis of HIV infection, destigmatize the testing process, link clinical care with prevention, and ensure immediate access to clinical care for persons with newly identified HIV infection, IOM and other health-care professionals with expertise (25,37,50,51) have encouraged adoption of routine HIV testing in all health-care settings.

Routine prenatal HIV testing with streamlined counseling and consent procedures has increased the number of pregnant women tested substantially (52). By contrast, the number of persons at risk for HIV infection who are screened in acute-care settings remains low, despite repeated recommendations in support of routine risk-based testing in health-care settings (9,10,15,34,53,54). In a survey of 154 health-care providers in 10 hospital EDs, providers reported caring for an average of 13 patients per week suspected to have STDs, but only 10% of these providers encouraged such patients to be tested for HIV while they were in the ED (54). Another 35% referred patients to confidential HIV testing sites in the community; however, such referrals have proven ineffective because of poor compliance by patients (55). Reasons cited for not offering HIV testing in the ED included lack of established mechanisms to ensure follow-up (51%), lack of the certification perceived as necessary to provide counseling (45%), and belief that the testing process was too time-consuming (19%) (54).
With the institution of HIV screening in certain hospitals and EDs, the percentage of patients who test positive (2%–7%) often has exceeded that observed nationally at publicly funded HIV counseling and testing sites (1.5%) and STD clinics (2%) serving persons at high risk for HIV (53, 56--59). Because patients rarely were seeking testing when screening was offered at these hospitals, HIV infections often were identified earlier than they might otherwise have been (29). Targeted testing programs also have been implemented in acute-care settings; nearly two thirds of patients in these settings accept testing, but because risk assessment and prevention counseling are time-consuming, only a limited proportion of eligible patients can be tested (29). Targeted testing on the basis of risk behaviors fails to identify a substantial number of persons who are HIV infected (34, 35, 39). A substantial number of persons, including persons with HIV infection, do not perceive themselves to be at risk for HIV or do not disclose their risks (53, 56, 59). Routine HIV testing reduces the stigma associated with testing that requires assessment of risk behaviors (60--63). More patients accept recommended HIV testing when it is offered routinely to everyone, without a risk assessment (54, 56).

In 1999, to increase the proportion of women tested for HIV, IOM recommended 1) adopting a national policy of universal HIV testing of pregnant women with patient notification (opt-out screening) as a routine component of prenatal care, 2) eliminating requirements for extensive pretest counseling while requiring provision of basic information regarding HIV, and 3) not requiring explicit written consent to be tested for HIV (12). Subsequent studies have indicated that these policies, as proposed by IOM and other professional organizations (12, 64, 65), reflect an ethical balance among public health goals, justice, and individual rights (66, 67). Rates of HIV screening are consistently higher at settings that provide prenatal and STD services using opt-out screening than at opt-in programs, which require pre-test counseling and explicit written consent (52, 68--74). Pregnant women express less anxiety with opt-out HIV screening and do not find it difficult to decline a test (68, 74). In 2006, approximately 65% of U.S. adults surveyed concurred that HIV testing should be treated the same as screening for any other disease, without special procedures such as written permission from the patient (75).

Adolescents aged 13--19 years represent new cohorts of persons at risk, and prevention efforts need to be repeated for each succeeding generation of young persons (63). The 2005 Youth Risk Behavior Survey indicated that 47% of high school students reported that they had had sexual intercourse at least once, and 37% of sexually active students had not used a condom during their most recent act of sexual intercourse (76). More than half of all HIV-infected adolescents are estimated not to have been tested and are unaware of their infection (77, 78). Among young (aged 18--24 years) men who have sex with men (MSM) surveyed during 2004--2005 in five U.S. cities, 14% were infected with HIV; 79% of these HIV-infected MSM were unaware of their infection (56). The American Academy of Pediatrics recommends that clinicians obtain information from adolescent patients regarding their sexual activity and inform them how to prevent HIV infection (79). Evidence indicates that adolescents prefer to receive this information from their health-care providers rather than from their parents, teachers, or friends (80). However, fewer than half of clinicians provide such guidance (81). Health-care providers' recommendations also influence adolescents' decision to be tested. Among reasons for HIV testing provided by 528 adolescents who had primary care providers, 58% cited their provider's recommendation as their reason for testing (82).
The U.S. Preventive Services Task Force recently recommended that clinicians screen for HIV all adults and adolescents at increased risk for HIV, on the basis that when HIV is diagnosed early, appropriately timed interventions, particularly HAART, can lead to improved health outcomes, including slower clinical progression and reduced mortality (24). The Task Force also recommended screening all pregnant women, regardless of risk, but made no recommendation for or against routinely screening asymptomatic adults and adolescents with no identifiable risk factors for HIV. The Task Force concluded that such screening would detect additional patients with HIV, but the overall number would be limited, and the potential benefits did not clearly outweigh the burden on primary care practices or the potential harms of a general HIV screening program (24,83). In making these recommendations, the Task Force considered how many patients would need to be screened to prevent one clinical progression or death during the 3-year period after screening. On the basis of evidence available for its review, the Task Force was unable to calculate benefits attributable to the prevention of secondary HIV transmission to partners (84). However, a recent meta-analysis indicated that HIV-infected persons reduced high-risk behavior substantially when they became aware of their infection (5). Because viral load is the chief biologic predictor of HIV transmission (85), reduction in viral load through timely initiation of HAART might reduce transmission, even for HIV-infected patients who do not change their risk behavior (86). Estimated transmission is 3.5 times higher among persons who are unaware of their infection than among persons who are aware of their infection and contributes disproportionately to the number of new HIV infections each year in the United States (87). In theory, new sexual HIV infections could be reduced >30% per year if all infected persons could learn their HIV status and adopt changes in behavior similar to those adopted by persons already aware of their infection (87).

Recent studies demonstrate that voluntary HIV screening is cost-effective even in health-care settings in which HIV prevalence is low (26,27,86). In populations for which prevalence of undiagnosed HIV infection is >0.1%, HIV screening is as cost-effective as other established screening programs for chronic diseases (e.g., hypertension, colon cancer, and breast cancer) (27,86). Because of the substantial survival advantage resulting from earlier diagnosis of HIV infection when therapy can be initiated before severe immunologic compromise occurs, screening reaches conventional benchmarks for cost-effectiveness even before including the important public health benefit from reduced transmission to sex partners (86).

Linking patients who have received a diagnosis of HIV infection to prevention and care is essential. HIV screening without such linkage confers little or no benefit to the patient. Although moving patients into care incurs substantial costs, it also triggers sufficient survival benefits that justify the additional costs. Even if only a limited fraction of patients who receive HIV-positive results are linked to care, the survival benefits per dollar spent on screening represent good comparative value (26,27,88).

The benefit of providing prevention counseling in conjunction with HIV testing is less clear. HIV counseling with testing has been demonstrated to be an effective intervention for HIV-infected participants, who increased their safer behaviors and decreased their risk behaviors; HIV counseling and testing as implemented in the studies had little effect on HIV-negative participants (89). However, randomized controlled trials have demonstrated that the nature and duration of prevention counseling might influence its effectiveness (90,91). Carefully controlled, theory-based prevention counseling in STD clinics has helped HIV-negative participants reduce their risk behaviors compared with participants who received only a
didactic prevention message from health-care providers (90). A more intensive intervention among HIV-negative MSM at high risk, consisting of 10 theory-based individual counseling sessions followed by maintenance sessions every 3 months, resulted in reductions in unprotected sex with partners who were HIV infected or of unknown status, compared with MSM who received structured prevention counseling only twice yearly (91). Timely access to diagnostic HIV test results also improves health outcomes. Diagnostic testing in health-care settings continues to be the mechanism by which nearly half of new HIV infections are identified. During 2000--2003, of persons reported with HIV/AIDS who were interviewed in 16 states, 44% were tested for HIV because of illness (8). Compared with HIV testing after patients were admitted to the hospital, expedited diagnosis by rapid HIV testing in the ED before admission led to shorter hospital stays, increased the number of patients aware of their HIV status before discharge, and improved entry into outpatient care (92). However, at least 28 states have laws or regulations that limit health-care providers' ability to order diagnostic testing for HIV infection if the patient is unable to give consent for HIV testing, even when the test results are likely to alter the patient's diagnostic or therapeutic management (93).

Of the 40,000 persons who acquire HIV infection each year, an estimated 40%--90% will experience symptoms of acute HIV infection (94--96), and a substantial number will seek medical care. However, acute HIV infection often is not recognized by primary care clinicians because the symptoms resemble those of influenza, infectious mononucleosis, and other viral illnesses (97). Acute HIV infection can be diagnosed by detecting HIV RNA in plasma from persons with a negative or indeterminate HIV antibody test. One study based on national ambulatory medical care surveys estimated that the prevalence of acute HIV infection was 0.5%--0.7% among ambulatory patients who sought care for fever or rash (98). Although the long-term benefit of HAART during acute HIV infection has not been established conclusively (99), identifying primary HIV infection can reduce the spread of HIV that might otherwise occur during the acute phase of HIV disease (100,101). Perinatal HIV transmission continues to occur, primarily among women who lack prenatal care or who were not offered voluntary HIV counseling and testing during pregnancy. A substantial proportion of the estimated 144--236 perinatal HIV infections in the United States each year can be attributed to the lack of timely HIV testing and treatment of pregnant women (102). Multiple barriers to HIV testing have been identified, including language barriers; late entry into prenatal care; health-care providers' perceptions that their patients are at low risk for HIV; lack of time for counseling and testing, particularly for rapid testing during labor and delivery; and state regulations requiring counseling and separate informed consent (103). A survey of 653 obstetrical providers in North Carolina suggested that not all health-care providers embrace universal testing of pregnant women; the strength with which providers recommended prenatal testing to their patients and the numbers of women tested depended largely on the providers' perception of the patients' risk behaviors (21). Data confirm that testing rates are higher when HIV tests are included in the standard panel of screening tests for all pregnant women (52,69,104). Women also are much more likely to be tested if they perceive that their health-care provider strongly recommends HIV testing (105). As universal prenatal screening has become more widespread, an increasing proportion of pregnant women who had undiagnosed HIV infection at the time of delivery were found to have seroconverted during pregnancy (106). A second HIV test during the third trimester for women in settings
with elevated HIV incidence (≥17 cases per 100,000 person-years) is cost-effective and might result in substantial reductions in mother-to-child HIV transmission (107). Every perinatal HIV transmission is a sentinel health event, signaling either a missed opportunity for prevention or, more rarely, a failure of interventions to prevent perinatal transmission. When these infections occur, they underscore the need for improved strategies to ensure that all pregnant women undergo HIV testing and, if found to be HIV positive, receive proper interventions to reduce their transmission risk and safeguard their health and the health of their infants.

Recommendations for Adults and Adolescents

CDC recommends that diagnostic HIV testing and opt-out HIV screening be a part of routine clinical care in all health-care settings while also preserving the patient's option to decline HIV testing and ensuring a provider-patient relationship conducive to optimal clinical and preventive care. The recommendations are intended for providers in all health-care settings, including hospital EDs, urgent-care clinics, inpatient services, STD clinics or other venues offering clinical STD services, tuberculosis (TB) clinics, substance abuse treatment clinics, other public health clinics, community clinics, correctional health-care facilities, and primary care settings. The guidelines address HIV testing in health-care settings only; they do not modify existing guidelines concerning HIV counseling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans) (9).

Screening for HIV Infection

• In all health-care settings, screening for HIV infection should be performed routinely for all patients aged 13--64 years. Health-care providers should initiate screening unless prevalence of undiagnosed HIV infection in their patients has been documented to be <0.1%. In the absence of existing data for HIV prevalence, health-care providers should initiate voluntary HIV screening until they establish that the diagnostic yield is <1 per 1,000 patients screened, at which point such screening is no longer warranted.
• All patients initiating treatment for TB should be screened routinely for HIV infection (108).
• All patients seeking treatment for STDs, including all patients attending STD clinics, should be screened routinely for HIV during each visit for a new complaint, regardless of whether the patient is known or suspected to have specific behavior risks for HIV infection.

Repeat Screening

• Health-care providers should subsequently test all persons likely to be at high risk for HIV at least annually. Persons likely to be at high risk include injection-drug users and their sex partners, persons who exchange sex for money or drugs, sex partners of HIV-infected persons, and MSM or heterosexual persons who themselves or whose sex partners have had more than one sex partner since their most recent HIV test.
• Health-care providers should encourage patients and their prospective sex partners to be tested before initiating a new sexual relationship.
• Repeat screening of persons not likely to be at high risk for HIV should be performed on the basis of clinical judgment.
• Unless recent HIV test results are immediately available, any person whose blood or body fluid is the source of an occupational exposure for a health-care provider should be informed of the incident and tested for HIV infection at the time the exposure occurs.

Consent and Pretest Information

• Screening should be voluntary and undertaken only with the patient's knowledge and understanding that HIV testing is planned.
• Patients should be informed orally or in writing that HIV testing will be performed unless they decline (opt-out screening). Oral or written information should include an explanation of HIV infection and the meanings of positive and negative test results, and the patient should be offered an opportunity to ask questions and to decline testing. With such notification, consent for HIV screening should be incorporated into the patient's general informed consent for medical care on the same basis as are other screening or diagnostic tests; a separate consent form for HIV testing is not recommended.
• Easily understood informational materials should be made available in the languages of the commonly encountered populations within the service area. The competence of interpreters and bilingual staff to provide language assistance to patients with limited English proficiency must be ensured.
• If a patient declines an HIV test, this decision should be documented in the medical record.

Diagnostic Testing for HIV Infection

• All patients with signs or symptoms consistent with HIV infection or an opportunistic illness characteristic of AIDS should be tested for HIV.
• Clinicians should maintain a high level of suspicion for acute HIV infection in all patients who have a compatible clinical syndrome and who report recent high-risk behavior. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection (96).
• Patients or persons responsible for the patient's care should be notified orally that testing is planned, advised of the indication for testing and the implications of positive and negative test results, and offered an opportunity to ask questions and to decline testing. With such notification, the patient's general consent for medical care is considered sufficient for diagnostic HIV testing.

Similarities and Differences Between Current and Previous Recommendations for Adults and Adolescents
Aspects of these recommendations that remain unchanged from previous recommendations are as follows:

- HIV testing must be voluntary and free from coercion. Patients must not be tested without their knowledge.
- HIV testing is recommended and should be routine for persons attending STD clinics and those seeking treatment for STDs in other clinical settings.
- Access to clinical care, prevention counseling, and support services is essential for persons with positive HIV test results.

Aspects of these recommendations that differ from previous recommendations are as follows:

- Screening after notifying the patient that an HIV test will be performed unless the patient declines (opt-out screening) is recommended in all health-care settings. Specific signed consent for HIV testing should not be required. General informed consent for medical care should be considered sufficient to encompass informed consent for HIV testing.
- Persons at high risk for HIV should be screened for HIV at least annually.
- HIV test results should be provided in the same manner as results of other diagnostic or screening tests.
- Prevention counseling should not be required as a part of HIV screening programs in health-care settings. Prevention counseling is strongly encouraged for persons at high risk for HIV in settings in which risk behaviors are assessed routinely (e.g., STD clinics) but should not have to be linked to HIV testing.
- HIV diagnostic testing or screening to detect HIV infection earlier should be considered distinct from HIV counseling and testing conducted primarily as a prevention intervention for uninfected persons at high risk.

Recommendations for Pregnant Women

These guidelines reiterate the recommendation for universal HIV screening early in pregnancy but advise simplifying the screening process to maximize opportunities for women to learn their HIV status during pregnancy, preserving the woman's option to decline HIV testing, and ensuring a provider-patient relationship conducive to optimal clinical and preventive care. All women should receive HIV screening consistent with the recommendations for adults and adolescents. HIV screening should be a routine component of preconception care, maximizing opportunities for all women to know their HIV status before conception (109). In addition, screening early in pregnancy enables HIV-infected women and their infants to benefit from appropriate and timely interventions (e.g., antiretroviral medications [43], scheduled cesarean delivery [44], and avoidance of breastfeeding* [46]). These recommendations are intended for clinicians who provide care to pregnant women and newborns and for health policy makers who have responsibility for these populations.
HIV Screening for Pregnant Women and Their Infants

Universal Opt-Out Screening

- All pregnant women in the United States should be screened for HIV infection.
- Screening should occur after a woman is notified that HIV screening is recommended for all pregnant patients and that she will receive an HIV test as part of the routine panel of prenatal tests unless she declines (opt-out screening).
- HIV testing must be voluntary and free from coercion. No woman should be tested without her knowledge.
- Pregnant women should receive oral or written information that includes an explanation of HIV infection, a description of interventions that can reduce HIV transmission from mother to infant, and the meanings of positive and negative test results and should be offered an opportunity to ask questions and to decline testing.
- No additional process or written documentation of informed consent beyond what is required for other routine prenatal tests should be required for HIV testing.
- If a patient declines an HIV test, this decision should be documented in the medical record.

Addressing Reasons for Declining Testing

- Providers should discuss and address reasons for declining an HIV test (e.g., lack of perceived risk; fear of the disease; and concerns regarding partner violence or potential stigma or discrimination).
- Women who decline an HIV test because they have had a previous negative test result should be informed of the importance of retesting during each pregnancy.
  - Logistical reasons for not testing (e.g., scheduling) should be resolved.
  - Certain women who initially decline an HIV test might accept at a later date, especially if their concerns are discussed. Certain women will continue to decline testing, and their decisions should be respected and documented in the medical record.

Timing of HIV Testing

- To promote informed and timely therapeutic decisions, health-care providers should test women for HIV as early as possible during each pregnancy. Women who decline the test early in prenatal care should be encouraged to be tested at a subsequent visit.
- A second HIV test during the third trimester, preferably <36 weeks of gestation, is cost-effective even in areas of low HIV prevalence and may be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet one or more of the following criteria:
  --- Women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women aged 15--45 years. In 2004, these jurisdictions included Alabama, Connecticut, Delaware, the District of Columbia, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Mississippi, Nevada, New Jersey, New York,
North Carolina, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Tennessee, Texas, and Virginia.†

--- Women who receive health care in facilities in which prenatal screening identifies at least one HIV-infected pregnant woman per 1,000 women screened.
--- Women who are known to be at high risk for acquiring HIV (e.g., injection-drug users and their sex partners, women who exchange sex for money or drugs, women who are sex partners of HIV-infected persons, and women who have had a new or more than one sex partner during this pregnancy).
--- Women who have signs or symptoms consistent with acute HIV infection. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection (96).

Rapid Testing During Labor

- Any woman with undocumented HIV status at the time of labor should be screened with a rapid HIV test unless she declines (opt-out screening).
- Reasons for declining a rapid test should be explored (see Addressing Reasons for Declining Testing).
- Immediate initiation of appropriate antiretroviral prophylaxis (42) should be recommended to women on the basis of a reactive rapid test result without waiting for the result of a confirmatory test.

Postpartum/Newborn Testing

- When a woman's HIV status is still unknown at the time of delivery, she should be screened immediately postpartum with a rapid HIV test unless she declines (opt-out screening).
- When the mother's HIV status is unknown postpartum, rapid testing of the newborn as soon as possible after birth is recommended so antiretroviral prophylaxis can be offered to HIV-exposed infants. Women should be informed that identifying HIV antibodies in the newborn indicates that the mother is infected.
- For infants whose HIV exposure status is unknown and who are in foster care, the person legally authorized to provide consent should be informed that rapid HIV testing is recommended for infants whose biologic mothers have not been tested.
- The benefits of neonatal antiretroviral prophylaxis are best realized when it is initiated ≤12 hours after birth (110).

Confirmatory Testing

- Whenever possible, uncertainties regarding laboratory test results indicating HIV infection status should be resolved before final decisions are made regarding reproductive options, antiretroviral therapy, cesarean delivery, or other interventions.
If the confirmatory test result is not available before delivery, immediate initiation of appropriate antiretroviral prophylaxis (42) should be recommended to any pregnant patient whose HIV screening test result is reactive to reduce the risk for perinatal transmission.

Similarities and Differences Between Current and Previous Recommendations for Pregnant Women and Their Infants

Aspects of these recommendations that remain unchanged from previous recommendations are as follows:

- Universal HIV testing with notification should be performed for all pregnant women as early as possible during pregnancy.
- HIV screening should be repeated in the third trimester of pregnancy for women known to be at high risk for HIV.
  - Providers should explore and address reasons for declining HIV testing.
- Pregnant women should receive appropriate health education, including information regarding HIV and its transmission, as a routine part of prenatal care.
- Access to clinical care, prevention counseling, and support services is essential for women with positive HIV test results.

Aspects of these recommendations that differ from previous recommendations are as follows:

- HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women. Patients should be informed that HIV screening is recommended for all pregnant women and that it will be performed unless they decline (opt-out screening).
  - Repeat HIV testing in the third trimester is recommended for all women in jurisdictions with elevated HIV or AIDS incidence and for women receiving health care in facilities with at least one diagnosed HIV case per 1,000 pregnant women per year.
- Rapid HIV testing should be performed for all women in labor who do not have documentation of results from an HIV test during pregnancy. Patients should be informed that HIV testing is recommended for all pregnant women and will be performed unless they decline (opt-out screening). Immediate initiation of appropriate antiretroviral prophylaxis should be recommended on the basis of a reactive rapid HIV test result, without awaiting the result of confirmatory testing.

Additional Considerations for HIV Screening
Test Results

- **Communicating test results.** The central goal of HIV screening in health-care settings is to maximize the number of persons who are aware of their HIV infection and receive care and prevention services. Definitive mechanisms should be established to inform patients of their test results. HIV-negative test results may be conveyed without direct personal contact between the patient and the health-care provider. Persons known to be at high risk for HIV infection also should be advised of the need for periodic retesting and should be offered prevention counseling or referred for prevention counseling. HIV-positive test results should be communicated confidentially through personal contact by a clinician, nurse, mid-level practitioner, counselor, or other skilled staff. Because of the risk of stigma and discrimination, family or friends should not be used as interpreters to disclose HIV-positive test results to patients with limited English proficiency. Active efforts are essential to ensure that HIV-infected patients receive their positive test results and linkage to clinical care, counseling, support, and prevention services. If the necessary expertise is not available in the health-care venue in which screening is performed, arrangements should be made to obtain necessary services from another clinical provider, local health department, or community-based organization. Health-care providers should be aware that the Privacy Rule under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) prohibits use or disclosure of a patient's health information, including HIV status, without the patient's permission.

- **Rapid HIV tests.** Because of the time that elapses before results of conventional HIV tests are available, providing patients with their test results can be resource intensive and challenging for screening programs, especially in episodic care settings (e.g., EDs, urgent-care clinics, and STD clinics) in which continuing relationships with patients typically do not exist. The use of rapid HIV tests can substantially decrease the number of persons who fail to learn their test results and reduce the resources expended to locate persons identified as HIV infected. Positive rapid HIV test results are preliminary and must be confirmed before the diagnosis of HIV infection is established (111).

- **Participants in HIV vaccine trials.** Recipients of preventive HIV vaccines might have vaccine-induced antibodies that are detectable by HIV antibody tests. Persons whose test results are HIV positive and who are identified as vaccine trial participants might not be infected with HIV and should be encouraged to contact or return to their trial site or an associated trial site for the confirmatory testing necessary to determine their HIV status.

- **Documenting HIV test results.** Positive or negative HIV test results should be documented in the patient's confidential medical record and should be readily available to all health-care providers involved in the patient's clinical management. The HIV test result of a pregnant woman also should be documented in the medical record of her infant. If the mother's HIV test result is positive, maternal health-care providers should, after obtaining consent from the mother, notify pediatric care providers of the impending birth of an HIV-exposed infant and of any anticipated complications. If HIV is diagnosed in the infant first, health-care providers should discuss the implications for the mother's health and help her to obtain care.
Clinical Care for HIV-Infected Persons

Persons with a diagnosis of HIV infection need a thorough evaluation of their clinical status and immune function to determine their need for antiretroviral treatment or other therapy. HIV-infected persons should receive or be referred for clinical care promptly, consistent with USPHS guidelines for management of HIV-infected persons (96). HIV-exposed infants should receive appropriate antiretroviral prophylaxis to prevent perinatal HIV transmission as soon as possible after birth (42) and begin trimethoprim-sulfamethoxazole prophylaxis at age 4--6 weeks to prevent Pneumocystis pneumonia (112). They should receive subsequent clinical monitoring and diagnostic testing to determine their HIV infection status (113).

Partner Counseling and Referral

When HIV infection is diagnosed, health-care providers should strongly encourage patients to disclose their HIV status to their spouses, current sex partners, and previous sex partners and recommend that these partners be tested for HIV infection. Health departments can assist patients by notifying, counseling, and providing HIV testing for partners without disclosing the patient's identity (114). Providers should inform patients who receive a new diagnosis of HIV infection that they might be contacted by health department staff for a voluntary interview to discuss notification of their partners.

Special Considerations for Screening Adolescents

Although parental involvement in an adolescent's health care is usually desirable, it typically is not required when the adolescent consents to HIV testing. However, laws concerning consent and confidentiality for HIV care differ among states (79). Public health statutes and legal precedents allow for evaluation and treatment of minors for STDs without parental knowledge or consent, but not every state has defined HIV infection explicitly as a condition for which testing or treatment may proceed without parental consent. Health-care providers should endeavor to respect an adolescent's request for privacy (79). HIV screening should be discussed with all adolescents and encouraged for those who are sexually active. Providing information regarding HIV infection, HIV testing, HIV transmission, and implications of infection should be regarded as an essential component of the anticipatory guidance provided to all adolescents as part of primary care (79).

Prevention Services for HIV-Negative Persons

- Risk screening. HIV screening should not be contingent on an assessment of patients' behavioral risks. However, assessment of risk for infection with HIV and other STDs and provision of prevention information should be incorporated into routine primary care of all sexually active persons when doing so does not pose a barrier to HIV testing. Even when risk information is not sought, notifying a patient that routine HIV testing will be performed might result in acknowledgement of risk behaviors and offers an opportunity to discuss HIV infection and how it can be prevented. Patients
found to have risk behaviors (e.g., MSM or heterosexuals who have multiple sex partners, persons who have received a recent diagnosis of an STD, persons who exchange sex for money or drugs, or persons who engage in substance abuse) and those who want assistance with changing behaviors should be provided with or referred to HIV risk-reduction services (e.g., drug treatment, STD treatment, and prevention counseling).

- Prevention counseling. In health-care settings, prevention counseling need not be linked explicitly to HIV testing. However, because certain patients might be more likely to think about HIV and consider their risks at the time of HIV testing, testing might present an ideal opportunity to provide or arrange for prevention counseling to assist with behavior changes that can reduce risks for acquiring HIV infection. Prevention counseling should be offered or made available through referral in all health-care facilities serving patients at high risk for HIV and at facilities (e.g., STD clinics) in which information on HIV risk behaviors is elicited routinely.

<H

HIV/AIDS Surveillance

- Risk-factor ascertainment for HIV-infected persons. CDC recommends that providers ascertain and document all known HIV risk factors (115). Health-care providers can obtain tools and materials to assist with ascertainment and receive guidance on risk factors as defined for surveillance purposes from HIV/AIDS surveillance professionals in their state or local health jurisdiction. This risk-factor information is important for guiding public health decisions, especially for prevention and care, at clinical, local, state, and national levels.

- HIV/AIDS case reporting. All states require that health-care providers report AIDS cases and persons with a diagnosis of HIV infection to the state or local health department. Case report forms are available from the state or local health jurisdiction.
  - Pediatric exposure reporting. CDC and the Council for State and Territorial Epidemiologists recommend that all states and territories conduct surveillance for perinatal HIV exposure and contact providers after receiving reports of exposed infants to determine the infant's HIV-infection status. Information concerning dates of maternal HIV tests, receipt of prenatal care, maternal and neonatal receipt of antiretroviral drugs, mode of delivery, and breastfeeding is collected on the pediatric HIV/AIDS case report form (115).

<H

Monitoring and Evaluation

Recommended thresholds for screening are based on estimates of the prevalence of undiagnosed HIV infection in U.S. health-care settings, for which no accurate recent data exist. The optimal frequency for retesting is not yet known. Cost-effectiveness parameters for HIV screening were based on existing program models, all of which include a substantial counseling component, and did not consistently consider secondary infections averted as a
benefit of screening. To assess the need for revised thresholds for screening adults and adolescents or repeat screening of pregnant women and to confirm their continued effectiveness, screening programs should monitor the yield of new diagnoses of HIV infection, monitor costs, and evaluate whether patients with a diagnosis of HIV infection are linked to and remain engaged in care. With minor modifications, laboratory information systems might provide a practical alternative for clinicians to use in determining HIV prevalence among their patients who are screened for HIV.

Primary Prevention and HIV Testing in Nonclinical Settings

These revised recommendations are designed to increase HIV screening in health-care settings. Often, however, the population most at risk for HIV includes persons who are least likely to interact with the conventional health-care system (47, 116). The need to maintain primary prevention activities, identify persons at high risk for HIV who could benefit from prevention services, and provide HIV testing for persons who are at high risk for HIV in nonclinical venues remains undiminished. New approaches (e.g., enlisting HIV-infected persons and HIV-negative persons at high risk for HIV to recruit persons from their social, sexual, and drug-use networks for counseling, testing, and referral) have demonstrated considerable efficacy for identifying persons who were previously unaware of their HIV infection (117).

Regulatory and Legal Considerations

These public health recommendations are based on best practices and are intended to comply fully with the ethical principles of informed consent (67). Legislation related to HIV and AIDS has been enacted in every state and the District of Columbia (118), and specific requirements related to informed consent and pretest counseling differ among states (119). Certain states, local jurisdictions, or agencies might have statutory or other regulatory impediments to opt-out screening, or they might impose other specific requirements for counseling, written consent, confirmatory testing, or communicating HIV test results that conflict with these recommendations. Where such policies exist, jurisdictions should consider strategies to best implement these recommendations within current parameters and consider steps to resolve conflicts with these recommendations.

Other Guidelines

Issues that fall outside the scope of these recommendations are addressed by other USPHS guidelines (Box 1). Because concepts relevant to HIV management evolve rapidly, USPHS updates recommendations periodically. Current updates are available from the National Institutes of Health at http://aidsinfo.nih.gov/. Additional guidelines have been published by CDC and the U.S. Department of Health and Human Services, Office for Civil Rights (Box 2).

Acknowledgment
Ida M. Onorato, MD, Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (proposed), contributed to the writing and revision of this report.

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To eliminate the risk for postnatal transmission, HIV-infected women in the United States should not breastfeed. Support services for use of appropriate breast milk substitutes should be provided when necessary. In international settings, UNAIDS and World Health Organization recommendations for HIV and breastfeeding should be followed (46).

† A second HIV test in the third trimester is as cost-effective as other common health interventions when HIV incidence among women of childbearing age is ≥17 HIV cases per 100,000 person-years (107). In 2004, in jurisdictions with available data on HIV case rates, a rate of 17 new HIV diagnoses per year per 100,000 women aged 15--45 years was associated with an AIDS case rate of at least nine AIDS diagnoses per year per 100,000 women aged 15--45 years (CDC, unpublished data, 2005). As of 2004, the jurisdictions listed above exceeded these thresholds. The list of specific jurisdictions where a second test in the third trimester is recommended will be updated periodically based on surveillance data.

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CDC, Division of HIV/AIDS Prevention Revised Recommendations for HIV Testing in Health-Care Settings Project

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NOTE: For MMR CE Activity re: Revised Recommendations for HIV Testing of Adults, Adolescents and Pregnant Women in Health-Care Settings, please contact Debra Welborn, MIHS at 602-344-2628.
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Prenatal and Perinatal Human Immunodeficiency Virus Testing: Expanded Recommendations

ABSTRACT: Early identification and treatment of all pregnant women with human immunodeficiency virus (HIV) is the best way to prevent neonatal disease. Pregnant women universally should be tested for HIV infection with patient notification as part of the routine battery of prenatal blood tests unless they decline the test (ie, opt-out approach). Repeat testing in the third trimester and rapid HIV testing at labor and delivery are additional strategies to further reduce the rate of perinatal HIV transmission. The Committee on Obstetric Practice makes the following recommendations: follow an opt-out prenatal HIV testing approach where legally possible; repeat offer of HIV testing in the third trimester to women in areas with high HIV prevalence, women known to be at high risk for HIV infection, and women who declined testing earlier in pregnancy, as allowed by state laws and regulations; use conventional HIV testing for women who are candidates for third-trimester testing; use rapid HIV testing in labor for women with undocumented HIV status; and if a rapid HIV test result is positive, initiate antiretroviral prophylaxis (with consent) without waiting for the results of the confirmatory test.
Rapid HIV-1 Testing During Labor

A Multicenter Study

Marc Bulterys, MD, PhD; Denise J. Jamieson, MD, MPH; Mary Jo O'Sullivan, MD; Mardge H. Cohen, MD; Robert Maupin, MD; Steven Nesheim, MD; Mayris P. Webber, DrPH; Russell Van Dyke, MD; Jeffrey Wiener; Bernard N. Branson, MD; for the Mother-Infant Rapid Intervention At Delivery (MIRIAD) Study Group


ABSTRACT

Context  Timely testing of women in labor with undocumented human immunodeficiency virus (HIV) status could enable immediate provision of antiretroviral prophylaxis.

Objectives  To determine the feasibility and acceptance of rapid HIV testing among women in labor and to assess rapid HIV assay performance.

Design, Setting, and Patients  The Mother-Infant Rapid Intervention At Delivery (MIRIAD) study implemented 24-hour counseling and voluntary rapid HIV testing for women in labor at 16 US hospitals from November 16, 2001, through November 15, 2003. A rapid HIV-1 antibody test for whole blood was used.

Main Outcome Measures  Acceptance of HIV testing; sensitivity, specificity, and predictive value of the rapid test; time from blood collection to patient notification of results.

Results  There were 91 707 visits to the labor and delivery units in the study, 7381 of which were by eligible women without documentation of HIV testing. Of these, 5744 (78%) women were approached for rapid HIV testing and 4849 (84%) consented. HIV-1 test results were positive for 34 women (prevalence = 7/1000). Sensitivity and specificity of the rapid test were 100% and 99.9%, respectively; positive predictive value was 90% compared with 76% for enzyme immunoassay (EIA). Factors independently associated with higher test acceptance included younger age, being black or Hispanic, gestational age less than 32 weeks, and having had no prenatal care. Lower acceptance was associated with being admitted between 4 PM and midnight, particularly on Friday nights, but this may be explained in part by fewer available personnel. Median time from blood collection to patient notification of result was 66 minutes (interquartile range, 45-
Conclusions Rapid HIV testing is feasible and delivers accurate and timely test results for women in labor. It provides HIV-positive women prompt access to intrapartum and neonatal antiretroviral prophylaxis, proven to reduce perinatal HIV transmission, and may be particularly applicable to higher-risk populations.

INTRODUCTION

The Centers for Disease Control and Prevention (CDC) estimates that between 280 and 370 infants are born infected with human immunodeficiency virus (HIV) annually in the United States despite recommendations for universal prenatal HIV screening and widespread use of antiretroviral drugs in pregnant HIV-infected women. Perinatally acquired HIV infections may result from missed opportunities for prevention, such as inadequate prenatal care. Ideally, all pregnant women should receive early prenatal care with voluntary HIV testing. However, for those who do not, rapid testing during labor could provide HIV-infected women with immediate access to antiretroviral prophylaxis. Most women in the United States give birth in hospitals, presenting a crucial opportunity for systematically offering rapid HIV testing and, when indicated, interventions to decrease perinatal transmission.

We sought to determine the feasibility of rapid HIV testing during labor, assess barriers to HIV testing, and facilitate comprehensive care for HIV-infected mothers and their infants. A US Food and Drug Administration treatment investigational device exemption permitted the use of a rapid test before its approval in November 2002. This test yields HIV results in 20 minutes, making it ideally suited for point-of-care use. This report describes the experience of performing rapid HIV testing during labor and the factors associated with acceptance of rapid testing.

METHODS

The CDC funded 16 hospitals in 6 US cities (Atlanta, Ga; Baton Rouge, La; Chicago, Ill; Miami, Fla; New Orleans, La; and New York, NY) to participate in the MIRIAD (Mother-Infant Rapid Intervention At Delivery) study, which offered HIV counseling, voluntary rapid testing, and, if indicated, antiretroviral prophylaxis to women with undocumented HIV status late in pregnancy. Counseling, voluntary rapid testing, and antiretroviral prophylaxis (as well as study enrollment) were offered by labor and delivery nurses, midwives, and obstetrics/gynecology residents in most hospitals. MIRIAD staff performed study interviews (usually post partum) and medical record reviews for the study at each hospital. Women were offered enrollment if they were in active labor (defined as having regular strong contractions and ruptured membranes or cervical dilation $>4$ cm) at a minimum of 24 weeks' gestation (potentially viable neonate). Women not in active labor were enrolled only if they presented at 34 weeks' gestation or later to the labor and delivery unit (standard HIV testing could be offered at $<34$ weeks per hospital protocol).

We developed a standardized procedure for obtaining written informed consent for rapid testing and study participation during labor that included use of a flipchart, which pictorially reviews the main study aspects. The study was approved by institutional review boards of the CDC and each participating institution. One MIRIAD study hospital did not allow collection of variables (cervical dilation, membrane status, frequency of contractions, gestational age, number of prenatal care visits, age, years of education,
Hispanic ethnicity, and race) on the eligibility form (all other study hospitals permitted this) from women who were not approached or who declined rapid testing and study participation (but this hospital did allow collection of time of admission). Thus, this hospital is not represented by variables from this group in relevant analyses herein.

Blood was collected for both rapid testing and enzyme immunoassay (EIA) and, when indicated, Western blot confirmatory testing. Laboratory technicians and labor and delivery staff performed rapid test proficiency panels for quality assurance. The EIA, and if needed, Western blot testing, was performed immediately following rapid HIV testing in the MIRIAD protocol. Nine institutions used the Abbott HIV-1/HIV-2 EIA (Abbott Laboratories, Abbott Park, Ill) and the Genetic Systems HIV-1 Western blot (BioRad Laboratories, Hercules, Calif); 7 institutions used the Genetic Systems HIV-1/HIV-2 Peptide EIA (BioRad Laboratories) and 4 of these used the Genetic Systems HIV-1 Western blot (BioRad Laboratories) and 3 used the Cambridge Biotech HIV-1 Western blot (Calypte Biomedical, Rockville, Md). In all institutions, initially reactive EIAs and rapid tests were repeated in duplicate; specimens with repeatedly reactive EIA or rapid tests were tested using Western blot. Women identified as HIV-positive by the OraQuick Rapid HIV-1 Antibody Test (Ora-Sure Technologies Inc, Bethlehem, Pa) or EIA, and those with discordant rapid test and EIA/Western blot results were followed up together with their infant for at least 6 months. The infants were tested using HIV DNA polymerase chain reaction (PCR) at less than 48 hours, 2 weeks, 6 weeks, and 3 months, and if having an indeterminate status, at 6 months.

To determine factors associated with acceptance of HIV testing, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression, adjusting for study site and other covariates. Reported ORs should not be misinterpreted as relative risks. Sensitivity, specificity, and positive and negative predictive values were determined using the EIA/Western blot algorithm as the gold standard. For each of these measures, CIs were estimated using exact binomial methods. Median turnaround times were compared using the Wilcoxon rank-sum test. We used SAS statistical software version 8 (SAS Institute Inc, Cary, NC) and S-Plus version 6.1 (Seattle, Wash). All P values reported are 2-sided and $P \leq 0.05$ was considered statistically significant.

RESULTS

Between November 16, 2001, and November 15, 2003, there were 91,707 visits to the labor and delivery units of the 16 participating hospitals and 7381 women (8% of all visits recorded) were eligible for rapid HIV testing. Of these, 1637 women (22%) were not approached for rapid HIV testing for reasons that included no staff member being available or verification for HIV testing during pregnancy still pending. Every attempt was made to have continuous labor and delivery coverage but some hospitals were less successful (implementation issues are being addressed in separate analyses). The remaining 5744 women were offered rapid HIV testing. Data on frequency of visiting the units were not collected and some women may have visited the units more than once. Written informed consent for both rapid testing and study participation was obtained from 4849 (84%) women.

Thirty-four women tested HIV-1 positive with both rapid test and EIA, and all were confirmed by Western blot (prevalence = 7/1000). There were 4 false-positive and no false-negative rapid test results. All 4 patients presented in active labor and were given antiretroviral prophylaxis, which was stopped when clinicians were notified that the rapid test result was false-positive. Sensitivity of the rapid test was 100% (95% CI, 90%-100%) and specificity was 99.9% (95% CI, 99.78%-99.98%). Negative predictive value was 100%; positive predictive value was 90% (95% CI, 75%-97%). The EIA had 11 false-positive results: 5 in women with an indeterminate Western blot result (usually a single p24 band) and 6 others with

http://jama.ama-assn.org/cgi/content/full/292/2/219?ijkey=118cab3f36c7f076e693899f372ef99e4b26bb32 9/26/2005
negative Western blot results. All 11 women had negative rapid test results. No false-negative EIA results were identified. The specificity of EIA was estimated to be 99.8% (95% CI, 99.6%-99.9%); positive predictive value was 76% (95% CI, 61%-87%).

In analyses adjusted for study site, acceptance of HIV testing during labor was associated with younger age, Hispanic ethnicity, gestation of less than 32 weeks, time of admission, and no prenatal care (Table 1). In multivariate analysis, black as well as Hispanic women were more likely than white women to accept testing. Younger age, gestation less than 32 weeks, and no prenatal care also remained significant (Table 1). Hospital admission between 4 PM and midnight was associated with lower HIV test acceptance (adjusted odds ratio [AOR], 0.7; 95% CI, 0.5-0.9); acceptance was lowest on Friday nights (P = .001).

<table>
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<tr>
<th>Table 1. Odds of Accepting if Approached for Rapid HIV Testing During Labor, by Characteristics (n = 5744)</th>
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| Median time from blood collection to patient notification of rapid test result was 66 minutes (interquartile range, 45-120 minutes). In contrast, the median time from blood collection to receipt of EIA results was 28 hours (P<.001), with more significant delays for specimens obtained on weekends vs weekdays (39 vs 25 hours; P<.001).

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<th>Table 2. Multivariate Analysis of Factors Associated With Receipt of Rapid HIV Test Results After Instead of Before Delivery in 4073 Women in Active Labor*</th>
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| Twenty-seven of the 34 HIV-infected women identified were in active labor when they first arrived. Of those, 18 received intrapartum zidovudine (8 of these also received intrapartum single-dose nevirapine). The remaining 9 women who arrived in active labor did not receive intrapartum prophylaxis because they arrived near the time of delivery and could not receive the rapid test result in time to start prophylaxis. The median time between receipt of rapid test result and zidovudine dosing was 33 minutes; zidovudine was started on average 6 hours prior to delivery (range, 1-18 hours). All HIV-exposed infants received zidovudine prophylaxis soon after birth (median, 3.8 hours); 17 infants also received single-dose nevirapine (prophylaxis protocols varied by institution). Two foreign-born HIV-infected women presenting late in pregnancy but who were not in active labor could not be followed up (they may have returned to their home country).

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<td>Of the remaining 32 HIV-exposed infants in the study, 17 were delivered vaginally and 15 by cesarean delivery (none of these 32 infants were breastfed). Three infants were found to be HIV-infected: 2 were already DNA-PCR positive at birth and the other infant was negative at birth but positive by 6 weeks of age. The mother of this infant arrived too late for intrapartum prophylaxis. Two of the 3 infected infants had a vaginal delivery. The infant who was DNA-PCR negative at birth but positive by 6 weeks was delivered vaginally. Of the 32 infants, 27 were followed up for 6 months. Many of the women have started</td>
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highly active antiretroviral therapy for their own health (follow-up of women testing positive is continuing
and being addressed in separate analyses). Of the 34 HIV-infected women identified, 30 were black, of
whom 21 (70%) were born in the United States and 9 (30%) were immigrants from Africa and the
Caribbean. Regarding test performance with non-clade B HIV-1, there was 100% sensitivity in use of the
rapid test with whole blood and no indication in the MIRIAD study that specificity was decreased in African
women.

COMMENT

We found that rapid HIV testing yielded accurate and timely results to women in

labor and that implementing rapid testing was acceptable and feasible. Overall test

acceptance was nearly 85%. Lower acceptance during evening shifts may be

explained in part by fewer available personnel. Informed consent was obtained not

only for rapid HIV testing but also for participation in a research study.

Based on the feasibility of rapid testing demonstrated in MIRIAD, the CDC now recommends routine rapid

HIV testing using an opt-out approach (ie, a woman is informed that HIV testing will be routinely done
during labor if her HIV status is unknown but she may decline testing). Each woman should be

informed that a preliminary positive rapid test result means that she is likely HIV infected but that this

result will need to be confirmed. If her rapid test result is positive, she should be notified that antiretroviral

drugs will be offered to her and to her newborn. If her rapid test result is negative, she should be notified

that she is almost certainly not HIV infected. One practical approach to implementing routine rapid testing

would be for each hospital to put in place standing orders to immediately inform any woman in labor whose

HIV status is unknown that she will be tested unless she declines.

The rationale for focusing on women in labor is that there is a brief window of opportunity for interventions
to decrease HIV transmission to the newborn. This rationale is related to the pharmacokinetics of the
antiretroviral drugs used for prophylaxis. In decision analysis modeling, rapid HIV testing during labor is
cost-saving to the medical system. Our study demonstrates that, in general, results are timely and that
antiretroviral prophylaxis can be provided promptly to HIV-infected women and their infants. In addition,
we have previously shown that point-of-care rapid testing has the potential to save valuable time compared
with sending specimens to the laboratory.

Appropriate training of staff and quality assurance processes are essential to ensure accurate rapid HIV test
results. Despite high test performance, there were still instances in which preliminary HIV-1 screening
tests (rapid test or EIA) yielded false-positive results. The decision to recommend antiretroviral prophylaxis
on the basis of an unconfirmed test result will continue to require clinical judgment and knowledge about
HIV prevalence and the performance characteristics of each test. Although EIA has been the mainstay of
HIV screening, the rapid test demonstrated a higher positive predictive value in the present study.

Several study caveats should be considered. First, clinical interventions were not standardized but left up to
individual practitioners following US Public Health Service guidelines. Second, the total number of
encounters recorded included some women who visited the labor and delivery unit more than once.
Therefore, the percentage of eligibility reported in this study (8%) is likely an underestimate of the true
proportion of women with undocumented HIV status. Third, our findings about acceptance rates and the
informed consent process may not directly translate to a nonresearch setting. Fourth, the utility of the
program is in part contingent on accurate and accessible documentation of the HIV status to avoid
redundancy of effort.
The MIRIAD findings are important both in the United States and internationally. In many settings, including in the developing world, pregnant women with unknown HIV status are often seen by clinicians for the first time during labor. Rapid testing during labor can enable pregnant women with undocumented HIV status to learn their HIV infection status so they can receive antiretroviral prophylaxis and be referred for comprehensive medical care and follow-up.

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Author Contributions: As principal investigator, Dr Bulterys had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Supervision:** Bulterys, O'Sullivan, Maupin, Webber.

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The Long Journey to Health Equity
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Revisions to the July 6, 2006 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 have been made by the Perinatal HIV Guidelines Working Group.

It is emphasized that concepts relevant to HIV management evolve rapidly. The Task Force has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo Web site (http://AIDSinfo.nih.gov).
Cost-Effectiveness of Interventions to Reduce Vertical HIV Transmission from Pregnant Women Who Have Not Received Prenatal Care

Joseph M. Mrus, MD, MSc, Joel Tsevat, MD, MPH

To evaluate the cost-effectiveness of rapid HIV testing followed by treatment with zidovudine, nevirapine, or combination therapy for women presenting in the United States in active labor without prenatal care, the authors developed a decision analytic model from a societal perspective comparing 2 basic strategies: 1) not testing for HIV and 2) offering rapid HIV testing and treatment to women testing positive. HIV transmission rates, test characteristics, and costs were derived from the literature and local sources. Outcomes included number of infected infants, costs, and incremental cost-effectiveness in dollars per quality-adjusted life year saved. The authors found that offering rapid HIV testing and administering zidovudine treatment to women testing positive would prevent 27 cases of HIV each year and save $3,000,000/year compared with no intervention. If more expensive treatments were used (e.g., zidovudine rather than nevirapine, or combination therapy rather than monotherapy), the relative risk reduction in HIV transmission for the more expensive strategies would need to be only slightly better to make the more expensive strategies relatively cost-effective in comparison with the less expensive strategies. In an analysis including empiric nevirapine prophylaxis, the authors found that empiric therapy would prevent 32 HIV cases and save $2.1 million per year compared with no intervention. In conclusion, rapid HIV testing and treatment for women presenting in labor without prior prenatal care would prevent HIV infections and save costs. At sites where rapid HIV testing is not possible, empiric treatment would also prevent HIV infection and save costs and is thus preferred to a strategy of neither testing nor treating. Effectiveness in reducing transmission drives the cost-effectiveness ratio much more so than drug cost and should be the basis on which a particular prophylactic regimen is selected. Key words: HIV; testing; vertical transmission; cost-effectiveness. (Med Decis Making 2004;24:30-39)

Huge strides have been made in the past decade in reducing vertical transmission of HIV in the United States. AIDS Clinical Trials Group protocol 076 showed that a 3-part regimen of zidovudine therapy given to HIV-infected women and their infants substantially reduced vertical transmission rates. Subsequent studies have shown that even shorter antiretroviral regimens given only during labor to HIV-infected women and postpartum to their infants can significantly reduce HIV transmission rates as well. HIV testing is recommended for all pregnant women in the United States; however, about 50,000 women present in labor without prior prenatal care (and HIV testing) each year. Compounding the problem is the fact...
that women without prenatal care have been found to have a relatively high prevalence of HIV infection.\textsuperscript{8,9} A rapid HIV-1 antibody test that can yield results in as little as 10 min is commercially available.\textsuperscript{10} Providing empiric HIV prophylaxis or testing for HIV and then providing prophylaxis to those women who test positive are options for preventing vertical HIV transmission in women without prenatal care. Rejegowda and coworkers showed that rapid HIV testing of women in labor is feasible,\textsuperscript{11} and previous cost-effectiveness analyses found rapid testing followed by zidovudine therapy to be relatively cost-effective.\textsuperscript{12,13} However, implementation of rapid HIV testing and treatment programs for pregnant women without prenatal care has not been universal, partly due to lack of consensus surrounding the effectiveness of implementing testing and treatment programs at sites where few women present without prenatal care and/or the prevalence of HIV is low.

The Perinatal HIV Guidelines Working Group suggests any of 4 antiretroviral prophylaxis options (zidovudine, nevirapine, zidovudine/nevirapine, and zidovudine/lamivudine) for HIV-infected women presenting in labor without prenatal care;\textsuperscript{14} one regimen (zidovudine/nevirapine) has not been studied. Furthermore, while studies suggest that intrapartum and postpartum antiretroviral therapy reduce HIV transmission rates by 14\% to 65\%,\textsuperscript{1,2,3,5} more precise risk reduction estimates and the comparative risk reduction of the various regimens are not currently available.

Our analysis sought to expand on the previous studies evaluating the cost-effectiveness of rapid HIV testing for women without prenatal care by 1) evaluating therapies other than zidovudine (nevirapine and combination therapy), 2) analyzing a possible alternative to rapid testing (empiric nevirapine treatment), and 3) using a metric ($/quality-adjusted life year saved) that allows comparisons with other interventions and conforms to recommendations of the Panel on Cost-Effectiveness in Health and Medicine.\textsuperscript{16}

**METHODS**

**Model Overview**

Using the decision analysis software program DATA, version 3.5 (TreeAge Software, Inc., Williams-town, MA), we developed a decision model analyzing outcomes for pregnant women presenting in labor without prenatal care and for their infants. In the basic model (Figure 1), we examined 2 strategies from a societal perspective: 1) not testing for HIV and 2) offering rapid HIV testing and administering antiretroviral prophylaxis for women testing positive.
medication has enough time to take effect. Women ultimately are truly either HIV infected or not. Without maternal HIV infection, there is no chance of HIV transmission to the infants. However, if women are HIV infected, they can transmit the virus to their infants. Women without adequate prophylaxis (do nothing mission to the infants. However, if women are HIV infected, they can transmit the virus to their infants than do women who receive adequate prophylaxis. In expanded models, we evaluated additional strategies of offering rapid HIV testing and administering nevirapine therapy or combination therapy (zidovudine/nevirapine or zidovudine/lamivudine), as well as a strategy of empiric nevirapine therapy.

We projected outcomes assuming that 50,000 pregnant women present without prenatal care each year (1.25% of 4 million deliveries each year). We assumed an average age of 36 years and a CD4 cell count of 200 cells/µl (if HIV infected). All the women included in this model were assumed to present in labor and therefore would deliver either vaginally or by a nonselective cesarean delivery. The particular mode of delivery was not included in the model because both delivery modes have been shown to yield similar HIV transmission rates (only elective cesarean delivery has been shown to reduce HIV transmission). Also, because it is debated whether earlier diagnosis and treatment of HIV affects overall health (improved immune function on one hand v. treatment side effects and antiretroviral resistance on the other) and costs (up-front treatment costs v. downstream prevention of opportunistic infections), we did not explicitly model the potential health and cost implications of earlier diagnosis of HIV infection in women or infected infants in the base case analysis; however, we did explore those issues in sensitivity analyses.

Costs were inflated to fiscal year 2000 dollars using the Consumer Price Index for Medical Care. All future costs were discounted at a 3% annual rate in the base case. To compare strategies, we calculated incremental cost-effectiveness ratios, defined as the difference in cost divided by the difference in benefit for the strategies. For some comparisons, we asked how much more effective must more costly therapies (zidovudine compared with nevirapine, and combination therapy compared with zidovudine monotherapy) be to be cost neutral with less expensive strategies. We also evaluated the incremental cost-effectiveness of empiric nevirapine therapy for all women presenting without prenatal care. For that analysis, we assumed that (1) nevirapine would have the same effectiveness as zidovudine in reducing HIV transmission, (2) the same proportion of women would deliver before the drug took effect, (3) minimal counseling would be required, and (4) all infants would require full testing (3 serial HIV polymerase chain reaction [PCR] tests) to exclude HIV infection.

Parameter Estimates

Parameter estimates for probabilities, costs, and quality-adjusted life expectancy are summarized in Table 1. The required parameters, the values used in the base case analysis, and the sources for the parameter estimates are explained in detail in the subsequent sections.

Prevalence of HIV infection. The prevalence of HIV infection in pregnant women in the United States has been estimated to be approximately 1.7/1000. Women without prenatal care have been shown to have a relative risk of HIV infection that ranges from 2 to 4. In our base case analysis, we assumed a relative risk of HIV infection of 3 for women without prenatal care, which equates to a prevalence of 5.1/1000.

Vertical transmission risk without intervention. For women in developed countries, estimates of vertical HIV transmission risk without directed intervention have ranged from 19% to more than 30%. In this study, we used a risk of 26.6% in the base case.

Effectiveness of antiretroviral prophylaxis. The AIDS Institute of the New York State Department of Public Health reviewed information on perinatal zidovudine treatment and found an abbreviated zidovudine regimen (intrapartum and postpartum zidovudine) to be effective at reducing perinatal HIV transmission (relative risk reduction of 62% compared with no therapy). A North Carolina group reported similar results with this 2-part regimen (relative risk reduction of 65%). In a meta-analysis, the International Perinatal HIV Group found that in women not undergoing elective cesarean section, an abbreviated regimen of zidovudine reduced vertical HIV transmission rates to 16.4% from 19% without therapy (relative risk reduction of 14%). Other abbreviated antiretroviral regimens studied in developing countries have yielded similar risk reduction (about 50%).
# COST-EFFECTIVENESS OF INTERVENTIONS FOR WOMEN WITHOUT PRENATAL CARE

## Table 1 Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Ranges for Sensitivity Analyses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of HIV in women without prenatal care</td>
<td>5.1/1000</td>
<td>0.1–50/1000</td>
<td>18–21</td>
</tr>
<tr>
<td>HIV transmission without intervention</td>
<td>26.6%</td>
<td>15.0%–30.0%</td>
<td>1–3, 15</td>
</tr>
<tr>
<td>Relative risk reduction in transmission with prophylactic therapy</td>
<td>0.62</td>
<td>0–1</td>
<td>2–4, 15, 22, 23</td>
</tr>
<tr>
<td>Rapid HIV test characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.999</td>
<td>0.99–0.999</td>
<td>10, 24–27</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.996</td>
<td>0.89–0.999</td>
<td>10, 24–27</td>
</tr>
<tr>
<td>Willingness to accept rapid HIV testing</td>
<td>0.96</td>
<td>0–1</td>
<td>11</td>
</tr>
<tr>
<td>Proportion of women delivering before treatment is effective</td>
<td>0.25</td>
<td>0–1</td>
<td>12</td>
</tr>
<tr>
<td>Costs (2000 US dollars)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrapartum zidovudine</td>
<td>163</td>
<td>0–336</td>
<td>13</td>
</tr>
<tr>
<td>Additional cost if combined with nevirapine</td>
<td>7</td>
<td>—</td>
<td>30</td>
</tr>
<tr>
<td>Additional cost if combined with lamivudine</td>
<td>7</td>
<td>—</td>
<td>30</td>
</tr>
<tr>
<td>Infant follow-up with zidovudine prophylaxis</td>
<td>162</td>
<td>81–324</td>
<td>13, 30, Hosp</td>
</tr>
<tr>
<td>Additional cost if combined with nevirapine</td>
<td>7</td>
<td>—</td>
<td>30</td>
</tr>
<tr>
<td>Additional cost if combined with lamivudine</td>
<td>67</td>
<td>—</td>
<td>30</td>
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<tr>
<td>Infant follow-up with zidovudine prophylaxis if rapid test is falsely positive</td>
<td>73</td>
<td>38–140</td>
<td>30, Hosp</td>
</tr>
<tr>
<td>Additional cost if combined with nevirapine</td>
<td>7</td>
<td>—</td>
<td>30</td>
</tr>
<tr>
<td>Additional cost if combined with lamivudine</td>
<td>16</td>
<td>—</td>
<td>30</td>
</tr>
<tr>
<td>Rapid HIV test with pretest counseling</td>
<td>39</td>
<td>19–104</td>
<td>12, 13, 18, 21, 24, Hosp</td>
</tr>
<tr>
<td>Western blot</td>
<td>52</td>
<td>26–104</td>
<td>Hosp</td>
</tr>
<tr>
<td>Posttest counseling (if test result positive)</td>
<td>92</td>
<td>46–104</td>
<td>12, 18, 21</td>
</tr>
<tr>
<td>HIV-infected infant (discounted lifetime cost)</td>
<td>185,000</td>
<td>95,000–420,000</td>
<td>17, 29, 33</td>
</tr>
<tr>
<td>HIV-infected woman (discounted lifetime cost)</td>
<td>106,000</td>
<td>53,000–212,000</td>
<td>36</td>
</tr>
<tr>
<td>Additional cost associated with earlier HIV treatment (compared with delayed HIV treatment)</td>
<td>—</td>
<td>0–200,000</td>
<td></td>
</tr>
<tr>
<td>Discounted quality-adjusted life expectancy (QALYs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-infected infant</td>
<td>9.7</td>
<td>6.8–24.8</td>
<td>17</td>
</tr>
<tr>
<td>Uninfected infant</td>
<td>29.7</td>
<td>15.0–30.0</td>
<td>17</td>
</tr>
<tr>
<td>HIV-infected woman</td>
<td>7.8</td>
<td>6.0–20.0</td>
<td>36</td>
</tr>
<tr>
<td>Decrement in QALYs associated with early diagnosis, prophylaxis, and treatment</td>
<td>—</td>
<td>0–2.5</td>
<td></td>
</tr>
<tr>
<td>Uninfected woman</td>
<td>22.6</td>
<td>10.0–25.0</td>
<td>7, 37, 39</td>
</tr>
</tbody>
</table>

QALY = quality-adjusted life years gained; Hosp = hospital cost accounting system.

62% for zidovudine prophylaxis, but given the range of values in the literature, we varied the relative risk reduction over a wide range in sensitivity analyses.

Test and treatment acceptance rate. Rajegowda and colleagues reported that 86% of women with unknown HIV status consented to rapid HIV testing in labor. Grubman and Garcia used a similar value (derived from different sources) in their analysis. In our base case analysis, we assumed that 86% of women without prenatal care would accept HIV testing and subsequent treatment, but we varied the value over a wide range in sensitivity analysis.

Percentage of women delivering before preventative therapy can take effect. Grubman and Garcia reported that 55% of women without prenatal care will have delivered within 4 h of presentation. For our base case analysis, we assumed that about 2 h would be needed to test, treat, and derive benefit from the prophylactic drug. In the absence of data, we assumed that 25% of women would deliver before the medication could be effective (i.e., about half of 55%). Because the results that are available regarding the effectiveness of antiretroviral prophylaxis given only to infants are conflicting, we made the conservative assumptions that...
there would be no benefit to the infant from the prophylactic therapy given to women delivering before antiretroviral therapy could be effective and that there would be no benefit from prophylaxis given only postpartum to the infant; however, the full cost of HIV prophylaxis and infant follow-up would still be incurred.

**Rapid HIV antibody test characteristics.** SUDS (Abbott Diagnostics) is a Food and Drug Administration-approved rapid HIV-1 antibody test commercially available in the United States. It can yield results in as little as 10 min and has been reported to be 99.9% sensitive and 99.6% specific.\(^{10,24}\) However, other U.S. studies have found its specificity to be slightly lower (98.9%).\(^{25-27}\) With the SUDS test, negative results are generally considered definitive, but positive results must be confirmed.\(^{28}\) In our model, positive results were confirmed within 48 h by a Western blot test (which was considered to be definitive), but initial prophylactic treatment decisions were based on the results of the rapid test.

**Costs**

**HIV-infected children.** Annual cost estimates for HIV-infected children were derived from charges obtained from the AIDS Cost and Service Utilization Survey (ACSUS).\(^{12}\) Because those data reflect the standard of care prior to the advent of highly-active antiretroviral therapy (HAART) and routine viral load testing, we updated the costs by adding the cost of a 2nd reverse transcriptase inhibitor (average cost for zidovudine, dideoxynosine, lamivudine, and stavudine), a protease inhibitor (average cost for ritonavir and nelfinavir), and quarterly viral load testing. Drug costs were obtained from the Red Book.\(^{13}\) We adjusted drug costs for overstatement of acquisition costs and added a monthly dispensing cost.\(^{31}\) Costs associated with viral load testing were obtained from a study by Rawlings and colleagues.\(^{32}\)

Using these component costs and assuming the yearly treatment costs associated with AIDS (as opposed to HIV infection without AIDS) in the last 2 years of life only, we derived average updated annual costs in a similar fashion as Holtgrave and associates.\(^{18}\) For the lower bound of the plausible range, we used lifetime costs from Hsia and colleagues reflecting care during the antiretroviral monotherapy era.\(^{29}\) For the upper bound, we modified estimates from Havens and colleagues in the same manner as we did for the base-line costs.\(^{34}\) We converted the ACSUS-derived HIV-associated charges to costs using a cost-to-charge ratio of 0.6, in the manner of Freedberg and colleagues.\(^{35}\)

**HIV-infected women.** Discounted lifetime costs for women with HIV were obtained from work by Schackman and colleagues.\(^{36,37}\) In the base case analysis, we did not address potential cost implications of earlier diagnosis of HIV infection. However, in sensitivity analyses, we explored potential ramifications of earlier diagnosis and treatment of HIV by varying the discounted lifetime costs for women diagnosed with HIV in labor.

**Testing costs.** Rapid HIV test, Western blot, and infant testing (HIV qualitative DNA PCR test and complete blood count [CBC]) costs were derived from the literature\(^{13,15,34}\) and an urban teaching hospital’s cost accounting system (McKesson/HBOC, Atlanta, GA). Testing costs were varied over a plausible range in sensitivity analyses.

**Drug costs.** We modeled continuous intravenous zidovudine therapy, a single dose of nevirapine, or a single dose of lamivudine for the various intrapartum therapies. For the infants, we modeled 6 weeks of zidovudine therapy, a single dose of nevirapine, or 6 weeks of lamivudine therapy. Intrapartum zidovudine costs were based on a study by Stringer and Rouse.\(^{13}\) Other drug costs were obtained from the Red Book,\(^{29}\) and pharmacy dispensing costs were added to drug costs.\(^{13}\)

**Infant follow-up costs.** Infant follow-up costs were derived by adding drug costs (inpatient and outpatient) and testing costs (3 serial HIV PCR tests and 2 CBCs).\(^{13}\) We assumed that false positive rapid HIV tests would be discovered using confirmatory Western blot testing prior to the infant’s leaving the hospital, so testing and treatment regimens for infants of women with false positive tests were limited to costs that would be incurred in the first 48 h of life (1 HIV PCR, 1 CBC, and 2 days of antiretroviral therapy).

**Counseling costs.** Counseling costs were derived from the literature.\(^{13,18,27}\) We assumed that all women presenting without prenatal care would require counseling prior to testing. We assumed additional counseling would be required if the rapid test returned positive; however, we assumed there would be no posttest counseling (only notification of the result) if the rapid test yielded a negative result.
COST-EFFECTIVENESS OF INTERVENTIONS FOR WOMEN WITHOUT PRENATAL CARE

Quality-Adjusted Life Expectancy

Quality-adjusted life expectancy values were computed to express results in units of cost per quality-adjusted life year (QALY) gained. The discounted (3%/year) values for HIV-infected infants were derived as detailed in another study. In brief, for HIV-infected infants, we assumed a life expectancy of 15 years and calculated quality-adjusted life expectancy assuming utility (quality-of-life weight) estimates similar to those reported by Havens and others. To estimate the lower bound of the plausible range of quality-adjusted life expectancy, we used data reflecting life expectancy prior to the availability of HAART. We assumed an upper-bound life expectancy of 50 years and incorporated higher published utility estimates in another sensitivity analysis.

The discounted quality-adjusted life expectancy for HIV-infected women was derived from a study by Schackman and colleagues. In the base case analysis, we did not address potential health implications of earlier diagnosis of HIV infection in women. However, in sensitivity analyses, we explored potential ramifications of earlier diagnosis and treatment of HIV by varying the discounted QALYs for women diagnosed with HIV in labor.

For uninfected infants and women, we estimated life expectancy using published national estimates. We used age-adjusted utility estimates from the Beaver Dam Health Outcomes Study, which reported sex-specific data for people older than age 45. Since that study did not report utilities for persons younger than 45, we assumed that the utility for non-HIV-infected people younger than age 45 was 1.0. Given that our analysis involved a relatively high-risk population (i.e., would likely have shorter life expectancies than the national averages), we varied the life expectancies of both uninfected women and infants widely in sensitivity analyses.

Additional Sensitivity Analyses

We conducted univariate and multivariate sensitivity analyses, varying model parameters singly and in combination over broad ranges to assess the stability of the results to the underlying data and assumptions. The range over which each model parameter was evaluated in the sensitivity analyses is provided in Table 1.

RESULTS

Basic Model

Rapid HIV testing in labor and zidovudine prophylaxis for those testing positive would both prevent vertical transmission of HIV and save costs compared with no intervention. Assuming 50,000 women without prenatal care deliver each year in the United States, offering rapid HIV testing followed by zidovudine prophylaxis would result in 387 women testing positive for HIV (170 [44%] falsely positive), prevent 27 cases of HIV, and save $3 million each year relative to no intervention.

Alternative Prophylactic Regimens

Rapid testing followed by nevirapine prophylaxis would be preferred over zidovudine prophylaxis if the relative risk reduction of transmission with nevirapine prophylaxis was >0.61. Of note, even though intrapartum zidovudine prophylaxis is more than 20 times more expensive than nevirapine prophylaxis, the relative risk reduction in transmission with zidovudine needs to be only slightly better than with nevirapine (0.62 compared with 0.61) to save more money and prevent more cases of neonatal HIV infection. When we evaluated how much more effective the combinations of zidovudine/nevirapine or zidovudine/lamivudine must be to be cost neutral with zidovudine monotherapy, we found similar results. Prophylactic administration to both mother and infant of either nevirapine or lamivudine in addition to zidovudine requires that the combination be only minimally more effective when compared with zidovudine monotherapy (relative risk reduction about 0.001-0.002 greater) to save additional costs.

In an analysis including empiric nevirapine prophylaxis, we found that empiric nevirapine therapy would be the preferred strategy if 1) rapid testing were not available (empiric therapy prevents 32 HIV cases and saves $2.1 million per year compared with no intervention), 2) the acceptance rate of rapid HIV testing and treatment were 0.68 (and empiric therapy were universal), 3) the relative risk reduction with nevirapine prophylaxis were somewhat better than with zidovudine (0.71 relative risk reduction for nevirapine compared with 0.62 for zidovudine prophylaxis), or 4) all infants were not ruled out for HIV with HIV PCR testing (empiric nevirapine prophylaxis would then save $5.1 million per year).
Table 2  Thresholds in Univariate Sensitivity Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Thresholds</th>
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<tbody>
<tr>
<td></td>
<td>Cost ($20,000/QALY)</td>
</tr>
<tr>
<td>Willingness to accept rapid HIV testing</td>
<td>0.26</td>
</tr>
<tr>
<td>Proportion delivering before treatment is effective</td>
<td>0.70</td>
</tr>
<tr>
<td>Prevalence of HIV in women without prenatal care</td>
<td>0.0020</td>
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<tr>
<td>Relative risk reduction in HIV transmission with therapy</td>
<td>0.25</td>
</tr>
<tr>
<td>Additional cost associated with beginning HIV care earlier</td>
<td>$13,000</td>
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Note: QALY = quality-adjusted life years gained.

Sensitivity Analyses

The results were quite robust to variations in the model parameters. Sensitivity analyses showed that performing rapid testing and administering zidovudine would be cost saving in women without prenatal care, with a few exceptions (summarized in Table 2): 1) if the acceptance rate of rapid testing were 0.26 (base case estimate = 0.86), 2) if the proportion of women delivering before treatment was effective were 0.70 (base case estimate = 0.25), 3) if the prevalence of HIV in women without prenatal care were 2/1000 (base case estimate = 5.1/1000), 4) if the relative risk reduction in vertical HIV transmission were 0.25 (base case estimate = 0.62), or 5) if the additional cost associated with earlier HIV treatment (compared with delayed treatment) were $13,000 (base case estimate = no difference). Furthermore, rapid HIV testing with subsequent treatment for those testing positive would still be relatively cost-effective even at more extreme parameter estimates. For example, if the testing acceptance rate were 0.04, the proportion delivering before the treatment was effective were 0.95, the prevalence of HIV were 0.3/1000 in women without prenatal care, or the relative risk reduction in HIV transmission were 0.04, the incremental cost-effectiveness of rapid HIV testing and zidovudine treatment would be $50,000/QALY saved.

Earlier diagnosis of maternal HIV (i.e., in labor) compared with diagnosis later in the disease would have to more than double the discounted lifetime cost of HIV care to make rapid testing not cost-effective (> $50,000/QALY; Table 2). Also, treatment side effects from therapy to reduce the risk of transmission and from earlier treatment of HIV would need to reduce the discounted quality-adjusted life expectancy in the HIV-infected women and children by a total of 2.4 QALYs to negate those QALYs gained through prevention of HIV transmission.

The key variables evaluated in multivariate sensitivity analyses were the relative risk reduction in HIV transmission with therapy, the proportion of women accepting rapid HIV testing, and the proportion of women delivering before the treatment would be effective. Varying 2 of those variables simultaneously (2-way sensitivity analysis) produced scenarios in which the incremental cost-effectiveness ratio of rapid HIV testing and treatment exceeded $50,000/QALY; however, variable values had to be relatively extreme. As shown in Figures 2 and 3, unless the relative risk reduction in HIV transmission with zidovudine prophylaxis were less than 0.2 (base case was 0.62), the proportion accepting rapid HIV testing would have to be less than 0.1 (base case was 0.86) or the proportion delivering before the treatment was effective would have to be greater than 0.8 (base case was 0.24) for the incremental cost-effectiveness ratio of rapid HIV testing and treatment to exceed $50,000/QALY.
DISCUSSION

Our analysis demonstrates that offering rapid testing to women presenting in labor without prior prenatal care coupled with antiretroviral prophylaxis for those testing positive would reduce HIV infection rates in infants and save money. Our results corroborate and expand on those of Grobman and Garcia\textsuperscript{12} and Stringer and Rouse\textsuperscript{13} by evaluating not only zidovudine therapy but also other regimens, by examining empiric nevirapine therapy, and by exploring potential implications of early HIV diagnosis in mothers.

Because randomized trials in HIV-infected women in the United States are lacking, it is unclear what the effectiveness of the prophylactic regimens recommended by the Perinatal HIV Guidelines Working Group\textsuperscript{14} would be in practice. Our analysis showed that if prophylaxis were even modestly effective, it would likely be cost saving. We also showed that whichever regimen is the most effective of the 4 recommended regimens\textsuperscript{14} is likely to also be the most cost-effective. Strategies with higher drug costs (zidovudine v. nevirapine, or combination therapy v. monotherapy) require only small improvements in effectiveness to be cost saving. Therefore, assuming that combination prophylaxis is more effective than single-drug prophylaxis,\textsuperscript{10} combination prophylaxis (zidovudine/lamivudine or zidovudine/nevirapine) should be used.

It has been debated whether HIV testing in labor should be limited to women at substantial risk for HIV infection (> 1%)\textsuperscript{13} or extended to more general populations presenting without prior HIV testing.\textsuperscript{12} In our univariate sensitivity analyses, rapid testing and treatment was cost saving at a prevalence of HIV equal to the average prevalence for all pregnant women (approximately 2 per 1000), suggesting that testing all women in labor who have not had prenatal care would be clinically and economically worthwhile.

Empiric antiretroviral prophylaxis for women without prenatal care has not been advocated; however, it is an interesting option. We modeled an empiric nevirapine strategy. We chose nevirapine because of its ease of administration (single dose to mother and child) and favorable cost. We found that empiric treatment is preferred to a strategy of neither testing nor treating and could be preferred to rapid testing and treating under certain scenarios: if rapid testing were not available (or not practical because few women present without prenatal care) or if testing to exclude HIV infection in the infants were not routinely performed.

Because it is debatable whether earlier diagnosis and treatment of HIV affects overall health (improved immune function on one hand v. treatment side effects and viral resistance on the other) and costs (treatment costs v. prevention of opportunistic infections), we did not explicitly model the potential health and cost implications of earlier diagnosis of HIV infection in women or infected infants in the base case analysis. However, we did explore potential implications of early HIV diagnosis in sensitivity analyses and found that earlier diagnosis of HIV (i.e., in labor) compared with diagnosis later in the disease would have to more than double the discounted lifetime cost of HIV care to make rapid testing not cost-effective (> $50,000/QALY). Such a large cost increase is unlikely given that Schackman and coworkers found that earlier treatment of HIV (starting at a CD4 cell count of 500 cells/ul instead of 200 cells/ul) added only about $6,000 to the discounted lifetime cost of HIV care.\textsuperscript{36} We also found that side effects from therapy aimed at prevention of transmission and from earlier treatment of HIV would need to reduce the discounted QALYs in the HIV-infected women and children by 2.4 to negate the QALYs gained through prevention of HIV transmission. Such a large decrement is also unlikely given that Schackman and colleagues found that earlier treatment of HIV in-
creased (not decreased) discounted QALYs by about 0.6.36

As discussed, rapid testing and treatment for HIV is likely to be cost saving; however, the 2-way sensitivity analyses showed that if the effectiveness of prophylaxis were substantially lower than expected, then factors such as the test acceptance rate and the proportion of women delivering before getting the benefit of treatment could become important determinants of whether the program is cost saving. Because the true effectiveness of prophylaxis is not known, facilities should be cognizant of such factors when developing such programs. Also, given a relatively low prevalence of HIV infection, facilities need to be aware that a substantial proportion (approximately 44%) of positive results from rapid HIV testing will be false positives. Therefore, staff at sites performing rapid testing need to be trained in appropriate explanation of the rapid test results to patients (i.e., to communicate the probability of HIV infection), and sites need to quickly confirm the tests, prior to patient discharge, to limit the potential catastrophic outcomes of false positive diagnoses of HIV, such as suicide, partner abandonment, and litigation. In practice, rapid HIV testing has been found to be acceptable to patients.11,14

Our analysis has some limitations. We did not model the impact of testing and treatment on breastfeeding rates. Women found to be HIV infected by rapid HIV testing would be advised not to breastfeed. Reducing breastfeeding rates in HIV-infected women would favor the rapid testing strategies and yield greater savings from rapid testing. Also, although our analysis was performed from a societal perspective, we did not explicitly include time costs, that is, the monetary value of the patient's time expended when undergoing care, the cost of orphaned children, or the implications of test results on subsequent pregnancies. Given the great amount of time involved in providing care for an HIV-infected child, incorporating time costs would have only favored the intervention strategies by wider margins, as would including potential HIV cases prevented in future pregnancies. Given the high-risk population that presents without prenatal care, it is likely that many of the children would qualify for public assistance, be cared for by extended family members, or be placed in foster care. Therefore, it is unclear how including issues surrounding orphaned children would have affected the outcomes.

These limitations notwithstanding, we conclude that offering rapid HIV testing to women presenting without prenatal care and administering antiretroviral prophylaxis to women testing positive would decrease the number of HIV-infected infants and save money. At sites where rapid HIV testing is not practical, empiric treatment would prevent cases of HIV and save costs and is thus preferred to a strategy of neither testing nor treating. Effectiveness in preventing vertical transmission of HIV drives the cost-effectiveness ratio much more so than does drug cost; therefore, the most effective prophylactic antiretroviral regimen is likely to also be the most cost-effective.

REFERENCES

COST-EFFECTIVENESS OF INTERVENTIONS FOR WOMEN WITHOUT PRENATAL CARE


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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

SUMMARY

These recommendations update the July 6, 2006 guidelines developed by the Public Health Service for the use of zidovudine (ZDV) to reduce the risk for perinatal human immunodeficiency virus type 1 (HIV-1) transmission*. This report provides health care providers with information for discussion with HIV-1 infected pregnant women to enable such women to make an informed decision regarding the use of antiretroviral drugs during pregnancy and use of elective cesarean delivery to reduce perinatal HIV-1 transmission. Various circumstances that commonly occur in clinical practice are presented, and the factors influencing treatment considerations are highlighted in this report. The Perinatal HIV-1 Guidelines Working Group recognizes that strategies to prevent perinatal transmission and concepts related to management of HIV disease in pregnant women are rapidly evolving and will continually review new data and provide regular updates to the guidelines. The most recent information is available from the AIDSInfo Web site (available at http://aidsinfo.nih.gov/).

In February 1994, the results of Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 documented that ZDV chemoprophylaxis could reduce perinatal HIV-1 transmission by nearly 70%. Epidemiologic data have since confirmed the efficacy of ZDV for reduction of perinatal transmission and have extended this efficacy to children of women with advanced disease, low CD4+ T-lymphocyte counts, and prior ZDV therapy.

Additionally, substantial advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of persons with HIV-1 disease. These advances have resulted in changes in standard antiretroviral therapy for HIV-1 infected adults. More aggressive combination drug regimens that maximally suppress viral replication are now recommended. Although considerations associated with pregnancy may affect decisions regarding timing and choice of therapy, pregnancy is not a reason to defer standard therapy. Use of antiretroviral drugs in pregnancy requires unique considerations, including the possible need to alter dosage as a result of physiologic changes associated with pregnancy, the potential for adverse short- or long-term effects on the fetus and newborn, and the effectiveness of the drugs in reducing the risk for perinatal transmission. Data to address many of these considerations are not yet available. Therefore, offering antiretroviral therapy to HIV-1 infected women during pregnancy, whether primarily for HIV-1 infection, for reduction of perinatal transmission, or for both purposes, should be accompanied by a discussion of the known and unknown short- and long-term benefits and risks of such therapy to infected women and their infants. Standard antiretroviral therapy should be discussed with and offered to HIV-1 infected pregnant women. Additionally, to prevent perinatal transmission, ZDV chemoprophylaxis should be incorporated into the antiretroviral regimen.

* Information included in these guidelines may not represent approval by the Food and Drug Administration (FDA) or approved labeling for the particular product or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.
INTRODUCTION

In February 1994, the Pediatric AIDS Clinical Trials Group (PACTG) Protocol 076 demonstrated that a three-part regimen of zidovudine (ZDV) could reduce the risk for mother-to-child human immunodeficiency virus type 1 (HIV-1) transmission by nearly 70% [1]. The regimen includes oral ZDV initiated at 14–34 weeks' gestation and continued throughout pregnancy, followed by intravenous ZDV during labor and oral administration of ZDV to the infant for six weeks after delivery (Table 1). In August 1994, a U.S. Public Health Service (USPHS) task force issued recommendations for the use of ZDV for reduction of perinatal HIV-1 transmission [2], and in July 1995, USPHS issued recommendations for universal prenatal HIV-1 counseling and HIV-1 testing with consent for all pregnant women in the United States [3]. Since the publication of the results of PACTG 076, epidemiologic studies in the United States and France have demonstrated dramatic decreases in perinatal transmission with incorporation of the PACTG 076 ZDV regimen into general clinical practice [4-9].

Since 1994, advances have been made in the understanding of the pathogenesis of HIV-1 infection and in the treatment and monitoring of HIV-1 disease. The rapidity and magnitude of viral turnover during all stages of HIV-1 infection are greater than previously recognized; plasma virions are estimated to have a mean half-life of only 6 hours [10]. Thus, current therapeutic interventions focus on administration of aggressive combination antiretroviral regimens to maximally suppress viral replication, preserve immune function, and reduce the development of resistance [11]. Potent antiretroviral drugs that inhibit the protease enzyme of HIV-1 are now available. When a protease inhibitor is used in combination with nucleoside analogue reverse transcriptase inhibitors, plasma HIV-1 RNA levels can be reduced for prolonged periods to levels that are undetectable by current assays. Improved clinical outcome and survival have been observed among adults receiving such regimens [12, 13]. Additionally, viral load can now be more directly quantified through assays that measure HIV-1 RNA copy number; these assays have provided powerful new tools to assess disease stage, risk for progression, and the effects of therapy. These advances have led to substantial changes in the standard of treatment and monitoring for HIV-1 infected adults in the United States [14]. (See the “Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents”).

Advances also have been made in the understanding of the pathogenesis of perinatal HIV-1 transmission. Most perinatal transmission likely occurs close to the time of or during childbirth [15]. Additional data that demonstrate the short-term safety of the ZDV regimen are now available as a result of follow-up of infants and women enrolled in PACTG 076; however, data from studies of animals concerning the potential for transplacental carcinogenicity of ZDV affirm the need for long-term follow-up of children with antiretroviral exposure in utero [16].

These advances have implications for maternal and fetal health. Health-care providers considering the use of antiretroviral agents for HIV-1 infected women during pregnancy must take into account two separate but related issues:

1. antiretroviral treatment of maternal HIV-1 infection, and
2. antiretroviral chemoprophylaxis to reduce the risk for perinatal HIV-1 transmission.

The benefits of antiretroviral therapy for a pregnant woman must be weighed against the risk of adverse events to the woman, fetus, and newborn. Although ZDV chemoprophylaxis alone has substantially reduced the risk for perinatal transmission, antiretroviral monotherapy is now considered suboptimal for treatment of HIV-1 infection, and combination drug regimens are considered the standard of care for therapy [14].

This report:
- reviews the special considerations regarding use of antiretroviral drugs for pregnant women,
- updates the results of PACTG 076 and related clinical trials and epidemiologic studies,
- discusses the use of HIV-1 RNA and antiretroviral drug resistance assays during pregnancy,
- provides updated recommendations on antiretroviral chemoprophylaxis for reducing perinatal transmission, and
- provides recommendations related to use of elective cesarean delivery as an intervention to reduce perinatal transmission.

These recommendations have been developed for use in the United States. Although perinatal HIV-1 transmission occurs worldwide, alternative strategies may be appropriate in other countries. Policies and practices in other countries regarding the use of antiretroviral drugs for reduction of perinatal HIV-1 transmission may differ from the recommendations in this report and will depend on local considerations, including availability and cost of antiretroviral drugs, access by pregnant women to facilities for safe intravenous infusions during labor, local recommendations regarding breastfeeding by HIV-1-infected women, and alternative interventions being evaluated in that area.
BACKGROUND

Considerations Regarding the Use of Antiretroviral Drugs by HIV-1 Infected Pregnant Women and Their Infants

Treatment recommendations for pregnant women infected with HIV-1 have been based on the belief that therapies of known benefit to women should not be withheld during pregnancy unless there are known adverse effects on the mother, fetus, or infant and unless these adverse effects outweigh the benefit to the woman [17]. Combination antiretroviral therapy, usually consisting of two nucleoside analogue reverse transcriptase inhibitors and a protease inhibitor, is the recommended standard treatment for HIV-1 infected adults who are not pregnant [14]. (See the “Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents”.) Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of infected pregnant women are subject to unique considerations. These include

a. possible changes in dosing requirements resulting from physiologic changes associated with pregnancy,

b. potential effects of antiretroviral drugs on the pregnant woman, and

c. the potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, which may not be known for certain antiretroviral drugs.

The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussing with her health-care provider the known and unknown benefits and risks to her and her fetus.

Physiologic changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, biotransformation, and elimination, thereby also affecting requirements for drug dosing and potentially altering the susceptibility of the pregnant woman to drug toxicity. During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation and are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in metabolic enzyme pathways in the liver. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, biotransformation of drugs by the fetus and placenta, and elimination of drugs by the fetus also can affect drug pharmacokinetics in the pregnant woman. Additional considerations regarding drug use in pregnancy are

a. the effects of the drug on the fetus and newborn, including the potential for teratogenicity, mutagenicity, or carcinogenicity, and

b. the pharmacokinetics and toxicity of transplacentally transferred drugs.

The potential harm to the fetus from maternal ingestion of a specific drug depends not only on the drug itself, but on the dose ingested, the gestational age of the fetus at exposure, the duration of exposure, the interaction with other agents to which the fetus is exposed, and, to an unknown extent, the genetic makeup of the mother and fetus.

Information regarding the safety of drugs in pregnancy is derived from animal toxicity data, anecdotal experience, registry data, and clinical trials. Data are limited for antiretroviral drugs, particularly when used in combination therapy. Drug choice should be individualized and must be based on discussion with the woman and available data from preclinical and clinical testing of the individual drugs. Preclinical data include results of in vitro and animal in vivo screening tests for carcinogenicity, clastogenicity/mutagenicity, and reproductive and teratogenic effects. However, the predictive value of such tests for adverse effects in humans is unknown. For example, of approximately 1,200 known animal teratogens, only about 30 are known to be teratogenic in humans [18]. In addition to antiretroviral agents, certain drugs commonly used to treat HIV-1 related illnesses demonstrate positive findings on one or more of these screening tests. For example, acyclovir is positive in some in vitro carcinogenicity and clastogenicity assays and is associated with fetal abnormalities in rats; however, data collected on the basis of human experience from the Acyclovir in Pregnancy Registry have indicated no increased risk for birth defects in infants with in utero exposure to acyclovir [19]. Limited data exist regarding placental passage and long-term animal carcinogenicity for the FDA-approved antiretroviral drugs (Table 2).

Although clinical data on antiretroviral drugs in pregnant women are more limited than in non-pregnant individuals, there are sufficient data on some of the available antiretroviral drugs to be able to provide recommendations related to drug choice. Table 3 provides information on pharmacokinetics in pregnancy and pregnancy-related concerns for each of the available antiretroviral drugs; drugs are classified for use in pregnancy as recommended, alternative, insufficient information, or not recommended. This
Combination Antiretroviral Therapy and Pregnancy Outcome

Data are conflicting as to whether receipt of combination antiretroviral therapy during pregnancy is associated with adverse pregnancy outcomes such as preterm delivery. A retrospective Swiss report evaluated the pregnancy outcome of 37 HIV-1 infected pregnant women treated with combination therapy; all received two reverse transcriptase inhibitors and 16 received one or two protease inhibitors [20]. Almost 80% of women experienced one or more typical adverse effects of the drugs, such as anemia, nausea/vomiting, amniantransferase elevation, or hyperglycemia. A possible association of combination antiretroviral therapy with preterm births was noted; 10 of 30 babies were born prematurely. The preterm birth rate did not differ between women receiving combination therapy with or without protease inhibitors. The contribution of maternal HIV-1 disease stage and other covariates that might be associated with a risk for prematurity was not assessed.

The European Collaborative Study and the Swiss Mother + Child HIV-1 Cohort Study investigated the effects of combination retroviral therapy in a population of 3,920 mother child pairs. Adjusting for CD4+ T-lymphocyte count (CD4+ count) and intravenous drug use, they found a 2.6-fold (95% confidence interval [CI] = 1.4–4.8) increased odds of preterm delivery for infants exposed to combination therapy with or without protease inhibitors compared with no treatment; women receiving combination therapy that had been initiated before their pregnancy were twice as likely to deliver prematurely as those starting therapy during the third trimester [21]. However, combination therapy was received by only 323 (8%) women studied. Exposure to monotherapy was not associated with prematurity.

In contrast, in an observational study of pregnant women with HIV-1 infection in the United States (PACTG 367) in which 1,150 (78%) of 1,472 women received combination therapy, no association was found between receipt of combination therapy and preterm birth (R. Tuomala, July 2000 PACTG meeting). The highest rate of preterm delivery was among women who had not received any antiretroviral therapy, which is consistent with several other reports demonstrating elevated preterm birth rates among untreated women with HIV-1 infection [22-24]. In a French open-label study of 445 HIV-1 infected women receiving ZDV who had lamivudine (3TC) added to their therapy at 32 weeks' gestation, the rate of preterm delivery was 6%, similar to the 9% rate in a historical control group of women receiving only ZDV [25]. Additionally, in a large meta-analysis of seven clinical studies that included 2,123 HIV-1-infected pregnant women who delivered infants during 1990–1998 and had received antenatal antiretroviral therapy and 1,143 women who did not receive antenatal antiretroviral therapy, use of multiple antiretroviral drugs as compared with no treatment or treatment with one drug was not associated with increased rates of preterm labor, low birth weight, low Apgar scores, or stillbirth [26].

Until more information is known, HIV-1 infected pregnant women who are receiving combination therapy for their HIV-1 infection should continue their provider-recommended regimen. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities.

Nevirapine and Hepatic/Rash Toxicity

Increases in hepatic transaminase levels (ALT and AST) associated with rash or systemic symptoms may be observed during the first 18 weeks of treatment with nevirapine. These toxicities have been reported in patients on chronic therapy, and have not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. Signs and symptoms of systemic toxicity may be non-specific, and can include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal hepatic transaminases [27]. The development of severe nevirapine-associated skin rash has been reported to be 5.5 to 7.3 times more common in women than men, and has been reported in pregnant women [28-30]. Other studies have found that hepatic adverse events with systemic symptoms (predominantly rash) were 3.2 fold more common in women than men [31, 32]. The degree of risk for hepatic toxicity varies with CD4+ cell count. In a summary analysis of data from 17 clinical trials of nevirapine therapy, women with CD4+ counts greater than 250 cells/mm³ were 9.8 times more likely than women with lower CD4+ counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity [31, 32]. Higher CD4+ cell counts have
also been associated with increased risk of severe nevirapine-associated skin rash [29]. In controlled clinical trials, clinical hepatic events, regardless of severity, occurred in 4.0% (range 2.5–11.0%) of patients who received nevirapine; however, the risk of nevirapine-associated liver failure or hepatic mortality has been lower, ranging between 0.04–0.40% [33, 34]. Severe or life threatening rash occurs in approximately 2% of patients receiving nevirapine [34].

Although deaths due to hepatic failure have been reported in HIV-infected pregnant women receiving nevirapine as part of a combination antiretroviral regimen, it is unknown if pregnancy increases the risk of hepatotoxicity in women receiving nevirapine or other antiretroviral drugs [35, 36]. Women initiating nevirapine with CD4⁺ counts > 250 cells/mm³, including pregnant women receiving antiretroviral drugs solely for prevention of transmission, have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal [33]. Nevirapine should therefore be used as a component of a combination regimen in this setting only if the benefit clearly outweighs the risk. Regardless of maternal CD4⁺ cell count, if nevirapine is used, health care providers should be aware of this potential complication and should conduct frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., ALT and AST), particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, monthly through month 4, and every 1 to 3 months thereafter (see Hepatotoxicity section of table 16a in the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). In patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy, and then monthly [27]). Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST), or who have asymptomatic but severe transaminase elevations, should stop nevirapine and not receive nevirapine therapy in the future. Hepatic toxicity has not been seen in women receiving single dose nevirapine during labor for prevention of perinatal transmission of HIV-1. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4⁺ count.

Protease Inhibitor Therapy and Hyperglycemia

Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported with receipt of protease inhibitor antiretroviral drugs by HIV-1 infected patients [37–40]. In addition, pregnancy is itself a risk factor for hyperglycemia; it is unknown if the use of protease inhibitors will increase the risk for pregnancy-associated hyperglycemia. Clinicians caring for HIV-1 infected pregnant women who are receiving protease inhibitor therapy should be aware of the risk of this complication and closely monitor glucose levels. Symptoms of hyper-glycemia should be discussed with pregnant women who are receiving protease inhibitors.

Postpartum Hemorrhage, Antiretroviral Drugs, and Methergine Use

Women experiencing postpartum hemorrhage due to uterine atony are often managed with oral or parenteral methergine as a first-line agent. However, methergine should not be coadministered with drugs that are potent CYP3A4 enzyme inhibitors, including protease inhibitors and the non-nucleoside reverse transcriptase inhibitors efavirenz and delavirdine. The concomitant use of ergotamines and protease inhibitors has been associated with exaggerated vasoconstrictive responses. When uterine atony results in excessive postpartum bleeding in women receiving protease inhibitors or efavirenz or delavirdine as a component of an antiretroviral regimen, methergine should only be used if alternative treatments (e.g., prostaglandin F2 alpha, misoprostol, or oxytocin) are not available. If there are no alternative medications available and the need for pharmacologic treatment outweighs the risks, methergine should be used in as low a dosage and for as short a duration as possible.

Mitochondrial Toxicity and Nucleoside Analogue Drugs

Nucleoside analogue drugs are known to induce mitochondrial dysfunction because the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA depletion and dysfunction [41]. The relative potency of the nucleosides in inhibiting mitochondrial gamma DNA polymerase in vitro is highest for zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), ZDV, 3TC, abacavir (ABC), and tenofovir [42]. Toxicity related to mitochondrial
dysfunction has been reported to occur in infected patients receiving long-term treatment with nucleoside analogues and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested [41]. These toxicities may be of particular concern for pregnant women and infants with in utero exposure to nucleoside analogue drugs.

**During Pregnancy**

Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may have a female preponderance [43]. These syndromes have similarities to rare but life-threatening syndromes that occur during pregnancy, most often during the third trimester: acute fatty liver, and the combination of hemolysis, elevated liver enzymes and low platelets (the HELLP syndrome). Several investigators have correlated these pregnancy-related disorders with a recessively inherited mitochondrial abnormality in the fetus/infant that results in an inability to oxidize fatty acids [44-46]. Since the mother would be a heterozygotic carrier of the abnormal gene, the risk for liver toxicity might be increased during pregnancy because the mother would be unable to properly oxidize both maternal and accumulating fetal fatty acids [47]. Additionally, animal studies have demonstrated that in late gestation, pregnant mice have significant reductions (25%-50%) in mitochondrial fatty acid oxidation and that exogenously administered estradiol and progesterone can reproduce these effects [48, 49]; whether this can be translated to humans is unknown. However, these data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in the development of acute fatty liver of pregnancy and HELLP syndrome and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity.

Lactic acidosis with microvascular hepatic steatosis is a toxicity related to nucleoside analogue drugs that is thought to be related to mitochondrial toxicity; it has been reported to occur in infected persons treated with nucleoside analogue drugs for long periods (>6 months). Initially, most cases were associated with ZDV, but later other nucleoside analogue drugs, particularly d4T, have been associated with the syndrome. In a report from the FDA Spontaneous Adverse Event Program of 106 patients with this syndrome (60 receiving combination and 46 receiving single nucleoside analogue therapy), typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness [43]. Metabolic acidosis with elevated serum lactate and elevated hepatic enzymes was common. Patients described in that report were predominantly female and overweight. The incidence of this syndrome may be increasing, possibly as a result of increased use of combination nucleoside analogue therapy or increased recognition of the syndrome. In a cohort of infected patients receiving nucleoside analogue therapy followed at Johns Hopkins University during 1989–1994, the incidence of the hepatic steatosis syndrome was 0.13% per year [50]. However, in a report from a cohort of 964 HIV-1 infected persons followed in France for 2 years during 1997–1999, the incidence of symptomatic hyperlactatemia was 0.8% per year for all patients and 1.2% for patients receiving a regimen including d4T [51].

The frequency of this syndrome in pregnant HIV-1 infected women receiving nucleoside analogue treatment is unknown. In 1999, Italian researchers reported a case of severe lactic acidosis in an infected pregnant woman who was receiving d4T-3TC at the time of conception and throughout pregnancy and who experienced symptoms and fetal death at 38 weeks' gestation [52]. Bristol-Myers Squibb has reported three maternal deaths due to lactic acidosis, two with and one without accompanying pancreatitis, among women who were either pregnant or postpartum and whose antepartum therapy during pregnancy included d4T and ddI in combination with other antiretroviral agents (either a protease inhibitor or nevirapine) [53, 54]. All women were receiving treatment with these agents at the time of conception and continued for the duration of pregnancy; all presented late in gestation with symptomatic disease that progressed to death in the immediate postpartum period. Two cases were also associated with fetal death. Non-fatal cases of lactic acidosis in pregnant women receiving combination d4T-ddI have also been reported [55].

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome that has been reported for nonpregnant persons receiving nucleoside analogue treatment. However, because pregnancy itself can mimic some of the early symptoms of the lactic acidosis/ hepatic steatosis syndrome or be associated with other disorders of liver metabolism, these cases emphasize the need for physicians caring for HIV-1 infected pregnant women receiving nucleoside analogue drugs to be alert for early signs of this syndrome. Pregnant women receiving nucleoside analogue drugs should have hepatic enzymes and electrolytes assessed more frequently during the last trimester of pregnancy,
and any new symptoms should be evaluated thoroughly. Additionally, because of the reports of several cases of maternal mortality secondary to lactic acidosis with prolonged use of the combination of d4T and ddI by HIV-1 infected pregnant women, clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analogue drug combinations have failed or have caused unacceptable toxicity or side effects.

In Utero Exposure

A study conducted in France reported that in a cohort of 1,754 uninfected infants born to HIV-1 infected women who received antiretroviral drugs during pregnancy, eight infants with in utero or neonatal exposure to either ZDV-3TC (four infants) or ZDV alone (four infants) developed indications of mitochondrial dysfunction after the first few months of life [56]. Two of these infants (both of whom had been exposed to ZDV-3TC) contracted severe neurologic disease and died, three had mild to moderate symptoms, and three had no symptoms but had transient laboratory abnormalities.

A further evaluation of mitochondrial toxicity was conducted in 4,392 uninfected or HIV-indeterminate children (2,644 with perinatal antiretroviral exposure) followed within the French Pediatric Cohort or identified within a France National Register developed for reporting of possible mitochondrial dysfunction in HIV-exposed children. Evidence of mitochondrial dysfunction was identified in 12 children (including the previous 8 reported cases), all of whom had perinatal antiretroviral exposure, an 18-month incidence of 0.26% [57]. Risk was higher among infants exposed to combination antiretroviral drugs (primarily ZDV/3TC) than ZDV alone. All children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or a significant episode of hyperlactatemia, and all had an identified deficit in one of the mitochondrial respiratory chain complexes and/or abnormal muscle biopsy histology. An additional 14 children with “possible” mitochondrial dysfunction had unexplained clinical and/or laboratory findings for which mitochondrial dysfunction could be included in the differential diagnosis, although none had respiratory chain enzyme deficits or histologic abnormalities. In a separate publication, the same group reported an increased risk of simple febrile seizures during the first 18 months of life among uninfected infants with antiretroviral exposure [58].

A small study quantified mitochondrial DNA in cord blood and peripheral blood leukocytes at age 1 and 2 years in HIV-exposed infants with (N=10) and without (N=10) perinatal ZDV exposure and infants born to HIV-uninfected women (N=30) [59]. Mitochondrial DNA quantity was lower in infants born to HIV-infected women overall compared to those born to uninfected women, and was lowest among those HIV-exposed infants with ZDV exposure compared to those without exposure. In another study, transient hyperlactatemia during the first few weeks of life was reported among 17 HIV-exposed infants with perinatal antiretroviral exposure; lactate levels returned to normal in all children and none developed symptoms of mitochondrial dysfunction during follow-up [60]. Thus, the clinical significance of these laboratory findings is unclear, and further studies are needed to validate these findings.

In infants followed through age 18 months in PACTG 076, the occurrence of neurologic events was rare; seizures occurred in one child exposed to ZDV and two exposed to placebo, and one child in each group had reported spasticity. Mortality at 18 months was 1.4% among infants given ZDV compared with 3.5% among those given placebo [61]. The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring among children born to HIV-1 infected women and followed during 1986–1999 in five large prospective U.S. perinatal cohorts. No deaths similar to those reported from France or with clinical findings attributable to mitochondrial dysfunction were identified in a database of >16,000 uninfected children born to HIV-1 infected women with and without antiretroviral drug exposure [62]. However, most of the infants with antiretroviral exposure had been exposed to ZDV alone and only a relatively small proportion (approximately 6%) had been exposed to ZDV-3TC.

In an African perinatal trial (PETRA) that compared three regimens of ZDV-3TC (during pregnancy starting at 36 weeks' gestation, during labor, and through 1 week postpartum; during labor and postpartum; and during labor only) with placebo for prevention of transmission, data have been reviewed relating to neurologic adverse events among 1,798 children who participated. No increased risk of neurologic events was observed among children treated with ZDV-3TC compared with placebo, regardless of the intensity of treatment [63]. The European Collaborative Study reviewed clinical symptoms in 2,414 uninfected children in their cohort, 1,008 of who had perinatal antiretroviral exposure. The median length of follow-up was 2.2 years (maximum, 16 years). No association of clinical manifestations suggestive of mitochondrial abnormalities was found with perinatal antiretroviral exposure. Of the 4 children with seizures in this cohort, none had perinatal antiretroviral exposure.
Finally, in a study of 382 uninfected infants born to HIV-1 infected women, echocardiograms were prospectively performed every 4 to 6 months during the first 5 years of life; 9% of infants had been exposed to ZDV prenatally [64]. No significant differences in ventricular function were observed between infants exposed and not exposed to ZDV.

Thus, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure. If this association is demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and should be compared against the clear benefit of antiretroviral prophylaxis in reducing transmission of a fatal infection by 70% or more [65-67]. Mitochondrial dysfunction should be considered in uninfected children with perinatal antiretroviral exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings. These results emphasize the importance of the existing Public Health Service recommendation for long-term follow-up for any child with in utero exposure to antiretroviral drugs.

Antiretroviral Pregnancy Registry

Health-care providers who are treating HIV-1 infected pregnant women and their newborns are strongly advised to report instances of prenatal exposure to antiretroviral drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. This registry is an epidemiologic project to collect observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The Antiretroviral Pregnancy Registry is a collaborative project of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. The registry does not use patient names, and registry staff obtain birth outcome follow-up information from the reporting physician.

Referrals should be directed to
Antiretroviral Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405
Telephone: 1–800–258–4263
Fax: 1–800–800–1052
Internet access [www.APRegistry.com]

Update on PACTG 076 Results and Other Studies Relevant to ZDV Chemoprophylaxis for Perinatal HIV-1 Transmission

In 1996, final results were reported for all 419 infants enrolled in PACTG 076. The results concur with those initially reported in 1994; the Kaplan-Meier estimated HIV-1 transmission rate for infants who received placebo was 22.6%, compared with 7.6% for those who received ZDV, a 66% reduction in risk for transmission [68].

The mechanism by which ZDV reduced transmission in PACTG 076 participants has not been fully defined. The effect of ZDV on maternal HIV-1 RNA does not fully account for the observed efficacy of ZDV in reducing transmission. Preexposure prophylaxis of the fetus or infant may offer substantial protection. If so, transplacental passage of antiretroviral drugs would be crucial for prevention of transmission. Additionally, in placental perfusion studies, ZDV has been metabolized into the active triphosphate within the placenta [69, 70], which could provide additional protection against in utero transmission. This phenomenon may be unique to ZDV because metabolism to the active triphosphate form within the placenta has not been observed in the other nucleoside analogues that have been evaluated (i.e., ddi and ddc) [71, 72].

In PACTG 076, similar rates of congenital abnormalities occurred among infants with and without in utero ZDV exposure. Data from the Antiretroviral Pregnancy Registry also have demonstrated no increased risk for congenital abnormalities among infants born to women who receive ZDV antenatally compared with the general population [73]. Among uninfected infants from PACTG 076 followed from birth to a median age of 4.2 years (range 3.2–5.6 years), no differences were noted in growth, neurodevelopment, or immunologic status between infants born to mothers who received ZDV compared with those born to mothers who received placebo [74]. No malignancies have been observed in short-term (i.e., up to age 6 years) follow-up of >727 infants from PACTG 076 or from a prospective cohort study involving infants with in utero ZDV exposure [75]. However, follow-up is too limited to provide a definitive assessment of carcinogenic risk with human exposure. Long-term monitoring continues to be recommended for all infants who have received in utero ZDV exposure or in utero exposure to any of the antiretroviral drugs.

The efficacy of ZDV chemoprophylaxis for reducing HIV-1 transmission among populations of infected women with characteristics unlike those of the PACTG 076 population has been evaluated in another perinatal
protocol (PACTG 185) and in prospective cohort studies. PACTG 185 enrolled pregnant women with advanced HIV-1 disease and low CD4^+ counts who were receiving antiretroviral therapy; 24% had received ZDV before the current pregnancy [76]. All women and infants received the three-part ZDV regimen combined with either infusions of hyperimmune HIV-1 immunoglobulin (HIVIG) containing high levels of antibodies to HIV-1 or standard intravenous immunoglobulin (IVIG) without HIV-1 antibodies. Because advanced maternal HIV-1 disease has been associated with increased risk for perinatal transmission, the transmission rate in the control group was hypothesized to be 11%–15% despite the administration of ZDV. At the first interim analysis, the transmission rate for the combined group was only 4.8% and did not substantially differ by whether the women received HIVIG or IVIG or by duration of ZDV use [76]. The results of this trial confirm the efficacy of ZDV observed in PACTG 076 and extend this efficacy to women with advanced disease, low CD4^+ count, and prior ZDV therapy. Rates of perinatal transmission have been documented to be as low as 3%–4% among women with HIV-1 infection who receive all three components of the ZDV regimen, including women with advanced HIV-1 disease [6, 76].

At least two studies suggest that antenatal use of combination antiretroviral regimens might further reduce transmission. In an open-label, nonrandomized study of 445 women with HIV-1 infection in France, 3TC was added at 32 weeks' gestation to standard ZDV prophylaxis; 3TC was also given to the infant for 6 weeks in addition to ZDV [25]. The transmission rate in the ZDV-3TC group was 1.6% (95% CI = 0.7%–3.3%); in comparison, the transmission rate in a historical control group of women receiving only ZDV was 6.8% (95% CI = 5.1%–8.7%). In a longitudinal epidemiologic study conducted in the United States since 1990, transmission was observed in 20% of women with HIV-1 infection who received no antiretroviral treatment during pregnancy, 10.4% who received ZDV alone, 3.8% who received combination therapy without protease inhibitors, and 1.2% who received combination therapy with protease inhibitors [66].

International Antiretroviral Prophylaxis Clinical Trials

In a trial evaluating short-course antenatal/intrapartum ZDV prophylaxis and perinatal transmission among non-breastfeeding women in Thailand, administration of ZDV 300 mg twice daily for 4 weeks antenatally and 300 mg every 3 hours orally during labor was shown to reduce perinatal transmission by approximately 50% compared with placebo [77]. The transmission rate was 19% in the placebo group versus 9% in the ZDV group. A second, four-arm factorial design trial in Thailand compared administration of ZDV antenatally starting at 28 or 36 weeks' gestation, orally intrapartum, and to the neonate for 3 days or 6 weeks. At an interim analysis, the transmission rate in the arm receiving ZDV antenatally starting at 36 weeks and postnatally for 3 days to the infant was 10%, which was significantly higher than for the long arm (antenatal starting at 28 weeks and infant administration for 6 weeks) [78]. The transmission rate in the short arm of this study was similar to the 9% observed with short antenatal/intrapartum ZDV in the first Thai study. The rate of in utero transmission was higher among women in the short antenatal arms compared with those receiving longer antenatal therapy, suggesting that longer treatment of the infant cannot substitute for longer treatment of the mother.

A third trial in Africa (PETRA trial) among breastfeeding HIV-1-infected women has shown that a combination regimen of ZDV and 3TC administered starting at 36 weeks' gestation, orally intrapartum, and for 1 week postpartum to the woman and infant reduced transmission at age 6 weeks by approximately 63% compared with placebo [63]. The transmission rate at age 6 weeks was 15% in the placebo group versus 6% with the three-part ZDV-3TC regimen. This efficacy is similar to the efficacy observed in the Thailand study of antepartum/intrapartum short-course ZDV in non-breastfeeding women [77].

Investigators have identified two possible intrapartum/postpartum regimens (either ZDV-3TC or nevirapine) that could provide an effective intrapartum/postpartum intervention for women for whom the diagnosis of HIV-1 is not made until near to or during labor. The PETRA African ZDV-3TC trial among breastfeeding HIV-1 infected women also demonstrated that an intrapartum/postpartum regimen, started during labor and continued for 1 week postpartum in the woman and infant, reduced transmission at age 6 weeks from 15% in the placebo group to 9% in the group receiving the two-part ZDV-3TC regimen, a reduction of 42% [63]. In this trial, oral ZDV-3TC administered solely during the intrapartum period was not effective in lowering transmission. Another study in Uganda (HIVNET 012), again in a breastfeeding population, demonstrated that a single 200-mg oral dose of nevirapine given to the mother at onset of labor combined with a single 2-mg/kg oral dose given to her infant at age 48–72 hours reduced transmission by nearly 50% compared with a very short regimen of ZDV given orally during labor and to the infant for 1 week [79]. Transmission at age 6 weeks was
12% in the nevirapine group compared with 21% in the ZDV group. A subsequent trial in South Africa demonstrated similar transmission rates with a modified HIVNET 012 nevirapine regimen (nevirapine given to the woman as a single dose during labor with a second dose at 48 hours postpartum, and a single dose to the infant at age 48 hours) compared with the PETRA regimen of oral ZDV–3TC during labor and for 1 week after delivery to the mother and infant [80]. Transmission rates at age 8 weeks were 12.3% in the nevirapine arm and 9.3% in the ZDV–3TC arm (p=0.11).

Two clinical trials have suggested that the addition of the HIVNET 012 single-dose nevirapine regimen to short-course ZDV may provide increased efficacy in reducing perinatal transmission. A study of nonbreastfeeding women in Thailand compared a short-course ZDV regimen (starting at 28 weeks’ gestation, given orally intrapartum, and for 1 week to the infant) with two combination regimens: short-course ZDV plus single-dose intrapartum/neonatal nevirapine, and short-course ZDV plus intrapartum maternal nevirapine only. In the short-course ZDV-only arm, enrollment was discontinued by the Data and Safety Monitoring Board at the first interim analysis because transmission was significantly higher among those receiving ZDV alone compared with those receiving the intrapartum/neonatal nevirapine combination regimen [81]. The study is continuing to enroll to allow comparison of the two combination arms. A second open-label study in Cote d'Ivoire reported a 7.1% transmission rate at age 4 weeks with administration of short-course ZDV (starting at 36 weeks, given orally intrapartum, and for 1 week to the infant) combined with single-dose intrapartum/neonatal nevirapine. This was lower than for a nonconcurrent historical control group receiving ZDV alone [82].

In contrast to these studies, which evaluated combining single-dose nevirapine with short-course ZDV, a study in the United States, Europe, Brazil, and the Bahamas (PACTG 316) evaluated whether the addition of the HIVNET 012 single-dose nevirapine regimen to standard antiretroviral therapy (at minimum the 3-part full ZDV regimen) would provide additional benefits in lowering transmission. In this study, 1,506 pregnant women with HIV-1 infection who were receiving antiretroviral therapy (77% were receiving combination antiretroviral regimens) were randomized to receive a single dose of nevirapine or nevirapine placebo at onset of labor, and their infants received a single dose (according to the maternal randomization) at age 48 hours. Transmission was not significantly different between groups, occurring in 1.6% of women in the placebo group and 1.4% among women in the nevirapine group [83].

Certain data indicate that postexposure antiretroviral prophylaxis of infants whose mothers did not receive antepartum or intrapartum antiretroviral drugs might provide some protection against transmission. Although data from some epidemiologic studies do not support efficacy of postnatal ZDV alone, other data demonstrate efficacy if ZDV is started rapidly following birth [6, 84, 85]. In a study from North Carolina, the rate of infection among HIV-1 exposed infants who received only postpartum ZDV chemoprophylaxis was similar to that observed among infants who received no ZDV chemoprophylaxis [6]. However, another epidemiologic study from New York State determined that administration of ZDV to the neonate for 6 weeks was associated with a significant reduction in transmission if the drug was initiated within 24 hours of birth (the majority of infants started within 12 hours) [84, 85]. Results from a clinical trial in Malawi of infant postexposure prophylaxis in breastfeeding infants, when no maternal antepartum or intrapartum antiretroviral drug was received, compared the efficacy of single dose infant nevirapine to single dose infant nevirapine plus one week of ZDV. Overall transmission at 6–8 weeks of age was 20.9% in the single dose nevirapine arm versus 15.3% in the combination arm, an efficacy of 26.8%; when evaluation was confined to only those infants who were uninfected at birth, infection rates at 6–8 weeks were 12.1% with single dose nevirapine versus 7.7% with the combination, a 36.4% efficacy [86]. In the U.S., the standard recommendation for infant prophylaxis in the absence of maternal therapy is 6 weeks of ZDV. While the Malawi data suggest that combining 1 week of ZDV with single dose nevirapine is more effective than single dose nevirapine alone, it does not address whether such a regimen is more effective than 6 weeks of ZDV. Therefore, no changes are recommended to the current USPHS recommendations to give 6 weeks of infant ZDV as the standard prophylaxis. Several ongoing clinical trials are attempting to determine the optimal postexposure antiretroviral prophylaxis regimen for infants.

**Perinatal HIV-1 Transmission and Maternal HIV-1 RNA Copy Number**

The correlation of HIV-1 RNA levels with risk for disease progression in nonpregnant infected adults suggests that HIV-1 RNA should be monitored during pregnancy at least as often as recommended for persons who are not pregnant (i.e., every 3 to 4 months or approximately once each trimester). In addition, HIV-1
RNA levels should be evaluated at 34–36 weeks of gestation to allow discussion of options for mode of delivery based on HIV-1 RNA results and clinical circumstances. Although no data indicate that pregnancy accelerates HIV-1 disease progression, longitudinal measurements of HIV-1 RNA levels during and after pregnancy have been evaluated in only a limited number of prospective cohort studies. In one cohort of 198 HIV-1 infected women, plasma HIV-1 RNA levels were higher at 6 months postpartum than during pregnancy in many women; this increase was observed in women regardless of ZDV use during and after pregnancy [87].

Initial data regarding the correlation of viral load with risk for perinatal transmission were conflicting, with some studies suggesting an absolute correlation between HIV-1 RNA copy number and risk of transmission [88]. However, although higher HIV-1 RNA levels have been observed among women who transmitted HIV-1 to their infants, overlap in HIV-1 RNA copy number has been observed in women who transmitted and those who did not transmit the virus. Transmission has been observed across the entire range of HIV-1 RNA levels (including in women with HIV-1 RNA copy number below the limit of detection of the assay), and the predictive value of RNA copy number for transmission in an individual woman has been relatively poor [87, 89, 90]. In PACTG 076, antenatal maternal HIV-1 RNA copy number was associated with HIV-1 transmission in women receiving placebo. In women receiving ZDV, the relationship was markedly attenuated and no longer statistically significant [68]. An HIV-1 RNA threshold below which there was no risk for transmission was not identified; ZDV was effective in reducing transmission regardless of maternal HIV-1 RNA copy number [68, 91].

More recent data from larger numbers of ZDV-treated infected pregnant women indicate that HIV-1 RNA levels correlate with risk of transmission even among women treated with antiretroviral agents [77, 92-94]. Although the risk for perinatal transmission in women with HIV-1 RNA below the level of assay quantitation appears to be extremely low, transmission from mother to infant has been reported among women with all levels of maternal HIV-1 RNA. Additionally, although HIV-1 RNA may be an important risk factor for transmission, other factors also appear to play a role [94-96].

Although there is a general correlation between viral load in plasma and in the genital tract, discordance has also been reported, particularly between HIV-1 proviral load in blood and genital secretions [97-100]. If exposure to HIV-1 in the maternal genital tract during delivery is a risk factor for perinatal transmission, plasma HIV-1 RNA levels might not always be an accurate indicator of risk. Long-term changes in one compartment (such as can occur with antiretroviral treatment) may or may not be associated with comparable changes in other body compartments. Further studies are needed to determine the effect of antiretroviral drugs on genital tract viral load and the association of such effects on the risk of perinatal HIV-1 transmission. In the short-course ZDV trial in Thailand, plasma and cervicovaginal HIV-1 RNA levels were reduced by ZDV treatment, and each independently correlated with perinatal transmission [101]. The full ZDV chemoprophylaxis regimen, alone or in combination with other antiretroviral agents, including intravenous ZDV during delivery and the administration of ZDV to the infant for the first 6 weeks of life, should be discussed with and offered to all infected pregnant women regardless of their HIV-1 RNA level.

Results of epidemiologic and clinical trials suggest that women receiving highly active antiretroviral regimens that effectively reduce HIV-1 RNA to <1,000 copies/mL or undetectable levels have very low rates of perinatal transmission [25, 66, 83, 102]. However, since transmission can occur even at low or undetectable HIV-1 RNA copy numbers, RNA levels should not be a determining factor when deciding whether to use ZDV for chemoprophylaxis. Additionally, the efficacy of ZDV is not solely related to lowering viral load. In one study of 44 HIV-1 infected pregnant women, ZDV was effective in reducing transmission despite minimal effect on HIV-1 RNA levels [103]. These results are similar to those observed in PACTG 076 [68]. Antiretroviral prophylaxis reduces transmission even among women with HIV-1 RNA levels <1,000 copies/mL [104]. Therefore, at a minimum, ZDV prophylaxis should be given even to women who have a very low or undetectable plasma viral load.

**PRECONCEPTIONAL COUNSELING AND CARE FOR HIV-1-INFECTED WOMEN OF CHILDBEARING AGE**

The Centers for Disease Control and Prevention (CDC), the American College of Obstetrics and Gynecology (ACOG), and other national organizations recommend offering all women of childbearing age the opportunity to receive preconception counseling and care as a component of routine primary medical care. The purpose of preconception care is to improve the health of each woman prior to conception by identifying risk...
factors for adverse maternal or fetal outcome, providing education and counseling targeted to the patient's individual needs, and treating or stabilizing medical conditions to optimize maternal and fetal outcomes [105]. Preconception care is not a single clinical visit, but rather a process of ongoing care and interventions integrated into primary care to address the needs of women during the different stages of reproductive life. Because more than half of all pregnancies are unintended [106], it is important that preconception care be integrated into routine health visits. Therefore, HIV care providers who routinely care for women of reproductive age play an important role in promoting preconception health.

The fundamental principles of preconception counseling and care have been outlined by the CDC Preconception Care Work Group’s “Recommendations to Improve Preconception Health and Health Care” [107]. In addition to the general components of preconception counseling and care that are appropriate for all women of reproductive age, HIV-1-infected women have specific needs that should be addressed [108]. Since many women infected with HIV-1 are aware of their HIV status prior to pregnancy, there may be opportunities to address issues that impact pregnancy prior to conception during routine medical care for their HIV disease. In addition to those outlined by the CDC Preconception Care Work Group [107], the following components of preconception counseling and care are recommended for HIV-infected women:

- Select effective and appropriate contraceptive methods to reduce the likelihood of unintended pregnancy. Providers should be aware of potential interactions of antiretroviral drugs with hormonal contraceptives that could lower contraceptive efficacy (See the “Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, Tables 21a and 21b”) [14].
- Counsel on safe sexual practices that prevent HIV transmission to sexual partners and protect women from acquiring sexually transmitted diseases and the potential to acquire more virulent or resistant HIV strains.
- Counsel on eliminating alcohol, illicit drug use, and cigarette smoking.
- Educate and counsel women about risk factors for perinatal HIV transmission, strategies to reduce those risks, and potential effects of HIV or treatment on pregnancy course and outcomes [109].
- When prescribing antiretroviral treatment to women of childbearing potential, considerations should include regimen effectiveness for treatment of HIV disease and the drugs’ potential for teratogenicity should pregnancy occur. Women who are planning to get pregnant should strongly consider use of antiretroviral regimens that do not contain efavirenz or other drugs with teratogenic potential, as well as regimens that are effective in preventing mother-to-child transmission.
- Attain a stable, maximally suppressed maternal viral load prior to conception in women who are on antiretroviral therapy and want to get pregnant.
- Evaluate and control for therapy-associated side effects which may adversely impact maternal-fetal health outcomes (e.g., hyperglycemia, anemia, hepatic toxicity).
- Evaluate for appropriate prophylaxis for opportunistic infections and administration of medical immunizations (e.g., influenza, pneumococcal, or hepatitis B vaccines) as indicated.
- Encourage sexual partners to receive HIV testing and counseling and appropriate HIV care if infected.
- Counsel regarding available reproductive options, such as intrauterine or intravaginal insemination, that prevent HIV exposure to an uninfected partner [110]; expert consultation is recommended.
- Breastfeeding by HIV-infected women is not recommended in the U.S. due to risk of HIV transmission.

**GENERAL PRINCIPLES REGARDING THE USE OF ANTIRETROVIRAL AGENTS IN PREGNANCY**

Medical care of the HIV-1 infected pregnant woman requires coordination and communication between the HIV specialist caring for the woman when she is not pregnant and her obstetrician. Decisions regarding use of antiretroviral drugs during pregnancy should be made by the woman after discussion with her healthcare provider about the known and unknown benefits and risks of therapy. Initial evaluation of an infected pregnant woman should include an assessment of HIV-1 disease status and recommendations regarding antiretroviral treatment or alteration of her current antiretroviral regimen.

This assessment should include the following:

a. evaluation of the degree of existing immunodeficiency determined by CD4+ count,

b. risk for disease progression as determined by the level of plasma RNA,

c. history of prior or current antiretroviral therapy,

d. gestational age, and

e. supportive care needs.
Decisions regarding initiation of therapy should be the same for women who are not currently receiving antiretroviral therapy and for women who are not pregnant, with the additional consideration of the potential impact of such therapy on the fetus and infant [14]. Similarly, for women currently receiving antiretroviral therapy, decisions regarding alterations in therapy should involve the same considerations as those used for women who are not pregnant. The three-part ZDV chemoprophylaxis regimen, alone or in combination with other antiretroviral agents, should be discussed with and offered to all infected pregnant women to reduce the risk for perinatal HIV-1 transmission.

Decisions regarding the use and choice of antiretroviral drugs during pregnancy are complex; several competing factors influencing risk and benefit must be weighed. Discussion regarding the use of antiretroviral drugs during pregnancy should include the following:

a. what is known and not known about the effects of such drugs on the fetus and newborn, including lack of long-term outcome data on the use of any of the available antiretroviral drugs during pregnancy;
b. what treatment is recommended for the health of the HIV-1 infected woman; and
c. the efficacy of ZDV for reduction of perinatal HIV-1 transmission.

Results from preclinical and animal studies and available clinical information about use of the various antiretroviral agents during pregnancy also should be discussed (Table 2 and 3). The hypothetical risks of these drugs during pregnancy should be placed in perspective with the proven benefit of antiretroviral therapy for the health of the infected woman and the benefit of ZDV chemoprophylaxis for reducing the risk for HIV-1 transmission to her infant.

Discussion of treatment options should be noncoercive, and the final decision regarding use of antiretroviral drugs is the responsibility of the woman. Decisions regarding use and choice of antiretroviral drugs for persons who are not pregnant are becoming increasingly complicated as the standard of care moves toward simultaneous use of multiple antiretroviral drugs to suppress viral replication below detectable limits. These decisions are further complicated in pregnancy because the long-term consequences for the infant who has been exposed to antiretroviral drugs in utero are unknown. A woman’s decision to refuse treatment with ZDV or other drugs should not result in punitive action or denial of care. Further, use of ZDV alone should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and therefore, after counseling, chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.

A long-term treatment plan should be developed after discussion between the patient and the health-care provider and should emphasize the importance of adherence to any prescribed antiretroviral regimen. Depending on individual circumstances, provision of support services, mental health services, and drug abuse treatment may be required. Coordination of services among prenatal care providers, primary care and HIV-1 specialty care providers, mental health and drug abuse treatment services, and public assistance programs is essential to ensure adherence of the infected woman to antiretroviral treatment regimens.

General counseling should include what is known regarding risk factors for perinatal transmission. Cigarette smoking, illicit drug use, and unprotected sexual intercourse with multiple partners during pregnancy have been associated with risk for perinatal HIV-1 transmission [111-115], and discontinuing these practices might reduce this risk. In addition, CDC recommends that infected women in the United States refrain from breastfeeding to avoid postnatal transmission of HIV-1 to their infants through breast milk [3, 116]; these recommendations also should be followed by women receiving antiretroviral therapy. Passage of antiretroviral drugs into breast milk has been evaluated for only a few antiretroviral drugs. ZDV, 3TC, and nevirapine can be detected in the breast milk of women, and ddI, d4T, abacavir, delavirdine, indinavir, ritonavir, saquinavir and amprenavir can be detected in the breast milk of lactating rats. Limited data are available regarding either the efficacy of antiretroviral therapy for the prevention of postnatal transmission of HIV-1 through breast milk or the toxicity of long-term antiretroviral exposure of the infant through breast milk.

Women who must temporarily discontinue therapy because of pregnancy-related hyperemesis should not resume therapy until sufficient time has elapsed to ensure that the drugs will be tolerated. To reduce the potential for emergence of resistance, if therapy requires temporary discontinuation for any reason during pregnancy, all drugs should be stopped and reintroduced simultaneously.
RECOMMENDATIONS FOR ANTIRETROVIRAL CHEMOPROPHYLAXIS TO REDUCE PERINATAL HIV-1 TRANSMISSION

The following recommendations for use of antiretroviral chemoprophylaxis to reduce the risk for perinatal transmission are based on situations that may be commonly encountered in clinical practice (Table 4), with relevant considerations highlighted in the subsequent discussion sections. These recommendations are only guidelines, and flexibility should be exercised according to the patient's individual circumstances. In the 1994 recommendations [2], six clinical situations were delineated on the basis of maternal CD4+ count, weeks of gestation, and prior antiretroviral use. Because current data indicate that the PACTG 076 ZDV regimen also is effective for women with advanced disease, low CD4+ count, and prior ZDV therapy, clinical situations based on CD4+ count and prior ZDV use are not presented. Additionally, because data indicate that most transmission occurs near the time of or during delivery, ZDV chemoprophylaxis is recommended regardless of weeks of gestation; thus, clinical situations based on weeks of gestation also are not presented.

The antenatal dosing regimen in PACTG 076 (100 mg administered orally five times daily) (Table 1) was selected on the basis of the standard ZDV dosage for adults at the time of the study. However, recent data have indicated that administration of ZDV three times daily will maintain intracellular ZDV triphosphate at levels comparable with those observed with more frequent dosing [117-119]. Comparable clinical response also has been observed in some clinical trials among persons receiving ZDV twice daily [120-122]. Thus, the current standard ZDV dosing regimen for adults is 200 mg three times daily, or 300 mg twice daily. Because the mechanism by which ZDV reduces perinatal transmission is not known, these dosing regimens may not have equivalent efficacy to that observed in PACTG 076. However, a regimen of two or three times daily is expected to increase adherence to the regimen.

The recommended ZDV dosage for infants was derived from pharmacokinetic studies performed among full-term infants [123]. ZDV is primarily cleared through hepatic glucuronidation to an inactive metabolite. The glucuronidation metabolic enzyme system is immature in neonates, leading to prolonged ZDV half-life and clearance compared with older infants (ZDV half-life: 3.1 hours versus 1.9 hours; clearance: 10.9 versus 19.0 mL/minute/kg body weight, respectively). Because premature infants have even greater immaturity in hepatic metabolic function than full-term infants, further prolongation of clearance may be expected. In a study of 15 premature infants who were at 26–33 weeks' gestation and who received different ZDV dosing regimens, mean ZDV half-life was 7.2 hours and mean clearance was 2.5 mL/minute/kg body weight during the first 10 days of life [124]. At a mean age of 18 days, a decrease in half-life (4.4 hours) and increase in clearance (4.3 mL/minute/kg body weight) were found. Results of a pharmacokinetic study of ZDV dosing in infants <35 weeks gestation at birth (PACTG 331) indicated that the appropriate dose of ZDV for preterm infants is 1.5 mg/kg/dose intravenously, or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if ≥30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth [125].

CLINICAL SITUATIONS AND RECOMMENDATIONS FOR USE OF ANTIRETROVIRAL PROPHYLAXIS

Scenario #1: HIV-1-Infected Pregnant Women Who Have Not Received Prior Antiretroviral Therapy

Recommendation

Pregnant women with HIV-1 infection must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed [14]. The three-part ZDV chemoprophylaxis regimen, initiated after the first trimester, is recommended for all pregnant women with HIV-1 infection, regardless of antenatal HIV-1 RNA copy number, to reduce the risk for perinatal transmission. The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV-1 infection is recommended for infected women whose clinical, immunologic, or virologic status requires treatment or whose HIV-1 RNA is > 1,000 copies/mL regardless of their clinical or immunologic status, and can be considered for women with HIV-1 RNA < 1,000 copies/mL. Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10–12 weeks' gestation.
**Discussion**

When ZDV is administered in the three-part PACTG 076 regimen, perinatal transmission is reduced by approximately 70%. Although the mechanism by which ZDV reduces transmission is not known, protection is likely multifactorial. Pre-exposure prophylaxis of the infant is provided by passage of ZDV across the placenta so that inhibitory levels of the drug are present in the fetus during the birth process. Although placental passage of ZDV is excellent, that of other antiretroviral drugs may be variable (Table 2). Therefore, when combination antiretroviral therapy is initiated during pregnancy, ZDV should be included as a component of antenatal therapy whenever possible. Because the mechanism by which ZDV reduces transmission is not known, the intrapartum and newborn ZDV components of the chemoprophylactic regimen should also be administered to reduce perinatal HIV-1 transmission. If a woman does not receive ZDV as a component of her antenatal antiretroviral regimen, intrapartum and newborn ZDV should still be recommended.

Because of the evolving and complex nature of the management of HIV-1 infection, a specialist with experience in the treatment of pregnant women with HIV-1 infection should be involved in their care. Women should be informed that potent combination antiretroviral regimens have substantial benefit for their own health and may provide enhanced protection against perinatal transmission. Several studies have indicated that for women with low or undetectable HIV-1 RNA levels (e.g., < 1,000 copies/mL), rates of perinatal transmission are extremely low, particularly when women have received antiretroviral therapy [66, 92, 93]. However, there is no threshold below which lack of transmission can be assured, and the long-term effects of in utero exposure to multiple antiretroviral drugs are unknown. Decisions regarding the use and choice of an antiretroviral regimen should be individualized based on discussion with the woman about the following factors:

a. her risk for disease progression and the risks and benefits of delaying initiation of therapy;
b. benefit of lowering viral load and reducing the risk of perinatal transmission;
c. independent benefit of combination antiretroviral regimens for reducing the risk of perinatal transmission [92];
d. potential drug toxicities and interactions with other drugs;
e. the need for strict adherence to the prescribed drug schedule to avoid the development of drug resistance;
f. unknown long-term effects of in utero drug exposure on the infant; and
g. preclinical, animal, and clinical data relevant to use of the currently available antiretroviral agents during pregnancy.

Because the period of organogenesis (when the fetus is most susceptible to potential teratogenic effects of drugs) is during the first 10 weeks of gestation, and the risks of antiretroviral therapy during that period are unknown, women in the first trimester of pregnancy might wish to delay initiation of therapy until after 10–12 weeks' gestation. This decision should be carefully considered by the health–care provider and the patient; a discussion should include an assessment of the woman's health status, the benefits and risks of delaying initiation of therapy for several weeks, and the fact that most perinatal HIV-1 transmission likely occurs late in pregnancy or during delivery. Treatment with efavirenz should be avoided during the first trimester because significant congenital central nervous system abnormalities were seen in cynomolgus monkeys born to mothers who received efavirenz during pregnancy at drug exposures similar to those representing human exposure. Severe central nervous system defects have been reported in four infants after first trimester exposure to efavirenz-containing regimens (three infants with meningomyelocele and one with a Dandy-Walker malformation). Based on these data, efavirenz has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk) (Table 2 and see **Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy**). Hydroxyurea is a potent teratogen in a variety of animal species, and should also be avoided during the first trimester.

When initiation of antiretroviral therapy is considered optional on the basis of current guidelines for treatment of nonpregnant persons [14], infected pregnant women should be counseled regarding the benefits of standard combination therapy for fetal protection and should be offered such therapy, including the three-part ZDV chemoprophylaxis regimen. Although such women are at low risk for clinical disease progression if combination therapy is delayed, antiretroviral therapy that successfully reduces HIV-1 RNA to levels < 1,000 copies/mL substantially lowers the risk of perinatal HIV-1 transmission and may lessen the need for consideration of elective cesarean delivery as an intervention to reduce transmission risk.

When combination therapy is administered, the regimen should be chosen from those recommended for nonpregnant adults [14]. However, women, particularly those with CD4+ counts > 250 cells/mm³, have an
increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity, which can be severe, life-threatening, and in some cases fatal [33]. Therefore, nevirapine should only be used as a component of a combination regimen when antiretroviral therapy is being initiated in women with CD4+ counts >250 cells/mm³, including pregnant women receiving antiretroviral drugs solely for prevention of transmission, if benefit clearly outweighs risk. If nevirapine is used, frequent and careful monitoring of transaminase levels, particularly during the first 18 weeks of treatment, is required (see Nevirapine and Hepatic/Rash Toxicity). Transaminase levels should be checked in all women who develop a rash while receiving nevirapine. Nevirapine should be stopped immediately in all women who develop signs or symptoms of hepatitis.

Dual nucleoside analogue therapy without the addition of either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor is not recommended for nonpregnant adults because of the potential for inadequate viral suppression and rapid development of resistance [126]. For pregnant women not meeting the criteria for antiretroviral therapy for their own health, and receiving antiretroviral drugs only for prevention of perinatal transmission, dual nucleoside therapy may be considered in selected circumstances (e.g., in those with HIV-1 RNA < 1,000 copies/mL).

If combination therapy is given principally to reduce perinatal transmission and would have been optional if the woman were not pregnant, consideration may be given to discontinuing therapy postnatally, with the option to reinstitute treatment according to standard criteria for nonpregnant women. Discussion regarding the decision to continue or stop combination therapy postpartum should occur before beginning therapy during pregnancy. Generally, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, if the drugs have significantly different half-lives, such a strategy may result in functional monotherapy for a period of time and potential development of resistance. Pharmacokinetic data demonstrate that detectable drug levels may persist for 21 days or more after discontinuation of nevirapine [127, 128]. To avoid a period of functional monotherapy, some experts would continue the dual nucleoside analogue components of the regimen for a period of time after nevirapine discontinuation. However, the optimal interval is not known, and further research is needed to assess appropriate strategies for stopping nevirapine-containing combination regimens that are used during pregnancy for prevention of mother-to-child transmission (see Clinical Research Needs).

Antiretroviral prophylaxis has been beneficial in preventing perinatal transmission even for infected pregnant women with HIV-1 RNA levels < 1,000 copies/mL. In a meta-analysis of factors associated with perinatal transmission among women whose infants were infected despite maternal HIV-1 RNA < 1,000 copies/mL at or near delivery, transmission was only 1.0% among women receiving antenatal antiretroviral therapy (primarily ZDV alone), compared with 9.8% among those receiving no antenatal therapy [104]. Therefore, use of antiretroviral prophylaxis is recommended for all pregnant women with HIV-1 infection, regardless of antenatal HIV-1 RNA level.

The time-limited use of ZDV alone during pregnancy for chemoprophylaxis against perinatal transmission is controversial. Standard combination antiretroviral regimens for treatment of HIV-1 infection should be discussed and should be offered to all pregnant women with HIV-1 infection regardless of viral load; they are recommended for all pregnant women with HIV-1 RNA levels > 1,000 copies/mL. There is some evidence that even with HIV-1 RNA levels < 1,000 copies/mL, combination antiretroviral regimens may further decrease perinatal transmission compared with ZDV alone [129]. However, some women may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy while still reducing the risk of transmitting HIV-1 to their infants. Additionally, for women with HIV-1 RNA levels < 1,000 copies/mL, time-limited use of ZDV during the second and third trimesters of pregnancy is less likely to induce the development of resistance than in women with higher viral loads because of the limited viral replication in the patient and the time-limited exposure to the antiretroviral drug. For example, the development of ZDV resistance was unusual among the healthy population of women who participated in PACTG 076 [130]. The use of ZDV chemoprophylaxis alone (or, in selected circumstances, dual nucleosides) during pregnancy might be an appropriate option for these women.

Scenario #2: HIV-1-Infected Women Receiving Antiretroviral Therapy During the Current Pregnancy

Recommendation

HIV-1 infected women receiving antiretroviral therapy whose pregnancy is identified after the first trimester...
should continue therapy. ZDV should be a component of the antenatal antiretroviral treatment regimen after the first trimester whenever possible, although this may not always be feasible. Women receiving antiretroviral therapy whose pregnancy is recognized during the first trimester should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance. Regardless of the antepartum antiretroviral regimen, ZDV administration is recommended during the intrapartum period and for the newborn.

**Discussion**

Women who have been receiving antiretroviral treatment for their HIV-1 infection should continue treatment during pregnancy. Discontinuation of therapy could lead to an increase in viral load, which could result in decline in immune status and disease progression as well as adverse consequences for both the fetus and the woman.

Although ZDV should be a component of the antenatal antiretroviral treatment whenever possible, there may be circumstances, such as the occurrence of significant ZDV-related toxicity, when this is not feasible. Additionally, women receiving an antiretroviral regimen that does not contain ZDV but who have HIV-1 RNA levels that are consistently very low or undetectable (e.g., <1,000 copies/mL) have a very low risk of perinatal transmission [66], and there may be concerns that the addition of ZDV to the current regimen could compromise adherence to treatment.

The maternal antenatal antiretroviral treatment regimen should be continued on schedule as much as possible during labor to provide maximal virologic effect and to minimize the chance of development of drug resistance. If a woman has not received ZDV as a component of her antenatal therapeutic antiretroviral regimen, intravenous ZDV should still be administered during the intrapartum period whenever feasible. ZDV and d4T should not be administered together because of potential pharmacologic antagonism; options for women receiving oral d4T as part of their antenatal therapy include either continuation of oral d4T during labor without intravenous ZDV or withholding oral d4T during the period of intravenous ZDV administration during labor. Additionally, the infant should receive the standard 6-week course of ZDV.

For women with suboptimal suppression of HIV-1 RNA (i.e., >1,000 copies/mL) near the time of delivery despite having received prenatal ZDV prophylaxis with or without combination antiretroviral therapy, it is not known if administration of additional antiretroviral drugs during labor and delivery provides added protection against perinatal transmission. In the HIVNET 012 study among Ugandan women who had not received antenatal antiretroviral therapy, a 2-dose nevirapine regimen (single dose to the woman at the onset of labor and single dose to the infant at age 48 hours) significantly reduced perinatal transmission compared with a very short intrapartum/1 week postpartum ZDV regimen [79]. For women in the United States, Europe, Brazil, and the Bahamas receiving antenatal antiretroviral therapy, addition of the 2–dose nevirapine regimen did not result in lower transmission rates [83]. Given the lack of further reduction of transmission with nevirapine added to one of the standard antepartum regimens used in developed countries and the potential development of nevirapine resistance (See Antiretroviral Drug Resistance and Resistance Testing in Pregnancy), addition of nevirapine during labor for women already receiving antiretroviral therapy is not recommended in the United States.

Women receiving antiretroviral therapy may realize they are pregnant early in gestation and want to consider temporarily stopping antiretroviral treatment until after the first trimester because of concern for potential teratogenicity. Data are insufficient to support or refute the teratogenic risk of antiretroviral drugs when administered during the first 10 weeks of gestation; certain drugs are of more concern than others. (Table 2 and see **Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy**). The decision to continue therapy during the first trimester should be carefully considered by the clinician and the pregnant woman. Discussions should include considerations such as gestational age of the fetus; the woman's clinical, immunologic, and virologic status; and the known and unknown potential effects of the antiretroviral drugs on the fetus. If antiretroviral therapy is discontinued during the first trimester, all agents should be stopped and restarted simultaneously in the second trimester to avoid the development of drug resistance. No data are available to address whether temporary discontinuation of therapy is harmful for the woman or fetus.

Health-care providers might consider administering ZDV in combination with other antiretroviral drugs to newborns of women with a history of prior antiretroviral therapy, particularly in situations in which the woman is infected with HIV-1 with documented
high-level ZDV resistance, has had disease progression while receiving ZDV, or has had extensive prior ZDV monotherapy. The efficacy of this approach is unknown but would be analogous to the use of multiple agents for postexposure prophylaxis for adults after inadvertent exposure. However, the appropriate dosage and short- and long-term safety of many antiretroviral agents in the neonate has not been established. The half-lives of ZDV, 3TC, and nevirapine are prolonged during the neonatal period because of immature liver metabolism and renal function, requiring specific dosing adjustments when these agents are administered to neonates. Optimal dosages for protease inhibitors in the neonatal period are still under study. The infected woman should be counseled regarding the theoretical benefit of combination antiretroviral drugs for the neonate, potential risks, and available data on appropriate dosing. She should also be informed that using antiretroviral drugs in addition to ZDV for prophylaxis of newborns is of unknown efficacy in reducing risk of perinatal transmission.

**Scenario #3: HIV-1-Infected Women in Labor Who Have Had No Prior Therapy**

**Recommendation**

Several effective regimens are available for intrapartum therapy for women who have had no prior therapy (Table 5).

1. intrapartum intravenous ZDV followed by six weeks of ZDV for the newborn;
2. oral ZDV and 3TC during labor, followed by one week of oral ZDV-3TC for the newborn;
3. a single dose of nevirapine at the onset of labor, followed by a single dose of nevirapine for the newborn at age 48 hours; and
4. the single-dose maternal/infant nevirapine regimen combined with intrapartum intravenous ZDV and six weeks of ZDV for the newborn.

If single-dose nevirapine is given to the mother, alone or in combination with ZDV, consideration should be given to adding maternal ZDV/3TC starting as soon as possible (intrapartum or immediately postpartum) and continuing for 3 to 7 days, which may reduce development of nevirapine resistance.

In the immediate postpartum period, the woman should have appropriate assessments (e.g., CD4 count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.

**Discussion**

Although intrapartum/neonatal antiretroviral medications will not prevent perinatal transmission that occurs before labor, most transmission occurs near to or during labor and delivery. Pre-exposure prophylaxis for the fetus can be provided by giving the mother a drug that rapidly crosses the placenta to produce systemic antiretroviral drug levels in the fetus during intensive exposure to HIV-1 in maternal genital secretions and blood during birth.

Several intrapartum/neonatal antiretroviral prophylaxis regimens are applicable for women in labor who have had no prior antiretroviral therapy (Table 5). Available epidemiologic data from non-breastfeeding populations support the efficacy of intrapartum intravenous ZDV followed by six weeks of infant ZDV. Two regimens, one using a combination of ZDV and 3TC, and the other using two doses of nevirapine (one each for the mother and infant), were shown to reduce perinatal transmission in randomized clinical trials among breastfeeding women. The fourth regimen, combining ZDV with nevirapine, is based upon theoretical considerations. However, data are not available to address the comparative efficacy of the four intrapartum/neonatal regimens. Therefore, choice of regimen should be based on the specific clinical situation and the judgment of the clinician. When maternal single-dose nevirapine is used, consideration should be given to adding maternal ZDV/3TC as soon as possible, either intrapartum or postpartum, and continuing for 3 to 7 days (often referred to as a ZDV/3TC “tail”); this may reduce the development of nevirapine resistance.

Epidemiologic data indicate that intravenous maternal intrapartum ZDV followed by oral ZDV for 6 weeks for the infant may significantly reduce transmission compared with no treatment (Table 5) [6, 84, 85]. In a study in New York State, transmission rates were 10% with intrapartum and neonatal ZDV compared with 27% without ZDV, a 62% reduction in risk [84, 85]. However, oral intrapartum ZDV combined with very short-term ZDV administration to infants postnatally, for example, the 1-week postnatal infant ZDV course in HIVNET 012 [79], was inferior to single-dose nevirapine. This underscores the necessity of recommending a full 6-week course of infant treatment when ZDV alone is used.

In the PETRA trial, conducted in a breastfeeding population in Uganda, South Africa, and Tanzania, ZDV and 3TC were administered orally intrapartum and to the woman and infant for 7 days postnatally (Table 5). At age 6 weeks, the rates of transmission were 9% in the...
ZDV-3TC arm versus 15% in the placebo arm, a 42% reduction in transmission [63]. However, no differences in transmission were observed when ZDV and 3TC were administered only during the intrapartum period (transmission of 14% in the ZDV-3TC arm versus 15% in the placebo arm), indicating that some postexposure prophylaxis is needed, at least in breastfeeding settings. In the United States, administration of ZDV-3TC to the mother postnatally in addition to the infant would not be required for prophylaxis against transmission because HIV-1 infected women in the U.S. are advised not to breastfeed their infants (although ZDV-3TC might be indicated as part of a combination postnatal treatment regimen for a woman who requires treatment).

In the HIVNET 012 trial, conducted in a breastfeeding population in Uganda, a regimen consisting of a single dose of oral nevirapine given to the woman at onset of labor and a single dose to the infant at age 48 hours was compared with oral ZDV given to the woman every 3 hours during labor and postnatally to the infant for 7 days (Table 4). At age 6 weeks, the rates of transmission were 12% in the nevirapine arm versus 21% in the ZDV arm, a 42% reduction in transmission [79]. No significant short-term toxicity was observed in either group.

In a trial in non-breastfeeding women in Thailand, combining single-dose nevirapine with a short-course ZDV regimen that includes ZDV administration during pregnancy was shown to have improved efficacy compared to ZDV alone [81]. However, in a study in breastfeeding women in Malawi, the addition of one week of infant ZDV to infant single-dose nevirapine did not provide any added benefit compared to single-dose maternal/infant nevirapine alone when the maternal intrapartum nevirapine dose was received. The combination did provide additional benefit when the maternal dose was not received [86, 131]. There are no studies that address whether the combination of single-dose nevirapine with a ZDV regimen that is given intrapartum and for 6 weeks to the infant provides added benefit over that observed with each regimen alone.

Theoretical advantages of combining the ZDV and nevirapine intrapartum/neonatal regimens include the known short-term safety of each regimen alone; excellent transplacental passage of both drugs; greater antiviral activity of nevirapine compared with ZDV, as well as the activity of nevirapine against extracellular and intracellular virus [132, 133]; and the known synergy of ZDV and nevirapine in inhibiting HIV-1 replication in vitro [134]. However, single-dose nevirapine has been associated with nevirapine-resistant virus in women and infants who become infected despite receiving nevirapine [135, 136], even when the mother receives additional antiretroviral drugs during pregnancy and intrapartum [137, 138] (see Antiretroviral Drug Resistance and Resistance Testing in Pregnancy).

Genotypic nevirapine resistance was detected at 6 weeks postpartum in 15% of women who received single-dose nevirapine and who had received ZDV alone or combination antiretroviral drugs during pregnancy and intrapartum [137, 138]. Thus, the potential benefits of combination prophylaxis with intrapartum/neonatal nevirapine and ZDV must be weighed against the increased cost, possible problems with nonadherence, the risk of emergence of nevirapine-resistant virus, and the lack of definitive data to show that combining the two intrapartum/postpartum regimens offers any additional benefit for prevention of transmission over the use of either drug alone.

Minimal data are available to address the relative efficacy of these four intrapartum/neonatal antiretroviral regimens for prevention of transmission. In a clinical trial (SAINT) in South Africa that compared a modified HIVNET 012 nevirapine regimen (in which the woman received a single dose of nevirapine at the onset of labor and a second dose at 48 hours postpartum, and the infant received a single dose at 48 hours) and the PETRA intrapartum/postpartum ZDV-3TC regimens, no significant differences were observed between the two regimens in terms of efficacy in reducing transmission or in maternal and infant toxicity [80]. In the absence of data to suggest the superiority of one or more of the possible regimens, choice should be based upon the specific circumstances of each woman.

Factors to be considered in the choice of which intrapartum/neonatal regimen to administer include: availability of the drug and appropriate formulation (e.g., intravenous ZDV); ability to adhere to the regimen, particularly to the infant postnatal component of the regimen; potential toxicity of the regimen; potential for development of drug resistance in the woman and infants infected despite prophylaxis (of particular concern for 3TC and nevirapine, where a single mutation is associated with resistance); and the implications of such resistance for future treatment options and the efficacy of prophylaxis for future pregnancies.

Development of resistance to 3TC given in an intrapartum/postpartum regimen is rare, although it does occur when 3TC is administered for longer periods during pregnancy as a component of a non-suppressive regimen. In a study in France of ZDV-3TC...
given during pregnancy and for 6 weeks to the infant, the M184V mutation associated with 3TC resistance was observed at 6 weeks postpartum in 52 of 132 women (39%) with HIV RNA levels > 200 copies/mL; resistance was only observed in women who had received antenatal ZDV-3TC for 4 weeks or longer [25]. However, no ZDV or 3TC resistance was observed with intrapartum/1 week postpartum ZDV-3TC in the SAINT study in South Africa [139].

The single-dose nevirapine regimen offers the advantage of lower cost, the possibility of directly observed therapy, and increased adherence compared with the other regimens. However, single-dose nevirapine can be associated with the transient detection of nevirapine resistance in women and in infants who become infected despite receiving nevirapine. Nevirapine resistance mutations were detected at 6 weeks postpartum in 25% of the subset of women with detectable viremia who received single-dose intrapartum nevirapine in HIVNET 012 [135, 136]. These mutations were no longer detectable in plasma virus at 13-18 months postpartum, in a setting where none of the women received postnatal antiretroviral therapy. Nevirapine resistance mutations were also detected at 6-8 weeks of age in 11 of 24 (46%) infants who became infected despite receiving nevirapine. Ten of the 11 infected infants with nevirapine resistance had positive HIV tests at birth, and the specific genotypic resistance mutations differed between the mother and infant, suggesting that the nevirapine resistance developed de novo in infants who were infected in utero and had active viral replication at the time of nevirapine exposure, as opposed to nevirapine resistant virus being transmitted from the mother. As in the mothers, these mutations were no longer detectable in plasma virus by 12 months of age.

In the SAINT trial, in which women received 2 doses rather than a single dose of nevirapine, nevirapine resistance was detected in 67% of women and 53% of infected infants [139]. Thus, a regimen containing two maternal doses of nevirapine (intrapartum and 48 hours postpartum) appears to offer no additional benefit over single-dose nevirapine in reducing transmission, but significantly increases the risk of developing nevirapine resistance, and is not recommended.

The clinical consequence of transient detection of NVP-resistant virus following single-dose nevirapine prophylaxis is uncertain, but there are concerns this could negatively impact the response to subsequent antiretroviral treatment that includes nevirapine or other non-nucleoside reverse transcriptase inhibitors (NNRTIs) with cross-resistance. In a study in Thailand, response to nevirapine-based therapy was assessed in immunocompromised women with and without prior single-dose nevirapine exposure. In women with exposure, receipt of single-dose nevirapine prior to initiation of therapy was recent (median 6 months after receipt of prophylaxis, interquartile range 3–14 months). The rate of maximal viral suppression (HIV-1 RNA <50 copies/mL) after 6 months of nevirapine-based therapy was lower in women with recent prior single-dose nevirapine exposure, although immunologic response and weight gain were not different [140]. Further research is ongoing to more definitively address this issue, including whether duration of time between receipt of single-dose nevirapine and initiation of therapy impacts response to therapy.

Research is ongoing to develop interventions to prevent development of resistance following single-dose nevirapine. Nevirapine has a prolonged half-life following single-dose exposure, with drug levels at which resistance could occur detected for as long as 21 days post-dose [128]. Preliminary data from studies in Africa suggest that administration of single-dose nevirapine combined with ZDV/3TC given intrapartum and for 3 to 7 days postpartum reduced the rate of development of resistance in mothers [141, 142]. Although final analyses of the data are needed before definitive conclusions can be drawn regarding the optimal regimen and duration of regimen following single-dose maternal/infant nevirapine, consideration should be given to including such a ZDV/3TC “tail” when single-dose maternal/infant nevirapine is used alone or in combination with ZDV. Several additional studies are evaluating alternative antiretroviral regimens and durations for prevention of resistance following single-dose nevirapine exposure.

**Scenario #4: Infants Born to Mothers Who Have Received No Antiretroviral Therapy During Pregnancy or Intrapartum**

**Recommendation**

The 6-week neonatal component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. ZDV should be initiated as soon as possible after delivery, preferably within 6–12 hours of birth. Some clinicians may use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission has not been
proven in clinical trials, and appropriate dosing regimens for neonates are incompletely defined for many drugs. In the immediate postpartum period, the woman should undergo appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health. The infant should undergo early diagnostic testing so that if he or she is HIV-1 infected, treatment can be initiated as soon as possible.

Discussion

Postexposure prophylaxis has prevented retroviral infection in some studies involving animals [143-145]. Definitive clinical trial data in humans are not available to address whether ZDV administered only during the neonatal period would reduce the risk of perinatal transmission. Epidemiologic data from a New York State study indicate a decline in transmission when infants were given ZDV for the first 6 weeks of life compared with no prophylaxis [84, 85]. Transmission rates were 9% (95% CI = 4.1%–17.5%) with ZDV prophylaxis of newborns only (initiated within 48 hours after birth) versus 18% (95% CI = 7.7%–34.3%) with prophylaxis initiated after 48 hours, and 27% (95% CI = 21%–33%) with no ZDV prophylaxis [84]. Epidemiologic data from North Carolina did not demonstrate a benefit of ZDV for newborns only compared with no prophylaxis [6]. Transmission rates were 27% (95% CI = 8%–55%) with prophylaxis of newborns only and 31% (95% CI = 24%–39%) with no prophylaxis. The timing of initiation of infant prophylaxis was not defined in this study.

Data from a clinical trial of infant post exposure prophylaxis in breastfeeding infants in Malawi indicated that the combination of single dose infant nevirapine with 1 week of ZDV was 36% more effective in preventing transmission than was single dose infant nevirapine alone (see International Antiretroviral Prophylaxis Clinical Trials) [86]. However, in the U.S., single dose infant nevirapine is not the recommended prophylaxis regimen for preventing transmission, and there has been no comparison of the standard infant prophylaxis regimen of 6 weeks of ZDV with other regimens. Thus, single dose infant nevirapine plus 1 week of ZDV is not recommended for infant prophylaxis when the mother has not received any antiretroviral drugs in the U.S., where the standard 6 weeks of ZDV prophylaxis can be administered.

The interval during which benefit may be gained from postexposure prophylaxis is undefined. When prophylaxis was delayed beyond 48 hours after birth in the New York State study, no efficacy could be demonstrated. For most infants in this study, prophylaxis was initiated within 24 hours [85]. Data from studies of animals indicate that the longer the delay in institution of prophylaxis, the less likely that infection will be prevented. In most studies of animals, antiretroviral prophylaxis initiated 24–36 hours after exposure has usually not been effective for preventing infection, although later administration has been associated with decreased viremia [143-145]. In cats, ZDV treatment initiated within the first 4 days after challenge with feline leukemia virus afforded protection, whereas treatment initiated 1 week postexposure did not [146]. The relevance of these animal studies to prevention of perinatal HIV-1 transmission in humans is unknown. HIV-1 infection is established in most infected infants by age 1–2 weeks. In a study of 271 infected infants, HIV-1 DNA polymerase chain reaction (PCR) was positive in 38% of samples from infants tested within 48 hours of birth. No substantial change in diagnostic sensitivity was observed within the first week of life, but detection increased rapidly during the second week of life, reaching 93% by age 14 days [147]. Initiation of postexposure prophylaxis after age 2 days is not likely to be efficacious in preventing transmission, and by age 14 days, infection would already be established in most infants.

When the mother has received neither the antenatal nor intrapartum parts of the three-part ZDV regimen, administration of antiretroviral drugs to the newborn provides chemoprophylaxis only after HIV-1 exposure has already occurred. Some clinicians view this situation as analogous to nosocomial postexposure prophylaxis [148] and may wish to provide ZDV in combination with one or more other antiretroviral agents. Such a decision must be accompanied by a discussion with the woman of the potential benefits and risks of this approach and the lack of data to address its efficacy and safety.
**ANTIRETROVIRAL DRUG RESISTANCE AND RESISTANCE TESTING IN PREGNANCY**

- HIV drug resistance testing is recommended for:
  - a. All pregnant women not currently receiving antiretrovirals, before starting treatment or prophylaxis.
  - b. All pregnant women receiving antenatal antiretroviral therapy who have virologic failure with persistently detectable HIV RNA levels or who have sub-optimal viral suppression after initiation of antiretroviral therapy.
- For optimal prevention of perinatal transmission, empiric initiation of antiretroviral therapy before results of resistance testing are available may be warranted, with adjustment as needed after the results are available.
- The use of highly active antiretroviral combination therapy to maximally suppress viral replication during pregnancy is the most effective strategy to prevent the development of resistance and to minimize the risk of perinatal transmission.
- All pregnant women should be counseled about the importance of adherence to prescribed antiretroviral medications to reduce the potential for development of resistance.
- The addition of single-dose maternal/infant NVP to an ongoing highly active combination antiretroviral therapy regimen does not provide additional efficacy in reducing perinatal transmission and may result in NVP drug resistance in the mother, and is therefore not recommended.
- NVP-based combination therapy should not be initiated in women with CD4 count $>250$ cells/mm$^3$ unless the benefit clearly outweighs the risk due to concern about increased risk of hepatic toxicity (see [Nevirapine and Hepatic/Rash Toxicity](#)). However, some pregnant women may receive an NVP-based combination antiretroviral therapy regimen for prophylaxis only, with plans to discontinue therapy after delivery. In this situation, consideration should be given to continuing the nucleoside analogue agents for 3-7 days after stopping NVP to minimize the risk of NVP resistance.

- Women who have documented ZDV resistance and are on regimens that do not include ZDV for their own health should still receive intravenous ZDV during labor whenever possible, along with their established antiretroviral regimens, and oral ZDV for their infants according to the PACTG 076 protocol. For women who are receiving a stavudine-containing regimen, stavudine should be discontinued during labor while intravenous ZDV is being administered.
- The optimal prophylactic regimen for newborns of women with ARV resistance is unknown. Therefore, ARV prophylaxis for an infant born to a woman with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist, preferably before delivery.

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**Indications for Antiretroviral Drug Resistance Testing in HIV-Infected Pregnant Women**

Resistance testing is recommended for all antiretroviral-naive pregnant women before initiating treatment or prophylaxis if prior resistance testing has not been done. Ideally, this testing would be done at a pre-conceptional visit to allow receipt of results and selection of an antiretroviral drug regimen to be used during pregnancy or started before pregnancy if maternal therapy is indicated. There is accumulating evidence that transmitted resistant mutants may persist for indefinite periods after initial infection; that these viral variants may be detectable by standard assays used in clinical practice; that the prevalence of resistance in antiretroviral-naive patients is increasing; and that baseline resistance may be associated with adverse virologic outcomes (149-156). For these reasons, baseline HIV resistance testing is now recommended for all patients with established infection, including pregnant women, prior to initiating treatment (157, 158).

Resistance testing should also be performed before initiation of therapy or prophylaxis in pregnant women who received prophylaxis in previous pregnancies and are now restarting antiretroviral drugs for prevention of perinatal transmission. There are no data currently addressing the utility of resistance testing in the setting...
of pregnancy, when short-term prophylactic therapy is often initiated in women who do not yet need treatment for their own disease, and women who have multiple pregnancies may undergo several periods of antiretroviral prophylaxis to prevent mother-to-child transmission. The identification of baseline resistance mutations may allow selection of more effective and more durable antiretroviral regimens in women needing treatment and greater preservation of future treatment options in women receiving ART only for perinatal prophylaxis. However, there is no evidence that baseline resistance testing in pregnancy is associated with a reduction in perinatal transmission rates.

For pregnant women who are already receiving antiretroviral therapy at the time they are seen, resistance testing is indicated if there is sub-optimal initial viral suppression following initiation of antiretroviral therapy or if there is persistently detectable HIV RNA levels indicative of virologic failure on the current regimen.

While in most settings the results of resistance testing would be used to guide selection of the initial regimen, in some clinical situations the clinician may choose to initiate empiric antiretroviral therapy or prophylaxis before the results of resistance testing are available in order to maximize prevention of perinatal transmission; the antiretroviral drug regimen may be modified as needed once resistance test results become available. Such situations include when women have initial resistance testing in the third trimester and test results may not be back in time to allow effective reduction of viral load before delivery. For women who had resistance testing performed in the latter half of the second trimester, experts were divided as to whether the benefit of immediate initiation of antiretroviral drugs and more rapid reduction of viral load outweighed the possible risk of initiating a regimen that could be sub-optimal due to pre-existing resistance.

Significance of Antiretroviral Drug Resistance in Pregnancy

The development of antiretroviral drug resistance is one of the major factors leading to therapy failure in HIV-1 infected persons. Resistant viral variants emerge under selective pressure, especially with incompletely suppressive regimens, because of the mutation-prone process of reverse transcription in viral replication. Although specific resistance mutations may become undetectable when selective drug pressure is removed, resistant viral variants are believed to be archived permanently in latent HIV reservoirs and can re-emerge with re-exposure to drugs to which decreased susceptibility had been established [159]. The administration of combination antiretroviral therapy with maximal suppression of viral replication to undetectable levels limits the development of antiretroviral resistance in both pregnant and nonpregnant persons.

In addition to the concerns about development of drug resistance in the general population, pregnancy presents some special concerns related to the development of drug resistance. Pre-existing resistance to a drug in an antiretroviral prophylaxis regimen may diminish efficacy of that regimen in preventing perinatal transmission. Development of resistance to drugs used during pregnancy for prophylaxis of perinatal transmission may limit future maternal treatment options or decrease the effectiveness of prophylactic regimens in the current pregnancy or future pregnancies. Additionally, if maternal resistance is present or develops and resistant virus is transmitted, infant treatment options may be limited.

Several factors unique to pregnancy may increase the chance of development of resistance. Antiretroviral drugs may be used during pregnancy solely for prophylaxis of perinatal transmission and discontinued after delivery in women who don’t require therapy for their own health. If regimens used for prophylaxis include drugs with significant differences in half-life, such as NVP combined with two nucleoside analogue drugs, discontinuation of all regimen components simultaneously postpartum may result in functional monotherapy and increase the risk of development of NVP resistance. Problems such as nausea and vomiting in early pregnancy may compromise adherence and increase the risk of resistance in women receiving antiretroviral treatment.

Prevalence of Antiretroviral Drug Resistance

**General population:** The reported prevalence of antiretroviral drug resistance varies depending on several factors, including characteristics of the population studied (e.g., newly infected versus chronically infected), prior and current exposure to antiretroviral drugs and type of regimen (highly active versus non-highly active antiretroviral therapy), geographic area, and type of resistance assay used (genotypic versus phenotypic). In genotypic resistance surveys from the United States and Europe of newly infected, therapy-naïve persons, rates of primary resistance mutations appear to be increasing over time.
and have been reported as high as 23% [153, 160, 161]. The presence of high-level phenotypic resistance (>10-fold increase in 50% inhibitory concentration [IC50]) increased from 3.4% in 1995-1998 to 12.4% in 1999-2000 in a retrospective analysis from 10 US cities, and was associated with longer time to viral suppression and shorter time to virologic failure [160].

More recently, studies have examined antiretroviral drug resistance in drug-naïve persons with newly diagnosed HIV infection of unknown duration, more typical of patients presenting for initial evaluation and care; 8.3% to 10.8% of patients had HIV with genotypic mutations associated with reduced antiretroviral susceptibility, with prevalence increasing over time [152, 153]. The highest rates of antiretroviral drug resistance have been reported in antiretroviral treatment-experienced individuals, with resistance rates as high as 88% reported in viremic individuals currently receiving therapy and 30% in individuals with a past history of treatment [162].

Pregnancy: There are limited data about the prevalence of antiretroviral drug resistance in pregnant women, but the available data suggest that rates of resistance are similar in pregnant women and in non-pregnant individuals, with antiretroviral drug resistance more frequent among antiretroviral-experienced women. A study from a university hospital in St. Louis found that 3 (17%) of 18 antiretroviral-naïve pregnant women followed at the hospital had primary genotypic resistance to non-nucleoside reverse transcriptase inhibitor drugs, which was equal to the overall prevalence of such resistance in the antiretroviral-naïve population in the same city [163]. In a retrospective review of 45 consecutive HIV-infected pregnant women with amplifiable virus presenting for care in New York, 0 of 22 antiretroviral-naïve pregnant women and 11 (48%) of 23 antiretroviral-experienced women had major drug resistance mutations [164]. Among 220 pregnant antiretroviral-experienced women in the Perinatal AIDS Collaborative Transmission Study, all of who had prior ZDV exposure in pregnancy from 1991-1997, 17.3% had ZDV-associated mutations [165]. In a substudy of the PACTG 316 protocol, an international multicenter clinical trial comparing single-dose NVP with placebo in HIV-infected pregnant women receiving standard antiretroviral therapy, 7 (3.2%) of 217 women with detectable HIV RNA had mutations associated with NVP resistance at 6 weeks postpartum, despite no history of prior exposure to non-nucleoside drugs or receipt of NVP at delivery [137]. Additionally, over 60% of women receiving combination therapy (either dual nucleosides or combinations containing a protease inhibitor) had the M184V mutation conferring resistance to 3TC, and 25 (11%) of 217 women had primary or secondary protease mutations [137].

Despite the increasing prevalence of drug resistance in treatment-naïve and -experienced individuals, there is currently no evidence to indicate on a population basis that antiretroviral drug resistance in HIV-infected pregnant women is compromising the efficacy of perinatal HIV prevention efforts in North America or Europe, where mother-to-child transmission rates remain under 3% [66, 166, 167].

Incidence of Antiretroviral Resistance with Perinatal Prophylactic Regimens

The presence of mutations conferring resistance to nucleoside analogue drugs appears to be correlated with more advanced maternal disease and duration of prior or current exposure to these drugs [165, 168-170]. Development of ZDV drug resistance with the PACTG 076 ZDV regimen alone appears uncommon in women with higher CD4 count and low viral load [130, 171], but is more of a concern in women who have more advanced disease and lower CD4 count [168].

Rapid development of resistance to 3TC, which requires only one point mutation for high-level resistance, was reported in 52 (39%) of 132 women with viral RNA samples amplified at 6 weeks postpartum in a French cohort in which 3TC was added at 32 weeks gestation to the PACTG 076 ZDV regimen [25]. When women received 3TC for more than two months, resistance was identified in 50% (37/74), as compared to none of 12 women receiving it for less than one month. In the PETRA study, 12% of women who received 1 month antepartum, intrapartum, and 1 week postpartum combination ZDV/3TC developed 3TC resistance, while none of the women who received only intrapartum and 1 week postpartum ZDV/3TC developed resistance; none of the women in either arm developed ZDV resistance [172].

NVP also has a low genetic barrier to resistance, with one point mutation conferring resistance to NVP and to other NNRTI drugs. Furthermore, its long half-life, with blood levels detectable up to 21 days after a single dose in labor, increases selection pressure and risk of resistance [128]. Factors associated with increased risk of resistance following single-dose NVP exposure include high baseline viral load, low baseline CD4 cell count, viral subtype, and number of maternal doses. The rate of genotypic resistance after exposure to single-dose NVP has varied in studies, ranging from 15% to 75% [135, 137, 139, 140, 173-178]. Studies...
using more sensitive real-time PCR techniques suggest that up to one-half of resistance that develops is not detected by conventional sequence analysis [177-180]. However, these studies demonstrate that while resistance occurs in the first few weeks post-exposure in the majority of women exposed to single-dose NVP, the prevalence of resistance declines rapidly over time and the proportion of resistant virus in those with detectable resistance 12 months after exposure is low; additionally, archiving of resistance in cellular provirus appears to be infrequent. In a study of virus from 67 South African women, using a sensitive allele-specific resistance assay, the K103N mutation was seen in 87% of women at 6 weeks, but in only 11% at 12 months after single-dose NVP exposure, with a median frequency of the mutation of 0.7% (range 0.5%–5.4%) in women with detectable resistance at 12 months. The K103N mutation was found in cellular DNA in only 4.2% of women at 12 months post-exposure [180].

Addition of single-dose NVP to other background regimens (77% of women received antenatal combination antiretroviral therapy) still resulted in NVP resistance in 14 of 95 (15%; 95% CI 8-23%) women in the PACTG 316 study [137]. Because PACTG 316 demonstrated that the addition of single-dose NVP in situations where combination antiretroviral therapy is being received did not provide any additional efficacy in prevention of mother-to-child transmission, and because there is a risk of NVP resistance, this approach is not recommended.

**Impact of Resistance in Pregnancy**

*Perinatal transmission:* Although perinatal transmission of resistant virus has been reported, it appears to be unusual, and there is little evidence that the presence of resistance mutations increases the risk of transmission when current recommendations for antiretroviral management in pregnancy are followed. A substudy of the Women and Infants Transmission Study followed pregnant women receiving ZDV monotherapy for treatment of HIV disease in the early 1990s. In this study, detection of ZDV resistance conferred an increased risk of transmission when analysis was adjusted for duration of membrane rupture and total lymphocyte count [168]; however, women in this cohort had characteristics that would indicate treatment with HAART under current USPHS recommendations for their own health and for prevention of perinatal transmission. When transmitting mothers had mixed viral populations of wild type and virus with low-level ZDV resistance, only wild type virus was found in the infant [181], and other studies have suggested that drug resistance mutations may diminish the fitness of the virus [182], possibly leading to a decrease in transmissibility. The prevalence of antiretroviral drug resistance was examined among HIV-infected newborns in New York State. Eleven (12.1%) of 91 infants born in 1989-99 and 8 (19%) of 42 infants born in 2001-2002 had mutations associated with decreased drug susceptibility. However, perinatal antiretroviral exposure was not found to be a significant risk factor for the presence of resistance in either time period [183, 184]. Neither resistance to NVP that develops as a result of exposure to single-dose NVP nor exposure to single-dose NVP in a prior pregnancy have been shown to affect perinatal transmission rates [185, 186].

**Maternal response to subsequent treatment regimens:** Although the development of drug resistance should be minimized by providing highly active combination drug regimens to all women during pregnancy to maximally suppress viral replication, some women with low HIV RNA levels and higher CD4 counts may choose the PACTG 076 ZDV regimen to minimize exposure of the fetus to antiretroviral drugs. Women who enrolled in PACTG 076 had to have CD4 cell counts above 200 cells/mm$^3$ at study entry. PACTG 288, a follow-up study of women enrolled in PACTG 076 and who were monitored for a median of >4 years postpartum, found no substantial differences in CD4 count, HIV RNA level, time to progression to AIDS or death, or development of ZDV resistance among women who received NVP compared with those who received placebo [187].

Because NVP resistance mutations can be detected in the postpartum period in a significant proportion of women receiving single-dose intrapartum/infant NVP prophylaxis, the response to non-nucleoside-based combination therapy when later required for maternal health reasons has been a concern. A study in Thailand reported lower rates of viral suppression to fewer than 50 copies/mL after 6 months of NVP-based combination therapy among women who had previously received single-dose NVP a median of 6 months prior to initiation of treatment, as compared to women without single-dose NVP exposure [140]. However, two other studies from Botswana and South Africa reported that women who received single-dose NVP responded similarly to women without such exposure when NVP-based antiretroviral therapy was initiated more than six months after single-dose NVP exposure. [188, 189]. Recent data using more sensitive resistance assays have demonstrated the fading of NVP resistant virus to very low frequency levels (0.7%) by 1 year post single-dose NVP exposure, with minimal persistent archiving of resistance in proviral DNA.
Management of Antiretroviral Drug Resistance during Pregnancy

Ideally, antiretroviral regimens used during pregnancy for treatment or prophylaxis should be chosen based on the results of antiretroviral resistance testing. However, antiretroviral drugs are also being used during pregnancy for prevention of mother-to-child HIV transmission. Although most transmission occurs during the intrapartum period, as much as 30% to 35% of transmission may occur in utero [190-192]; the majority of in utero infection is thought to occur later in pregnancy [190], and may be more likely in women with advanced HIV disease and/or high viral load [191, 192]. Therefore, delay in initiation of an antiretroviral drug regimen to await results of resistance testing could result in in utero infection of the infant, particularly in women at high risk of transmission or who are late in pregnancy at the time the drugs are initiated. In such circumstances, empiric initiation of antiretroviral prophylaxis may be warranted to maximize prevention of perinatal transmission, with the regimen being modified if needed once resistance testing results become available.

For women who have documented ZDV resistance and whose antepartum regimen does not include ZDV, intravenous ZDV during labor should still be administered whenever possible. If the woman’s antepartum regimen includes stavudine, which may be antagonistic to ZDV, stavudine should be stopped during the intrapartum period and restarted after delivery. Other antiretrovirals should be continued orally during labor to the extent possible. Oral ZDV for six weeks should also be administered to the infant. For an infant born to a woman with known ZDV resistant virus, many clinicians would choose to provide additional antiretroviral agents to the infant in combination with ZDV. Such a decision must be accompanied by a discussion with the woman of the potential benefits and risks of this approach and the lack of data to address its efficacy and safety. The optimal prophylactic regimen for newborns of women with antiretroviral drug resistant virus is unknown. Therefore, antiretroviral prophylaxis for the infant born to a woman with known or suspected drug resistant virus should be determined with a pediatric HIV specialist, preferably before delivery.

The rationale for including ZDV intrapartum and to the infant when a woman is known to harbor virus with ZDV resistance is based on several factors. Data thus far have suggested that when mothers have mixed populations of wild type virus and virus with low-level ZDV resistance, only wild type virus is found in the infant [181]. Other studies have suggested that drug resistance mutations may diminish viral fitness and possibly decrease transmissibility [182]. Efficacy of the PACTG 076 ZDV regimen appears to be based not only on reduction of HIV levels, but also on pre- and post-exposure prophylaxis in the infant [68, 84, 103]. ZDV crosses the placenta readily and has one of the highest maternal:cord blood ratios among the nucleoside analogue agents. Additionally, ZDV is metabolized to the active triphosphate within the placenta [69, 70], which may provide additional protection against transmission. Metabolism to the active triphosphate, which is required for activity of all nucleoside analogue agents, has not been observed within the placenta with other nucleoside analogues that have been evaluated (didanosine and zalcitabine) [71, 72]. In addition, ZDV has been shown to reduce genital HIV-1 RNA levels, and genital viral levels have been shown to correlate with perinatal transmission [101]. Data on levels of other nucleoside analogues in the genital tract are more limited, and it is unknown if other nucleoside analogue agents will provide a similar reduction in genital tract HIV-1 RNA levels [193-195]. ZDV has better penetration into the central nervous system compared to other nucleoside analogues with the exception of stavudine, whose CNS penetration is similar; this may help to eliminate a potential reservoir for transmitted HIV in the infant [196, 197]. Thus, intravenous intrapartum and oral ZDV for the infant should be included even in the presence of known ZDV resistance because of the unique characteristics of ZDV and its proven record in reducing perinatal transmission.
Prevention of Antiretroviral Drug Resistance

The most effective way to prevent the development of antiretroviral drug resistance in pregnancy is to use and adhere to an effective combination of antiretroviral drugs to achieve maximal viral suppression. Selection of a regimen should take into account prior antiretroviral treatment history, including documented clinical, immunologic, or virologic failure with or without genotypic or phenotypic resistance testing; history of nonadherence; and problems with intolerance.

When NVP is used as part of a prophylactic combination antiretroviral regimen that is stopped after delivery, there may be a risk of development of NVP resistance because of the drug’s prolonged half-life, leading to a period functional monotherapy if all drugs are discontinued at once. Studies in South Africa and Cote d’Ivoire have shown that the development of NVP resistance following exposure to single-dose intrapartum NVP (given alone or in combination with antenatal antiretroviral therapy) was significantly decreased (but not eliminated) if ZDV/3TC was given intrapartum and administered for 3 to 7 days postpartum after intrapartum NVP [141, 142]. Whether such a strategy will be useful when an antenatal NVP-based combination regimen is stopped after delivery is not known. In a cohort of 39 women who initiated combination antiretroviral therapy in pregnancy and had genotypic testing performed at 6 weeks postpartum, 5 (13%) had primary mutations detected [173]. All five were on combination regimens that included NVP, were treatment-naive prior to pregnancy, and had staggered drug discontinuation after delivery (the dual nucleoside component of the regimen was continued for 5 days after stopping NVP). It is not known whether the incidence of resistance would have been significantly higher if drug discontinuation had not been staggered. Non-nucleoside reverse transcriptase inhibitor drugs have long half-lives, and drug levels can persist for up to 2-3 weeks after stopping the drug [128, 198]. Further research is needed on the optimal duration of time and regimen to “cover” this period of prolonged NVP exposure to prevent emergence of resistance following discontinuation of NVP-based therapy.

PERINATAL HIV-1 TRANSMISSION AND MODE OF DELIVERY

The studies and data discussed below reflect experience in developed countries. Transmission rates and complications by mode of delivery are not clearly defined in developing countries, and local guidelines for prevention of perinatal transmission should be followed in those settings.

Transmission and Mode of Delivery

Optimal medical management during pregnancy should include antiretroviral therapy to suppress plasma HIV-1 RNA to undetectable levels. Labor and delivery management of HIV-1 infected pregnant women should focus on minimizing the risk for both perinatal transmission of HIV-1 and the potential for maternal and neonatal complications.

Several studies done before viral load testing and combination antiretroviral therapy became a routine part of clinical practice consistently showed that cesarean delivery performed before onset of labor and rupture of membranes (elective or scheduled) was associated with a significant decrease in perinatal HIV-1 transmission compared with other types of delivery, with reductions ranging from 55% to 80%. Data regarding transmission rates according to receipt of ZDV have been summarized in Table 6.

The observational data comprised individual patient information from 15 prospective cohort studies, including more than 7,800 mother-child pairs, analyzed in a meta-analysis [199]. In this meta-analysis, the rate of perinatal HIV-1 transmission among women undergoing elective cesarean delivery was significantly lower than that among similar women having either nonelective cesarean or vaginal delivery, regardless of whether they received ZDV. In an international randomized trial of mode of delivery, transmission was 1.8% among women randomized to elective cesarean delivery, many of whom received ZDV [200]. Although the magnitude of reduction in transmission after elective cesarean versus vaginal delivery among women receiving ZDV in the randomized trial was similar to that seen in untreated women, the overall transmission rates were lower, so this difference was not statistically significant. Additionally, in both studies, nonelective cesarean delivery (performed after onset of labor or rupture of membranes) was not associated with a significant decrease in transmission compared with vaginal delivery. The American College of Obstetricians and Gynecologists’[201] Committee on Obstetric Practice, after reviewing these data, has
issued a Committee Opinion concerning route of delivery, recommending consideration of scheduled cesarean delivery for HIV-1 infected pregnant women with HIV-1 RNA levels > 1,000 copies/mL near the time of delivery [202].

Transmission, Viral Load, and Combination Antiretroviral Therapy

After the meta-analysis and randomized trial, cohort studies in the pre-HAART era confirmed the benefit of elective cesarean delivery among women either not on antiretroviral therapy or on ZDV regimens. However, more recently, pregnant women are receiving highly active antiretroviral regimens, and transmission rates of 1.2 to 1.5%, unadjusted for mode of delivery, have been reported. Given the low transmission rates among women on HAART, the benefit of elective cesarean delivery is difficult to evaluate. Until further data are available, elective cesarean delivery should continue to be recommended for women on HAART who have HIV RNA levels above 1,000 copies/mL near delivery. Elective cesarean delivery should not be routinely provided for women on therapy who have HIV RNA below 1,000 copies/mL, unless they choose this procedure after thorough counseling regarding uncertain benefit and known risks.

Cohort studies evaluating the benefit of scheduled cesarean delivery among women receiving no antiretroviral therapy, ZDV monotherapy, or combination therapy have demonstrated benefit from elective cesarean delivery. The Italian Registry study found an approximately 50% reduction in transmission with scheduled cesarean delivery. The reduction was observed both among the 1985-95 cohort, in which 92% of women received no antiretrovirals (AOR 0.54 [0.38-0.78]), and among the 1996-99 cohort, in which 80% of women received antiretrovirals, primarily ZDV (AOR 0.54 [0.29-1.02]) [203]. In a meta-analysis of transmission among women with HIV RNA below 1,000 copies/mL at delivery, among the subset receiving therapy (primarily ZDV), transmission occurred among 0 of 270 women who delivered by scheduled or urgent cesarean; transmission occurred among 7 (1.8%) of 396 who delivered vaginally (p=0.05) [104]. Both the European Collaborative Study and the Women and Infants Transmission Study demonstrated a reduced risk of transmission in their total cohorts who delivered by elective cesarean (ECS AOR 0.42 [0.27-0.67]; WITS 0.27 [0.06-1.05]) [66, 204]. Both of these reports included approximately 25% of women receiving no antiretroviral therapy; the majority of the treated women received ZDV. In the WITS, among women receiving any antiretrovirals, transmission occurred among 2 (1.6%) of 127 women who delivered by elective cesarean and among 86 (8.4%) of 1,019 women who delivered vaginally (p=0.006) [66]. Thus these studies confirmed the benefit of elective cesarean delivery, but included few women on highly active antiretroviral regimens; most studies were not able to adjust for HIV RNA level, a key factor in transmission risk.

More recent data have demonstrated the benefit of HAART for reduction in perinatal transmission of HIV. Data from PACTG 316 demonstrated an overall transmission rate of 1.5% among women on antiretroviral therapy during pregnancy. 23% of the women were on ZDV, 36% on nucleoside analogue combination regimens, and 41% on combinations including protease inhibitors [83]. Data from PACTG 367, a chart review study including 2,756 women, found a transmission rate of 34 (1.3%) of 2,539 women on multiagent antiretroviral therapy [129]. In a recent report from the European Collaborative Study that included data from 4,525 women, the overall transmission rate among the subset of women on HAART was 11 (1.2%) of 918 [166]. These three studies also attempted to evaluate the potential benefit of elective cesarean delivery among the subsets of women with low HIV RNA levels or women on HAART, regardless of HIV RNA level. Among women enrolled in PACTG 316, all receiving antiretroviral therapy as described above, 34% delivered by elective cesarean; however, mode of delivery was not associated with transmission risk, so subset analyses by therapy were not done [83]. Data from PACTG 367 do not suggest benefit from elective cesarean delivery among women with HIV RNA levels below 1,000 copies/mL. Women with HIV RNA levels under 1,000 copies/mL on multiagent therapy had transmission rates of 0.8% with elective cesarean delivery and 0.5% with all other delivery modes (OR 1.4, 95% CI 0.2-6.4). Those on single agent therapy, usually ZDV, had a transmission rate of 4.3% after elective cesarean delivery and 1.8% with all other modes of delivery (OR 2.5, 95% CI 0.04-50.0) [129]. Data from the European Collaborative Study suggested a reduction in perinatal transmission of HIV with scheduled cesarean delivery among all women delivering in the HAART era [166]. Among the subset of 560 women with undetectable HIV RNA levels (200-500 copies/mL, depending on site), elective cesarean delivery was associated with a significant reduction in perinatal transmission on univariate analysis (OR 0.07, 95% CI 0.02-0.31, p=0.0004). However, after adjustment for antiretroviral therapy (none versus any), the effect was no longer significant (AOR 0.52, 95% CI 0.14-2.03, p=0.359). These data do
not confirm, but also do not rule out, a benefit from elective cesarean delivery among women with HIV RNA below 1,000 copies/mL who are receiving antiretroviral therapy. Pregnant women on antiretroviral therapy with HIV RNA levels below 1,000 copies/mL should be counseled regarding the low baseline rate of transmission, the uncertain benefits, and the known risks of elective cesarean delivery.

Given the overall transmission rates of 1.2 to 1.3% among women on HAART, the potential benefit of elective cesarean delivery among such women is difficult to evaluate. In the PACTG 367 study, women on multiagent therapy who had HIV RNA levels over 1,000 copies/mL near delivery had a transmission rate of 3.6% with elective cesarean delivery and 2.3% with other modes of delivery (OR 1.6, 95% CI 0.6-4.3) [129]. In the European Collaborative Study, among 759 women receiving antenatal HAART and regardless of HIV RNA level, elective cesarean delivery was associated with a non-significant reduction in transmission (OR 0.64, 95% CI 0.08-5.37, p=0.70). While the PACTG 367 study and the European Collaborative Study data did not demonstrate a significant reduction in transmission with elective cesarean delivery among women on HAART, studies of women with detectable HIV RNA on HAART have had inadequate numbers to assess the potential additional benefit. Women on HAART with HIV RNA above 1,000 copies/mL near delivery should be counseled regarding the potential benefits of scheduled cesarean delivery and the known risks of cesarean versus vaginal delivery. Until further data are available, elective cesarean delivery should continue to be recommended for women on HAART with HIV RNA levels above 1,000 copies/mL near delivery.

**Maternal Risks by Mode of Delivery**

Among women not infected with HIV-1, maternal morbidity and mortality are greater after cesarean than after vaginal delivery. Complications, especially postpartum infections, are approximately five to seven times more common after cesarean delivery, performed after labor or membrane rupture compared with vaginal delivery [205, 206]. Complications after scheduled cesarean delivery are more common than with vaginal delivery, but less than with urgent cesarean delivery [207-211]. Factors that increase the risk of postoperative complications include low socioeconomic status, genital infections, obesity or malnutrition, smoking, and prolonged labor or membrane rupture.

Several studies have compared the rate of postpartum complications between HIV-infected women delivering vaginally or by cesarean. In the European mode of delivery randomized trial among HIV-1 infected pregnant women, no major complications occurred in either the cesarean or vaginal delivery group [200]. However, postpartum fever occurred in two (1.1%) of 183 women who delivered vaginally and 15 (6.7%) of 225 who delivered by cesarean delivery (p = 0.002). Substantial postpartum bleeding and anemia occurred at similar rates in the two groups. Among the 497 women enrolled in PACTG 185, only endometritis, wound infection, and pneumonia were increased among women delivered by scheduled or urgent cesarean delivery compared with vaginal delivery [212]. Complication rates were within the range previously reported for similar general obstetric populations. An analysis of nearly 1,200 women enrolled in WITS demonstrated increased rate of postpartum fever without documented source of infection among women undergoing elective cesarean delivery compared with spontaneous vaginal delivery, but hemorrhage, severe anemia, endometritis, and urinary tract infections were not increased [213]. In the latter two studies, cesarean deliveries before onset of labor and ruptured membranes were done for obstetric indications such as previous cesarean delivery or severe pre-eclampsia and not for prevention of HIV-1 transmission, possibly resulting in higher complication rates than might be observed for scheduled cesarean delivery performed solely to reduce perinatal transmission. In a more recent study including a cohort of HIV-1 infected women with a larger proportion of women undergoing scheduled cesarean delivery specifically for prevention of HIV-1 transmission, fever was increased after cesarean when compared with vaginal delivery [214]. In a multivariate analysis adjusted for maternal CD4+ count and antepartum hemorrhage, the relative risk of any postpartum complication was 1.85 (95% CI = 1.00–3.39) after elective cesarean delivery and 4.17 (95% CI = 2.32–7.49) after emergency cesarean delivery, compared with that for women delivering vaginally. Febrile morbidity was increased among women with low CD4+ cell counts.

A study from the European HIV in Obstetrics Group compared outcomes both between HIV-infected women delivering vaginally or by elective cesarean delivery and matched controls of HIV-uninfected women with each mode of delivery [215]. Among HIV-infected subjects, minor complications (anemia, fever, wound infection, curettage, endometritis, urinary tract infection) occurred in 16.8% of women delivering vaginally and 48.7% of those with cesarean delivery, and major complications occurred in none of the women with vaginal delivery and 3.2% (5/158) of those with elective cesarean delivery. These frequencies were increased compared to matched HIV-uninfected
women, but the relative difference between vaginal and cesarean deliveries was similar in HIV-infected and HIV-uninfected women.

In addition to the European HIV in Obstetrics Group study, nine other studies have compared postoperative complications between HIV-infected women and similar HIV-uninfected women [216-224]. Many of these studies were retrospective. Two studies found similar outcomes among HIV-infected women compared to controls [222, 223]. Seven studies detected an increased risk of one or more complications among the HIV-infected women. The majority found increases in minor complications such as postoperative fever or mild anemia, but no difference in major complications such as sepsis or hemorrhage requiring transfusion. Cases of pneumonia were seen among HIV-infected women in four of the studies, while no cases occurred in the HIV-negative women. In the five studies where it was evaluated, an increased risk of complications was seen among HIV-infected women with more advanced disease as measured by CD4 lymphocyte count or percent, consistent with the cohort studies [213, 214].

In summary, data indicate that cesarean delivery is associated with a somewhat greater risk of complications among HIV-1 infected women than observed among uninfected women, with the difference most notable among women with more advanced disease. Scheduled cesarean delivery for prevention of HIV-1 transmission poses a risk greater than that of vaginal delivery and less than that of urgent or emergent cesarean delivery. Complication rates in most studies were within the range reported in populations of HIV-1 uninfected women with similar risk factors and were not of sufficient frequency or severity to outweigh the potential benefit of reduced transmission among women at heightened risk of transmission. HIV-1 infected women should be counseled regarding the increased risks and potential benefits associated with cesarean delivery based on their HIV-1 RNA levels and current antiretroviral therapy.

**Timing of Scheduled Cesarean Delivery**

If the decision is made to perform a scheduled cesarean delivery to prevent HIV-1 transmission, ACOG recommends that it be done at 38 weeks' gestation, determined by the best clinical estimate and avoiding amniocentesis [202]. For HIV-1 uninfected women, ACOG guidelines for scheduled cesarean delivery without confirmation of fetal lung maturity advise waiting until 39 completed weeks or the onset of labor to reduce the chance of complications in the neonate [225]. Cesarean delivery at 38 versus 39 weeks entails a small absolute but substantially increased risk of development of infant respiratory distress requiring mechanical ventilation [226, 227]. This increased risk must be balanced against the potential risk for labor or membrane rupture before the woman would reach 39 weeks of gestation. Women should be informed of the potential risks and benefits to themselves and their infants in choosing the timing and mode of delivery.

**Intrapartum Management**

For a scheduled cesarean delivery, intravenous ZDV should begin 3 hours before surgery, according to standard dosing recommendations [2]. Other antiretroviral medications taken during pregnancy should not be interrupted near the time of delivery, regardless of route of delivery. Because maternal infectious morbidity is potentially increased, clinicians should consider perioperative antimicrobial prophylaxis. Although no controlled studies have evaluated the efficacy of antimicrobial prophylaxis specifically for HIV-1 infected women undergoing scheduled operative delivery, use of prophylactic antibiotics at the time of cesarean delivery is generally recommended [228].

Unanswered questions remain regarding the most appropriate management of labor in cases in which vaginal delivery is attempted. Increasing duration of membrane rupture has been demonstrated consistently to be a risk factor for perinatal transmission among women not receiving any antiretroviral therapy [111, 229-231]. Among women receiving ZDV, some studies have shown an increased risk of transmission with ruptured membranes for four or more hours before delivery [9, 93], but others have not [92, 232]. Obstetric procedures increasing the risk of fetal exposure to maternal blood, such as amniocentesis and invasive monitoring, have been implicated in increasing vertical transmission rates by some, but not all, investigators [92, 233-235]. If labor is progressing and membranes are intact, artificial rupture of membranes or invasive monitoring should be avoided. These procedures should be considered only when obstetrically indicated and the length of time for ruptured membranes or monitoring is anticipated to be short. If spontaneous rupture of membranes occurs before or early during the course of labor, interventions to decrease the interval to delivery, such as administration of oxytocin, may be considered.
Recommendations

Considerations related to counseling of the HIV-1 infected pregnant woman regarding risks for vertical transmission of HIV-1 to the fetus/neonate and to the obstetric care of such women include the following:

- Efforts to maximize the health of the pregnant woman, including the provision of highly active combination antiretroviral therapy, can be expected to correlate with both reduction in viral load and low rates of vertical transmission. At a minimum for the reduction of perinatal HIV-1 transmission, ZDV prophylaxis according to the PACTG 076 regimen is recommended unless the woman is intolerant of ZDV.

- Plasma HIV-1 RNA levels should be monitored during pregnancy according to the guidelines for management of HIV-1 infected adults. The most recently determined viral load value should be used when counseling a woman regarding mode of delivery.

- Perinatal HIV-1 transmission is reduced by scheduled cesarean delivery among women with unknown HIV-1 RNA levels who are not receiving antiretroviral therapy or are receiving only ZDV for prophylaxis of perinatal transmission. Plasma HIV-1 RNA levels were not available in these studies to assess the potential benefit among women with low plasma HIV-1 RNA levels.

- Women with HIV-1 RNA levels > 1,000 copies/mL should be counseled regarding the potential benefit of scheduled cesarean delivery in reducing the risk of vertical transmission. The benefit among women on HAART is unproven.

- Data are insufficient to evaluate the potential benefit of cesarean delivery for neonates of antiretroviral-treated women with plasma HIV-1 RNA levels below 1,000 copies/mL. Given the low rate of transmission among this group, it is unlikely that scheduled cesarean delivery would confer additional benefit in reduction of transmission.

- Management of women originally scheduled for cesarean delivery who present with ruptured membranes or in labor must be individualized based on duration of rupture, progress of labor, plasma HIV-1 RNA level, current antiretroviral therapy, and other clinical factors. It is not clear that cesarean delivery after rupture or onset of labor provides benefit in reducing transmission.

- Women should be informed of the risks associated with cesarean delivery; these risks to the woman should be balanced with potential benefits expected for the neonate.

- Women should be counseled regarding the limitations of the current data. The woman’s autonomy to make an informed decision regarding route of delivery should be respected and honored.

CLINICAL SITUATIONS

The following recommendations are based on various hypothetical situations that may be encountered in clinical practice (Table 7), with relevant considerations highlighted in the subsequent discussion sections. These recommendations are only guidelines, and flexibility should be exercised according to the patient’s individual circumstances.

Scenario A

HIV-1 infected women presenting in late pregnancy (after approximately 36 weeks of gestation), known to be HIV-1 infected but not receiving antiretroviral therapy, and whose results for HIV-1 RNA level and lymphocyte subsets are pending but unlikely to be available before delivery.

Recommendation

Therapy options should be discussed in detail. Antiretroviral therapy, including at least the PACTG 076 ZDV regimen, should be initiated. In counseling, the woman should be informed that scheduled cesarean delivery is likely to reduce the risk of transmission to her infant. She should also be informed of the increased risks to her of cesarean delivery, including increased rates of postoperative infection, anesthesia risks, and other surgical risks. If cesarean delivery is chosen, the procedure should be scheduled at 38 weeks of gestation, based on the best available clinical information. When scheduled cesarean delivery is performed, the woman should receive continuous intravenous ZDV infusion beginning 3 hours before surgery, and her infant should receive 6 weeks of ZDV therapy after birth. Options for continuing or initiating combination antiretroviral therapy after delivery should be discussed with the woman as soon as her viral load and lymphocyte subset results are available.

Discussion

Women in these circumstances are similar to women enrolled in the European randomized trial and those evaluated in the meta-analysis [199, 200]. In both studies, the population not receiving antiretroviral therapy was shown to have a significant reduction in transmission with cesarean delivery done before labor or membrane rupture. HIV-1 RNA levels were not available in these studies. Without current therapy, HIV-1 RNA levels are unlikely to be < 1,000 copies/mL. Even if combination therapy were begun immediately, reduction in plasma HIV-1 RNA to undetectable levels usually takes several weeks, depending on the starting RNA level. ZDV
monotherapy could be started, with subsequent antiretroviral therapy decisions made after delivery based on the HIV-1 RNA level, CD4⁺ count, and the woman's preference regarding initiation of long-term combination therapy. Alternately, a highly active combination antiretroviral regimen could be initiated during pregnancy, with decisions regarding continuation postpartum based on HIV-1 RNA levels, CD4⁺ lymphocyte count, and patient preference. Scheduled cesarean delivery is likely to provide additional benefit in reducing risk of perinatal transmission of HIV-1 along with the three-part PACTG 076 ZDV regimen or highly active antiretroviral therapy, given initiation so late in pregnancy.

Scenario B

*HIV-1 infected women who began prenatal care early in the third trimester, are receiving highly active combination antiretroviral therapy, and have an initial virologic response, but have HIV-1 RNA levels that remain substantially over 1,000 copies/mL at 36 weeks of gestation.*

**Recommendation**

The current combination antiretroviral regimen should be continued because the HIV-1 RNA level is declining appropriately. The woman should be informed that although her HIV-1 RNA level is responding to the antiretroviral therapy, it is unlikely that it will reach <1,000 copies/mL before delivery. Therefore, scheduled cesarean delivery may provide additional benefit in preventing intrapartum transmission of HIV-1. She should also be informed of the increased risks to her of cesarean delivery, including increased rates of postoperative infection, anesthesia risks, and surgical risks. If she chooses scheduled cesarean delivery, it should be performed at 38 weeks' gestation, and intravenous ZDV should be started at least 3 hours before surgery. Other antiretroviral medications should be continued on schedule as much as possible before and after surgery. The infant should receive oral ZDV for 6 weeks after birth. The importance of adhering to therapy after delivery for her own health should be emphasized.

**Discussion**

Although current combination antiretroviral therapy regimens may be expected to suppress HIV-1 RNA to undetectable levels with continued use, these levels are likely to still be detectable within the period of expected delivery. Scheduled cesarean delivery might further reduce the rate of intrapartum HIV-1 transmission and should be recommended to women with HIV-1 RNA levels >1,000 copies/mL. Transmission rates among women on HAART have been below 2%, regardless of mode of delivery [83, 129, 204] and HIV RNA levels, similar to rates seen among women receiving ZDV and undergoing elective cesarean delivery. It is not clear if the impact on transmission is related to the lowering of maternal plasma HIV-1 RNA levels, pre-exposure prophylaxis of the infant, other mechanisms, or some combination. Until further data are available, women with HIV-1 RNA levels >1,000 copies/mL should be offered scheduled cesarean delivery regardless of maternal therapy, although a thorough discussion of the uncertain benefit among women on HAART and the potential maternal and infant risks of cesarean delivery must be included.

Regardless of mode of delivery, the woman should receive the PACTG 076 intravenous ZDV regimen intrapartum, and the infant should receive ZDV for 6 weeks after birth. Other maternal drugs should be continued on schedule as much as possible to provide maximal effect and minimize the chance of development of viral resistance. Oral medications may be continued preoperatively with sips of water. Medications requiring food ingestion for absorption could be taken with liquid dietary supplements, but consultation with the attending anesthesiologist should be obtained before administering in the preoperative period. If maternal antiretroviral therapy must be interrupted temporarily in the peripartum period, all drugs (except for intrapartum intravenous ZDV) should be stopped and reinstated simultaneously to minimize the chance of resistance developing.

Women with CD4⁺ counts <350 cells/mL or HIV-1 RNA levels >100,000 copies/mL before initiation of combination therapy during pregnancy are most likely to benefit from continued antiretroviral therapy after delivery [14]. Discussion regarding plans for antiretroviral therapy after delivery should be initiated during pregnancy. If the woman elects to continue therapy after delivery, the importance of continued adherence despite the increased responsibilities of newborn care should be emphasized, and any support available for the woman should be provided.

Scenario C

*HIV-1 infected women receiving highly active combination antiretroviral therapy who have an undetectable HIV-1 RNA level at 36 weeks of gestation.*
Recommendation

The woman should be informed that her risk of perinatal transmission of HIV-1 with a persistently undetectable HIV-1 RNA level is low, probably 2% or less, even with vaginal delivery. Current information suggests that performing a scheduled cesarean delivery will not lower her risk further. Cesarean delivery has an increased risk of complications for the woman compared with vaginal delivery, and these risks must be balanced against the uncertain benefit of cesarean delivery in this case.

Discussion

Scheduled cesarean delivery has been beneficial for women either receiving no antiretroviral therapy or receiving ZDV monotherapy, with rates of transmission of HIV-1 of approximately 1%–2% [199, 200]. Maternal HIV-1 RNA levels were not evaluated in these studies. Similar rates of transmission have been reported among women receiving antiretroviral therapy, with HIV-1 RNA levels undetectable near delivery [92, 93, 236]. Limited and conflicting data are available evaluating transmission rates by mode of delivery among women with undetectable HIV-1 RNA levels on ZDV or other antiretroviral therapy [66, 104, 129, 204]. Although a benefit of cesarean delivery in reducing transmission may be present, it would be of small magnitude given the low risk of transmission with vaginal delivery among women with HIV-1 RNA levels < 1,000 copies/mL who are receiving maternal antiretroviral therapy. Any benefit must be weighed against the known increased risks to the woman with cesarean delivery compared with vaginal delivery (i.e., a severalfold increased risk of postpartum infections, including uterine infections and pneumonia; anesthesia risks; and surgical complications). However, given limited data to indicate lack of benefit, if a woman chooses a scheduled cesarean delivery, her decision should be respected and cesarean delivery scheduled.

If vaginal delivery is chosen, the duration of ruptured membranes should be minimized because the transmission rate has been shown to increase with longer duration of membrane rupture among predominantly untreated women [229-231] and among ZDV-treated women in some [9, 93] but not all studies [92, 232]. Fetal scalp electrodes and operative delivery with forceps or the vacuum extractor may increase the risk of transmission and should be avoided [233, 234]. Intravenous ZDV should be given during labor, and other maternal antiretroviral drugs should be continued on schedule as much as possible to provide maximal effect and minimize the chance of development of viral resistance; the infant should be treated with ZDV for 6 weeks after birth.

Scenario D

HIV-1 infected women who have elected scheduled cesarean delivery but present in early labor or shortly after rupture of membranes.

Recommendation

Intravenous ZDV should be started immediately since the woman is in labor or has ruptured membranes. If cervical dilatation is minimal and a long period of labor is anticipated, the clinician may begin the loading dose of intravenous ZDV and proceed as expeditiously as possible with cesarean delivery to minimize the duration of membrane rupture and avoid vaginal delivery. Alternatively, the clinician might begin oxytocin augmentation to enhance contractions and potentially expedite delivery. If labor is progressing rapidly, the woman should be allowed to deliver vaginally. If the woman is allowed to labor, scalp electrodes and other invasive monitoring and operative delivery should be avoided if possible. Other antiretrovirals besides ZDV should be continued orally during labor. The infant should be treated with 6 weeks of ZDV therapy after birth.

Discussion

No data are available to address the question of whether performing cesarean delivery soon after membrane rupture to shorten labor and avoid vaginal delivery decreases the risk of vertical transmission of HIV-1. Most studies have shown the risk of transmission with cesarean delivery done after labor and membrane rupture for obstetric indications to be similar to that with vaginal delivery, although the duration of ruptured membranes in these women was often longer than 4 hours and HIV RNA measurements were not included [200, 237]. When an effect was demonstrated, the risk of transmission was twice as high among women with ruptured membranes for > 4 hours before delivery, compared with those with shorter duration of membrane rupture, although the risk increased continuously with increasing duration of rupture (see Scenario C).

If elective cesarean delivery had been planned and the woman presents with a short duration of ruptured membranes or labor, she should be informed that the benefit of cesarean delivery under these circumstances is unclear and be allowed to reassess her decision. If the woman presents after 4 hours of membrane rupture, cesarean delivery is less likely to affect transmission of HIV-1. The woman should be informed that the benefit of cesarean delivery is unclear and that her risks of
perioperative infection increase with increasing duration of ruptured membranes. If cesarean delivery is chosen, the loading dose of ZDV should be administered while preparations are made for cesarean delivery; the infusion should continue until cord clamping. Prophylactic antibiotics given after cord clamping have been shown to reduce the rate of postpartum infection among women of unknown HIV-1 status undergoing cesarean delivery after labor or rupture of membranes, and should be used routinely in this setting [228]. If vaginal delivery is chosen, intravenous ZDV and other antiretroviral agents the woman is currently taking should be administered and invasive procedures such as internal monitoring avoided. Oxytocin should be used as needed to expedite delivery.

RECOMMENDATIONS FOR MONITORING OF WOMEN AND THEIR INFANTS

Pregnant Woman and Fetus

HIV-1 infected pregnant women should be monitored according to the same standards for monitoring HIV-1 infected persons who are not pregnant. This monitoring should include measurement of CD4+ counts and HIV-1 RNA levels approximately every trimester (i.e., every three to four months) to determine
a. the need for antiretroviral therapy of maternal HIV-1 disease,
b. whether such therapy should be altered, and

c. whether prophylaxis against *Pneumocystis carinii* pneumonia should be initiated.

Changes in absolute CD4+ count during pregnancy may reflect the physiologic changes of pregnancy on hemodynamic parameters and blood volume as opposed to a long-term influence of pregnancy on CD4+ count; CD4+ percentage is likely more stable and might be a more accurate reflection of immune status during pregnancy [238, 239]. Long-range plans should be developed with the woman regarding continuity of medical care and antiretroviral therapy for her own health after the birth of her infant.

Monitoring for potential complications of administration of antiretroviral agents during pregnancy should be based on what is known about the side effects of the drugs the woman is receiving. For example, routine hematologic and liver enzyme monitoring is recommended for women receiving ZDV. Because combination antiretroviral regimens have been used less extensively during pregnancy, more intensive monitoring may be warranted for women receiving drugs other than or in addition to ZDV. For example, women receiving protease inhibitors should be monitored for development of hyperglycemia. Women, particularly those with CD4+ counts >250 cells/mm3, have an increased risk of developing symptomatic, rash-associated, nevirapine-associated hepatotoxicity [31, 32, 34]; thus, pregnant women receiving nevirapine should have frequent and careful monitoring of transaminase levels, particularly during the first 18 weeks of treatment (see section, Nevirapine and Hepatic/Rash Toxicity).

Antepartum fetal monitoring for women who receive only ZDV chemoprophylaxis should be performed as clinically indicated because data do not indicate that ZDV use in pregnancy is associated with increased risk for fetal complications. Less is known about the effect of combination antiretroviral therapy on the fetus during pregnancy. Thus, more intensive fetal monitoring should be considered for mothers receiving such therapy, including assessment of fetal anatomy with a level II ultrasound and continued assessment of fetal growth and wellbeing during the third trimester.

Neonate

A complete blood count and differential should be performed on the newborn as a baseline evaluation before administration of ZDV. Anemia has been the primary complication of the 6-week ZDV regimen in the neonate; thus, repeat measurement of hemoglobin is required at a minimum after the completion of the 6-week ZDV regimen. If abnormal, repeat measurement should be performed at age 12 weeks, by which time any ZDV-related hematologic toxicity should be resolved. Infants who have anemia at birth or who are born prematurely warrant more intensive monitoring.

Data are limited concerning potential toxicities in infants whose mothers have received combination antiretroviral therapy. More intensive monitoring of hematologic and serum chemistry measurements during the first few weeks of life is advised for these infants. However, it should be noted that the clinical relevance of lactate levels in the neonatal period to assess potential for mitochondrial toxicity has not been adequately evaluated.

To prevent *P. carinii* pneumonia, all infants born to women with HIV-1 infection should begin prophylaxis at age 6 weeks, after completion of the ZDV prophylaxis regimen [240]. Monitoring and diagnostic
evaluation of HIV-1 exposed infants should follow current standards of care [241]. Data do not indicate any delay in HIV-1 diagnosis in infants who have received the ZDV regimen [1, 242]. However, the effect of combination antiretroviral therapy in the mother or newborn on the sensitivity of infant virologic diagnostic testing is unknown. Infants with negative virologic test results during the first 6 weeks of life should have diagnostic evaluation repeated after completion of the neonatal antiretroviral prophylaxis regimen.

**Postpartum Follow-Up of Women**

Comprehensive care and support services are important for women with HIV-1 infection and their families. Components of comprehensive care include the following medical and supportive care services:

- Primary, obstetric, pediatric and HIV-1 specialty care;
- Family planning services;
- Mental health services;
- Substance-abuse treatment; and
- Coordination of care through case management for the woman, her children, and other family members.

Support services include case management, child care, respite care, assistance with basic life needs (e.g., housing, food, and transportation), and legal and advocacy services. This care should begin before pregnancy and should be continued throughout pregnancy and postpartum.

Maternal medical services during the postpartum period must be coordinated between obstetric care providers and HIV-1 specialists. Continuity of antiretroviral treatment when such treatment is required for the woman's HIV-1 infection is especially critical and must be ensured. Concerns have been raised about adherence to antiretroviral regimens during the postpartum period. Women should be counseled about the fact that the physical changes of the postpartum period, as well as the stresses and demands of caring for a new baby, can make adherence more difficult and additional support may be needed to maintain good adherence to their therapeutic antiretroviral regimen during this period [243, 244]. The health-care provider should be vigilant for signs of depression, which may require assessment and treatment and which may interfere with adherence. Poor adherence has been shown to be associated with virologic failure, development of resistance, and decreased long-term effectiveness of antiretroviral therapy [245-250]. Efforts to maintain good adherence during the postpartum period might prolong the effectiveness of therapy. The Adherence section in the *Guidelines for the Use of Antiretroviral Agents in HIV-

**Infected Adults and Adolescents*, is available at the AIDSInfo Web site ([http://AIDSinfo.nih.gov](http://AIDSinfo.nih.gov)).

All women should receive comprehensive health-care services that continue after pregnancy for their own medical care and for assistance with family planning and contraception. In addition, this is a good time to review immunization status and update vaccines, assess the need for prophylaxis against opportunistic infections, and reemphasize safer sex practices.

Data from PACTG 076 and 288 do not indicate adverse effects through 4 years postpartum among women who received ZDV during pregnancy. Women who have received only ZDV chemoprophylaxis during pregnancy should receive appropriate evaluation to determine the need for antiretroviral therapy during the postpartum period.

**Long-Term Follow-Up of Infants**

Data remain insufficient to address the effect that exposure to ZDV or other antiretroviral agents in utero might have on long-term risk for neoplasia or organ system toxicities in children. Data from follow-up of PACTG 076 infants through age 6 years do not indicate any differences in immunologic, neurologic, and growth parameters between infants who were exposed to the ZDV regimen and those who received placebo, and no malignancies have been seen [74, 75]. As discussed earlier in the section on Mitochondrial Toxicity and Nucleoside Analogue Drugs, there are conflicting data regarding whether mitochondrial dysfunction is associated with perinatal antiretroviral exposure. Mitochondrial dysfunction should be considered in uninfected children with perinatal antiretroviral exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings.

Continued evaluation of early and late effects of in utero antiretroviral exposure is ongoing through several mechanisms, including a long-term follow-up study in the Pediatric AIDS Clinical Trials Group (PACTG 219C), natural history studies, and HIV/AIDS surveillance conducted by state health departments and CDC. Because most of the available follow-up data relate to in utero exposure to antenatal ZDV alone and most pregnant women with HIV-1 infection currently receive combination therapy, it is critical that studies to evaluate potential adverse effects of in utero drug exposure continue to be supported.

Innovative methods are needed to provide follow-up of infants with in utero exposure to antiretroviral drugs. Information regarding such exposure should be part of
the ongoing permanent medical record of the child, particularly for uninfected children. Children with in utero antiretroviral exposure who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction [56]. Follow-up of children with antiretroviral exposure should continue into adulthood because of the theoretical concerns regarding potential for carcinogenicity of the nucleoside analogue antiretroviral drugs. Long-term follow-up should include yearly physical examinations of all children exposed to antiretroviral drugs and, for adolescent females, gynecologic evaluation with Pap smears.

HIV-1 surveillance databases from states that require HIV-1 reporting provide an opportunity to collect population-based information concerning in utero antiretroviral exposure. To the extent permitted by federal law and regulations, data from these confidential registries can be used to compare with information from birth defect and cancer registries to identify potential adverse outcomes.

**CLINICAL RESEARCH NEEDS**

The following clinical research needs are relevant to the United States and other developed countries. Study findings continue to evolve rapidly, and research needs and clinical practice will require continued reassessment over time. The current guidelines do not attempt to address the complex research needs or antiretroviral prophylaxis recommendations for resource-limited international settings.

**Evaluation of Drug Safety and Pharmacokinetics**

Many pregnant women with HIV-1 infection in the United States are receiving combination antiretroviral therapy for their own health care along with standard ZDV prophylaxis to reduce perinatal HIV-1 transmission. Additionally, data indicate that antenatal use of potent antiretroviral combinations capable of reducing plasma HIV-1 RNA copy number to very low or undetectable levels near the time of delivery may lower the risk of perinatal transmission to < 2% [66, 104]. While the number of antiretroviral agents and combination regimens used for treatment of infected persons is increasing rapidly, the number of drugs evaluated in pregnant women remains limited.

Preclinical evaluations of antiretroviral drugs for potential pregnancy- and fetal-related toxicities need to be completed for all existing and new antiretroviral drugs. More data are needed regarding the safety and pharmacokinetics of antiretroviral drugs in pregnant women and their neonates, particularly when used in combination regimens. Further research is also needed on whether the effects of intensive combination treatment on viral load differ in various body compartments, such as plasma and genital tract secretions, and how this may relate to risk of perinatal transmission.

Continued careful assessment for potential short- and long-term consequences of antiretroviral drug use during pregnancy for both the woman and her child is important. Consequences of particular concern include mitochondrial dysfunction; hepatic, hematologic, and other potential end-organ toxicities; development of antiretroviral drug resistance; and adverse effects on pregnancy outcome. Because the late consequences of in utero antiretroviral exposure for the child are unknown, innovative methods need to be developed to detect possible rare late toxicities of transient perinatal antiretroviral drug exposure that may not be observed until later in childhood or in adolescence or adulthood.

**Optimizing Neonatal Regimens for Perinatal Prophylaxis**

Several studies have demonstrated the efficacy of postnatal therapy to the newborn when the mother did not receive antenatal or intrapartum treatment. A six week course of ZDV, as well as single-dose nevirapine and single-dose nevirapine in combination with one week of ZDV given to the infant soon after birth, can result in a reduced risk of infection. Further research is needed to identify the optimal regimen for preventing infection in infants born to women who did not receive antiretroviral treatment during pregnancy or delivery. More potent regimens with two and three drug combinations may further reduce transmission risk. The efficacy of more potent prophylactic neonatal antiretroviral regimens, as well as their short and long term toxicities, requires further study.

**Assessment of Drug Resistance**

The risk of emerging drug resistance during pregnancy or the postpartum period requires further study. The administration of ZDV as a single drug for prophylaxis of transmission may increase the incidence of ZDV resistance mutations in women with viral replication that is not maximally suppressed. Administration of
drugs such as nevirapine and 3TC, for which a single point mutation can confer genotypic resistance, to pregnant women with inadequate viral suppression may result in the development of virus with genotypic drug resistance in a substantial proportion of women [135, 137]. The clinical consequences of emergence of genotypic resistance during pregnancy or in the postpartum period with respect to risk of transmission of resistant virus and future treatment options require further assessment.

**Stopping Antiretroviral Therapy**

When stopping antiretroviral therapy, current recommendations suggest discontinuing all antiretroviral drugs simultaneously to avoid the development of drug resistance. However, if the drugs have significant differences in half-life, such a strategy may result in functional monotherapy for a period of time; if there is actively replicating virus, this could lead to development of resistance. This issue is a particular concern with the NNRTI class of drugs, both because of their long half-lives and low genetic barrier to resistance. This has clinical relevance in pregnancy, as women may interrupt ongoing therapy in early pregnancy because of nausea and vomiting or concerns about first trimester fetal exposure. Additionally, many pregnant women may not yet meet criteria for maternal treatment and are prescribed combination antiretroviral therapy solely for prophylaxis against perinatal transmission. In this situation, therapy is routinely stopped after delivery.

Recent data indicate that there may be significant plasma levels of nevirapine or efavirenz for prolonged periods of time (more than 2 weeks) after stopping chronic therapy, as well as after receipt of single-dose nevirapine [127, 251]. Nevirapine resistance mutations have been identified postpartum in women who have received single-dose intrapartum nevirapine prophylaxis, as well as in women who have stopped nevirapine-containing combination regimens taken during pregnancy for prevention of mother-to-child transmission [135, 173]. In the latter study, nevirapine resistance was seen in 16% of women despite staggered stopping of the antiretroviral drugs (in which the nucleoside backbone was continued for 5 days after stopping nevirapine) [173]. Preliminary data from a South African study suggest that administration of single-dose nevirapine combined with ZDV/3TC given intrapartum and for 4 or 7 days postpartum may reduce, although not eliminate, the development of resistance compared with administration of single-dose nevirapine alone [252]. Further research is needed to assess appropriate strategies for stopping nevirapine-containing combination regimens that are used during pregnancy for prevention of mother-to-child transmission, and to prevent development of resistance after receipt of single-dose nevirapine for prevention of intrapartum transmission. Additionally, research is needed to evaluate the effect of transient nevirapine resistance on later treatment options.

**Optimizing Adherence**

The complexity of combination antiretroviral regimens and prophylaxis against opportunistic infections often leads to poor adherence among HIV-1 infected persons. Innovative approaches are needed to improve adherence in women with HIV-1 infection during and following pregnancy and to ensure that infants receive ZDV prophylaxis.

**Role of Cesarean Delivery Among Women with Undetectable Viral Load or with Short Duration of Ruptured Membranes**

Elective cesarean delivery has increased among women with HIV-1 infection since the demonstration that delivery before labor and membrane rupture can reduce intrapartum HIV-1 transmission [199, 200, 253]. Further study is needed regarding whether elective cesarean delivery provides clinically significant benefit to infected women with low or undetectable viral load and to those receiving combination antiretroviral therapy. Additionally, data from a meta-analysis by the International Perinatal HIV-1 Group indicate that, among women receiving ZDV or not receiving antiretroviral drugs, the risk of perinatal transmission increases by 2% for every 1-hour increase in duration of membrane rupture in infected women with < 24 hours of membrane rupture [254]. Therefore, further study is also needed to evaluate the role of nonelective cesarean delivery in reducing perinatal transmission in women on limited therapy with very short duration of ruptured membranes and/or labor.

**Management of Women with Premature Rupture of Membranes**

With evidence that increasing duration of membrane rupture is associated with an increasing transmission risk [254], more study is needed to determine the appropriate management of pregnant women with HIV-1 infection who present with ruptured membranes at different points in gestation.
Offering Rapid Testing at Delivery to Late Presenting Women

Women who have not received antenatal care and were not offered HIV-1 counseling and testing are one of the groups still at high risk for transmitting HIV-1 to their infants. The Mother-Infant Rapid Intervention at Delivery (MIRIAD) study has demonstrated the acceptability and feasibility of offering counseling and rapid HIV-1 testing to women of unknown HIV-1 status who present while in labor [25]. Rapid testing during labor can enable pregnant women with undocumeted HIV-1 status to learn their HIV-1 infection status so they can receive antiretroviral prophylaxis and be referred for comprehensive medical care and follow-up. A model protocol on implementing rapid HIV testing at labor/delivery is available from CDC at http://www.cdc.gov/hiv/rapid_testing/.

Antiretroviral prophylaxis should be initiated as soon as possible after a positive rapid HIV test result and prior to standard confirmatory testing, as the benefit of reducing the risk of mother-to-child HIV transmission outweighs the risk of exposure to an intrapartum course of antiretroviral medications. Further studies are needed to assess the relative acceptability and efficacy of intrapartum/postpartum versus postpartum infant interventions to reduce the risk of intrapartum transmission by women first identified as HIV-1 infected during delivery, and to identify the optimal antiretroviral prophylaxis regimen for this situation.
Table 1. Pediatric AIDS Clinical Trials Group (PACTG) 076 Zidovudine (ZDV) Regimen

<table>
<thead>
<tr>
<th>Time of ZDV Administration</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum</td>
<td>Oral administration of 100 mg ZDV five times daily*, initiated at 14-34 weeks gestation and continued throughout the pregnancy.</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>During labor, intravenous administration of ZDV in a one-hour initial dose of 2 mg/kg body weight, followed by a continuous infusion of 1 mg/kg body weight/hour until delivery.</td>
</tr>
<tr>
<td>Postpartum</td>
<td>Oral administration of ZDV to the newborn (ZDV syrup at 2 mg/kg body weight/dose every six hours) for the first six weeks of life, beginning at 8-12 hours after birth.**</td>
</tr>
</tbody>
</table>

* Oral ZDV administered as 200 mg three times daily or 300 mg twice daily is currently used in general clinical practice and is an acceptable alternative regimen to 100 mg orally five times daily.

** Intravenous dosage for full-term infants who cannot tolerate oral intake is 1.5 mg/kg body weight intravenously every six hours [123]. ZDV dosing for infants <35 weeks gestation at birth is 1.5 mg/kg/dose intravenously, or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if >30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth [125].
Table 2. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy
(see Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy for more detail on drugs)

<table>
<thead>
<tr>
<th>Antiretroviral drug</th>
<th>FDA pregnancy category</th>
<th>Placental passage newborn: mother drug</th>
<th>Long-term animal carcinogenicity</th>
<th>Animal teratogen studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside and nucleotide analogue reverse transcriptase inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (Ziagen, ABC)</td>
<td>C</td>
<td>Yes (rats)</td>
<td>Positive (malignant and non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)</td>
<td>Positive (rodent anasarca and skeletal malformations at 1000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits)</td>
</tr>
<tr>
<td>Didanosine ( VIDex, ddI)</td>
<td>B</td>
<td>Yes (human) [0.5]</td>
<td>Negative (no tumors, lifetime rodent study)</td>
<td>Negative</td>
</tr>
<tr>
<td>Emtricitabine (Emtriva, FTC)</td>
<td>B</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Lamivudine (Epivir, 3TC)</td>
<td>C</td>
<td>Yes (human) [-1.0]</td>
<td>Negative (no tumors, lifetime rodent study)</td>
<td>Negative</td>
</tr>
<tr>
<td>stavudine (Zerit, d4T)</td>
<td>C</td>
<td>Yes (rhesus monkey) [0.76]</td>
<td>Positive (mice and rats, at very high dose exposure, liver and bladder tumors)</td>
<td>Negative (but sternal bone calcium decreases in rodents)</td>
</tr>
<tr>
<td>Tenofovir DF (Viread)</td>
<td>B</td>
<td>Yes (rat and monkey)</td>
<td>Positive (hepatic adenomas in female mice at high doses)</td>
<td>Negative (osteomalacia when given to juvenile animals at high doses)</td>
</tr>
<tr>
<td>Zalcitabine (HIVID, ddC)</td>
<td>C</td>
<td>Yes (rhesus monkey) [0.30–0.50]</td>
<td>Positive (rodent, thymic lymphomas)</td>
<td>Positive (rodent-hydrocephalus at high dose)</td>
</tr>
<tr>
<td>Zidovudine/Retrovir (AZT, ZDV)</td>
<td>C</td>
<td>Yes (human) [0.85]</td>
<td>Positive (rodent, noninvasive vaginal epithelial tumors)</td>
<td>Positive (rodent-near lethal dose)</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine (Rescriptor)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats, bladder tumors in male mice)</td>
<td>Positive (rodent-ventricular septal defect)</td>
</tr>
<tr>
<td>Efavirenz (Sustiva)</td>
<td>D</td>
<td>Yes (cyonomologus monkey, rat, rabbit) [-1.0]</td>
<td>Positive (hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female but not male mice)</td>
<td>Positive (cyonomologus monkey-anencephaly, anophthalmia, microophthalmia)</td>
</tr>
<tr>
<td>Nevirapine (Viramune)</td>
<td>C</td>
<td>Yes (human) [-1.0]</td>
<td>Positive (hepatocellular adenomas and carcinomas in mice and rats)</td>
<td>Negative</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir (Agenerase)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (hepatocellular adenomas and carcinomas in male and female rats)</td>
<td>Negative (but deficient ossification and thymic elongation in rats and rabbits)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>B</td>
<td>Unknown</td>
<td>Positive (hepatocellular adenomas in female mice)</td>
<td>Negative</td>
</tr>
<tr>
<td>Darunavir (Prezista)</td>
<td>B</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Fosamprenavir (Lexiva)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (benign and malignant liver tumors in male rodents)</td>
<td>Negative (deficient ossification with amprenavir but not fosamprenavir)</td>
</tr>
<tr>
<td>Indinavir (Crixivan)</td>
<td>C</td>
<td>Minimal (humans)</td>
<td>Positive (thyroid adenomas in male rats at highest dose)</td>
<td>Negative (but extra ribs in rodents)</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir (Kaletra)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (hepatocellular adenomas and carcinomas in mice and rats)</td>
<td>Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)</td>
</tr>
<tr>
<td>Nelfinavir (Viracept)</td>
<td>B</td>
<td>Minimal (humans)</td>
<td>Positive (thyroid follicular adenomas and carcinomas in rats)</td>
<td>Negative</td>
</tr>
<tr>
<td>Ritonavir (Norvir)</td>
<td>B</td>
<td>Minimal (humans)</td>
<td>Positive (liver adenomas and carcinomas in male mice)</td>
<td>Negative (but cryptorchidism in rodents)</td>
</tr>
<tr>
<td>Saquinavir (Fortovase)</td>
<td>B</td>
<td>Minimal (humans)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Tipranavir (Aptivus)</td>
<td>C</td>
<td>Unknown</td>
<td>In progress</td>
<td>Negative (decreased ossification and pup weights in rats at maternally toxic doses)</td>
</tr>
<tr>
<td>Fusion inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide (Fuzeon)</td>
<td>B</td>
<td>Unknown</td>
<td>Not done</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Food and Drug Administration Pregnancy Categories:
A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
B - Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.
C - Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D - Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be unacceptable despite its potential risks.
X - Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.
Table 3: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (see also “Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy” supplement for additional toxicity data and “Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents” for detailed guidelines regarding treatment options)

<table>
<thead>
<tr>
<th>Antiretroviral Drug</th>
<th>Pharmacokinetics in Pregnancy</th>
<th>Concerns in Pregnancy</th>
<th>Rationale for Recommended Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs/ NtRTIs</td>
<td></td>
<td>See text for discussion of potential maternal and infant mitochondrial toxicity.</td>
<td>NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection (AZT alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA &lt;1,000 copies/mL).</td>
</tr>
<tr>
<td><strong>Recommended agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine*</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [256].</td>
<td>No evidence of human teratogenicity [73]. Well-tolerated, short-term safety demonstrated for mother and infant.</td>
<td>Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience; should be included in regimen unless significant toxicity or stavudine use.</td>
</tr>
<tr>
<td>Lamivudine*</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [257].</td>
<td>No evidence of human teratogenicity [73]. Well-tolerated, short-term safety demonstrated for mother and infant.</td>
<td>Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.</td>
</tr>
<tr>
<td><strong>Alternate agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [258].</td>
<td>Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together [53, 54].</td>
<td>Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [259].</td>
<td>No evidence of human teratogenicity [73]. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together [53, 54].</td>
<td>Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine due to potential for antagonism.</td>
</tr>
<tr>
<td>Abacavir*</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.</td>
<td>Hypersensitivity reactions occur in ~5-8% of non-pregnant persons; a much smaller percentage are fatal and are usually associated with rechallenge. Rate in pregnancy unknown. Patient should be educated regarding symptoms of hypersensitivity reaction.</td>
<td>Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen.</td>
</tr>
<tr>
<td><strong>Insufficient data to recommend use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenoforiv*</td>
<td>No studies in human pregnancy. Phase I study in late pregnancy in progress.</td>
<td>Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within two months of starting maternal therapy [260]. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown [261, 262].</td>
<td>Because of lack of data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of alternatives.</td>
</tr>
<tr>
<td><strong>Not recommended</strong></td>
<td></td>
<td>Rodent studies indicate potential for teratogenicity and developmental toxicity (see Table 2).</td>
<td>Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.</td>
</tr>
</tbody>
</table>
**Table 3. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy**

<table>
<thead>
<tr>
<th>Antiretroviral Drug</th>
<th>Pharmacokinetics in Pregnancy</th>
<th>Concerns in Pregnancy</th>
<th>Rationale for Recommended Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated [263].</td>
<td>No evidence of human teratogenicity [73]. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4+ counts &gt; 250/mm³ when first initiating therapy [31, 264]; uncertain if pregnancy increases risk.</td>
<td>Nevirapine should be initiated in pregnant women with CD4+ counts &gt; 250 cells/mm³ only if benefit clearly outweighs risk, due to the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4+ count.</td>
</tr>
<tr>
<td><strong>Not recommended</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>No studies in human pregnancy.</td>
<td>FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure; there were three case reports of neural tube defects in humans after first trimester exposure [73, 263, 265]; relative risk unclear.</td>
<td>Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of child bearing potential. Use after the second trimester of pregnancy can be considered if other alternatives are not available and if adequate contraception can be assured postpartum.</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>No studies in human pregnancy.</td>
<td>Rodent studies indicate potential for carcinogenicity and teratogenicity (see Table 2).</td>
<td>Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recommended agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Pharmacokinetic studies of standard dose of lopinavir/ritonavir capsules (3 capsules twice daily) during 3rd trimester indicated levels were significantly lower than during postpartum period and in non-pregnant adults; an increased dose of 4 capsules of lopinavir/ritonavir twice daily starting in the 3rd trimester resulted in adequate lopinavir exposure; by 2 weeks postpartum, standard dosing was again appropriate. Pharmacokinetic studies of the new lopinavir/ritonavir tablet formulation are underway, but data are not yet available.</td>
<td>No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated in phase I/II studies.</td>
<td>The capsule formulation is no longer available. Pharmacokinetic studies of the new tablet formulation are underway, but there are currently insufficient data to make a definitive recommendation regarding dosing in pregnancy. Some experts would administer standard dosing (2 tablets twice daily) throughout pregnancy and monitor virologic response and lopinavir drug levels, if available. Other experts, extrapolating from the capsule formulation pharmacokinetic data, would increase the dose of the tablet formulation during the 3rd trimester (from 2 tablets to 3 tablets twice daily), returning to standard dosing postpartum. Once daily lopinavir/ritonavir dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Adequate drug levels are achieved in pregnant women with nelfinavir 1250 mg, given twice daily [267].</td>
<td>No evidence of human teratogenicity [73]. Well-tolerated, short-term safety demonstrated for mother and infant. Nelfinavir dosing at 750 mg three times daily produced variable and generally low levels in pregnant women.</td>
<td>Given pharmacokinetic data and extensive experience with use in pregnancy compared to other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in non-pregnant adults, nelfinavir-based regimens had a lower rate of viral response compared to lopinavir/ritonavir or efavirenz-based regimens, but similar viral response compared with atazanavir or nevirapine-based regimens [268-271].</td>
</tr>
</tbody>
</table>
### Table 3. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

<table>
<thead>
<tr>
<th>Antiretroviral Drug</th>
<th>Pharmacokinetics in Pregnancy</th>
<th>Concerns in Pregnancy</th>
<th>Rationale for Recommended Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alternate agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Two studies including 18 women receiving indinavir 800 mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen [272, 273].</td>
<td>Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.</td>
<td>Alternate PI to consider if unable to use nelfinavir or saquinavir-SGC/ritonavir, but would need to give indinavir as ritonavir-boosted regimen. Optimal dosing for the combination of indinavir/ritonavir in pregnancy is unknown.</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum [274].</td>
<td><strong>Limited</strong> experience at full dose in human pregnancy; has been used as low-dose ritonavir boosting with other PIs.</td>
<td>Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose ritonavir “boost” to increase levels of second PI.</td>
</tr>
<tr>
<td>Saquinavir-SGC soft gel capsule (HGC) (Invirase®, (Inviirase®)</td>
<td>Pharmacokinetic studies of saquinavir-soft gel capsules (SGC) indicated that inadequate drug levels were achieved in pregnant women given 1,200 mg of saquinavir-SGC as a sole PI three times daily [275], but adequate levels were achieved when 800 mg saquinavir-SGC boosted with ritonavir 100 mg was given twice daily [276]. However, saquinavir-SGC are no longer produced. Limited pharmacokinetic data on saquinavir-hard gel capsule (HGC) suggest that 1,000 mg saquinavir-HGC/100 mg ritonavir given twice daily will achieve adequate saquinavir drug levels in pregnant women.</td>
<td>Saquinavir-SGC are no longer available. There are only limited pharmacokinetic data on saquinavir-HGC in pregnancy. Ritonavir-boosted saquinavir-HGC is an alternative PI for combination regimens in pregnancy, and is an alternative initial antiretroviral recommendation for non-pregnant adults.</td>
<td></td>
</tr>
</tbody>
</table>

**Insufficient data to recommend use**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetics in Pregnancy</th>
<th>Concerns in Pregnancy</th>
<th>Rationale for Recommended Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>No studies in human pregnancy.</td>
<td>Oral solution contraindicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolized during pregnancy.</td>
<td>Safety and pharmacokinetics in pregnancy data are insufficient to recommend use of capsules during pregnancy.</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>No studies in human pregnancy.</td>
<td>Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low.</td>
<td>Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td>Darunavir</td>
<td>No studies in human pregnancy.</td>
<td>No experience in human pregnancy.</td>
<td>Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>No studies in human pregnancy.</td>
<td>No experience in human pregnancy.</td>
<td>Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>No studies in human pregnancy.</td>
<td>No experience in human pregnancy.</td>
<td>Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.</td>
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</tbody>
</table>

**Fusion Inhibitors**

**Insufficient data to recommend use**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacokinetics in Pregnancy</th>
<th>Concerns in Pregnancy</th>
<th>Rationale for Recommended Use in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide</td>
<td>No studies in human pregnancy.</td>
<td>No experience in human pregnancy.</td>
<td>Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.</td>
</tr>
</tbody>
</table>

NRTI = nucleoside reverse transcriptase inhibitor; NRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft gel capsule; HGC = hard gel capsule.

* Zidovudine and lamivudine are included as a fixed-dose combination in Combivir®; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir®.

† Emtricitabine and tenofovir are included as a fixed-dose combination in Truvada®; emtricitabine, tenofovir, and efavirenz are included as a fixed-dose combination in Atripla™.

‡ Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based HAART regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based HAART regimen cannot be used (e.g., due to significant drug interactions). A study evaluating use of zidovudine/lamivudine/abacavir among pregnant women with HIV RNA < 55,000 copies/mL as a class-sparing regimen is in development.
### Table 4. Clinical Scenarios and Recommendations for the Use of Antiretroviral Drugs to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV-1) Transmission

<table>
<thead>
<tr>
<th>SCENARIO #1</th>
<th>HIV-1-infected pregnant women who have not received prior antiretroviral therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pregnant women with HIV-1 infection must receive standard clinical, immunologic, and virologic evaluation. Recommendations for initiation and choice of antiretroviral therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed.</td>
<td></td>
</tr>
<tr>
<td>- The three-part ZDV chemoprophylaxis regimen, initiated after the first trimester, is recommended for all pregnant women with HIV-1 infection regardless of antenatal HIV RNA copy number to reduce the risk for perinatal transmission.</td>
<td></td>
</tr>
<tr>
<td>- The combination of ZDV chemoprophylaxis with additional antiretroviral drugs for treatment of HIV-1 infection is recommended for infected women whose clinical, immunologic or virologic status requires treatment or who have HIV-1 RNA over 1,000 copies/mL regardless of clinical or immunologic status, and can be considered for women with HIV-1 RNA &lt; 1,000 copies/mL.</td>
<td></td>
</tr>
<tr>
<td>- Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10-12 weeks’ gestation.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCENARIO #2</th>
<th>HIV-1-infected women receiving antiretroviral therapy during the current pregnancy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- HIV-1 infected women receiving antiretroviral therapy in whom pregnancy is identified after the first trimester should continue therapy. ZDV should be a component of the antenatal antiretroviral treatment regimen after the first trimester whenever possible, although this may not always be feasible.</td>
<td></td>
</tr>
<tr>
<td>- For women receiving antiretroviral therapy in whom pregnancy is recognized during the first trimester, the woman should be counseled regarding the benefits and potential risks of antiretroviral administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance.</td>
<td></td>
</tr>
<tr>
<td>- Regardless of the antepartum antiretroviral regimen, ZDV administration is recommended during the intrapartum period and for the newborn.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCENARIO #3</th>
<th>HIV-1-infected women in labor who have had no prior therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Several effective regimens are available (Table 5). These include:</td>
<td></td>
</tr>
<tr>
<td>1. intrapartum intravenous ZDV followed by six weeks of ZDV for the newborn;</td>
<td></td>
</tr>
<tr>
<td>2. oral ZDV and 3TC during labor, followed by one week of oral ZDV-3TC for the newborn;</td>
<td></td>
</tr>
<tr>
<td>3. a single dose nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at age 48 hours; and</td>
<td></td>
</tr>
<tr>
<td>4. the single-dose maternal/infant nevirapine regimen combined with intrapartum intravenous ZDV and six week ZDV for the newborn.</td>
<td></td>
</tr>
<tr>
<td>- If single-dose nevirapine is given to the mother, alone or in combination with ZDV, consideration should be given to adding maternal ZDV/3TC starting as soon as possible (intrapartum or immediately postpartum) and continuing for 3 to 7 days, which may reduce development of nevirapine resistance.</td>
<td></td>
</tr>
<tr>
<td>- In the immediate postpartum period, the woman should have appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine whether antiretroviral therapy is recommended for her own health.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCENARIO #4</th>
<th>Infants born to mothers who have received no antiretroviral therapy during pregnancy or intrapartum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The six-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn.</td>
<td></td>
</tr>
<tr>
<td>- ZDV should be initiated as soon as possible after delivery - preferably within 6-12 hours of birth.</td>
<td></td>
</tr>
<tr>
<td>- Some clinicians may choose to use ZDV in combination with other antiretroviral drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission has not been proven in clinical trials, and appropriate dosing regimens for neonates are incompletely defined for many drugs.</td>
<td></td>
</tr>
<tr>
<td>- In the immediate postpartum period, the woman should undergo appropriate assessments (e.g., CD4+ count and HIV-1 RNA copy number) to determine if antiretroviral therapy is required for her own health. The infant should undergo early diagnostic testing so that if HIV-infected, treatment can be initiated as soon as possible.</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Discussion of treatment options and recommendations should be noncoercive, and the final decision regarding the use of antiretroviral drugs is the responsibility of the woman. A decision to not accept treatment with ZDV or other drugs should not result in punitive action or denial of care. Use of ZDV should not be denied to a woman who wishes to minimize exposure of the fetus to other antiretroviral drugs and who therefore chooses to receive only ZDV during pregnancy to reduce the risk for perinatal transmission.
Table 5. Comparison of Intrapartum/Postpartum Regimens for HIV-1-Infected Women in Labor Who Have Had No Prior Antiretroviral Therapy (Scenario #3)

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Source of Evidence</th>
<th>Maternal Regimen</th>
<th>Infant Postpartum</th>
<th>Data on Transmission</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>Epidemiologic data, U.S.; compared to no ZDV treatment</td>
<td>2 mg/kg intravenous bolus, followed by continuous infusion of 1 mg/kg/hr until delivery</td>
<td>2 mg/kg orally every six hours for six weeks*</td>
<td>Transmission 10% with ZDV compared to 27% with no ZDV treatment, a 62% reduction (95% CI, 19–82%)</td>
<td>Has been standard recommendation</td>
<td>Requires intravenous administration and availability of ZDV intravenous formulation Adherence to six week infant regimen Reversible, mild anemia with 6 week infant ZDV regimen</td>
</tr>
<tr>
<td>ZDV/3TC</td>
<td>Clinical trial, Africa; compared to placebo</td>
<td>ZDV 600 mg orally at onset of labor, followed by 300 mg orally every three hours until delivery AND 3TC 150 mg orally at onset of labor, followed by 150 mg orally every 12 hours until delivery</td>
<td>ZDV 4 mg/kg orally every 12 hours AND 3TC 2 mg/kg orally every 12 hours for seven days</td>
<td>Transmission at six weeks 9% with ZDV-3TC vs. 15% with placebo, a 42% reduction</td>
<td>Oral regimen Adherence easier than six weeks of ZDV</td>
<td>Requires administration of two drugs</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Clinical trial, Africa; compared to oral ZDV given intrapartum and for one week to the infant</td>
<td>Single 200 mg oral dose at onset of labor Consider adding intrapartum ZDV/3TC and 3–7 days of ZDV/3TC postpartum to reduce nevirapine resistance</td>
<td>Single 2 mg/kg oral dose at age 48–72 hours**</td>
<td>Transmission at six weeks 12% with nevirapine compared to 21% with ZDV, a 47% reduction (95% CI*, 20–64%)</td>
<td>Inexpensive Oral regimen Simple, easy to administer Can give directly observed treatment</td>
<td>Unknown efficacy if mother has nevirapine-resistant virus Nevirapine resistance mutations have been detected postpartum in some women and in infants who became infected despite prophylaxis</td>
</tr>
<tr>
<td>ZDV- Nevirapine</td>
<td>Theoretical</td>
<td>ZDV 2 mg/kg intravenous bolus, followed by continuous infusion of 1 mg/kg/hr until delivery AND Nevirapine single 200 mg oral dose at onset of labor Consider adding intrapartum ZDV/3TC and 3–7 days of ZDV/3TC postpartum to reduce nevirapine resistance</td>
<td>ZDV 2 mg/kg orally every six hours for six weeks AND Nevirapine single 2 mg/kg oral dose at age 48–72 hours**</td>
<td>No data</td>
<td>Potential benefit if maternal virus is resistant to either nevirapine or ZDV Synergistic inhibition of HIV replication with combination in vitro</td>
<td>Requires intravenous administration and availability of ZDV intravenous formulation Adherence to six week infant ZDV regimen Unknown if additive efficacy with combination Nevirapine resistance mutations have been detected postpartum in some women and in infants who became infected despite prophylaxis</td>
</tr>
</tbody>
</table>

ZDV, zidovudine; CI, confidence interval; 3TC, lamivudine

* ZDV dosing for infants <35 weeks gestation at birth is 1.5 mg/kg/dose intravenously, or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if ≥30 weeks gestation at birth or at 4 weeks of age if <30 weeks gestation at birth [125].

**If the mother received nevirapine less than one hour prior to delivery, the infant should be given 2 mg/kg oral nevirapine as soon as possible after birth and again at 48-72 hours [277].
Table 6. Rate of Perinatal Transmission According to Receipt of Zidovudine During Pregnancy and Mode of Delivery

<table>
<thead>
<tr>
<th>Study design</th>
<th>Therapy</th>
<th>Elective CS</th>
<th>Other modes</th>
<th>Odds ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational data [199]**</td>
<td>No ZDV</td>
<td>58/559 (10.4%)</td>
<td>1021/5385 (19%)</td>
<td>0.49 (0.4—0.7)</td>
</tr>
<tr>
<td></td>
<td>ZDV</td>
<td>4/196 (2%)</td>
<td>92/1255 (7.3%)</td>
<td>0.26 (0.07–0.7)</td>
</tr>
<tr>
<td>Randomized trial [200]***</td>
<td>No ZDV</td>
<td>2/51 (4%)</td>
<td>16/82 (20%)</td>
<td>0.20 (0–0.8)</td>
</tr>
<tr>
<td></td>
<td>ZDV</td>
<td>1/119 (1%)</td>
<td>5/117 (4%)</td>
<td>0.20 (0–1.7)</td>
</tr>
</tbody>
</table>

* Confidence interval.


Table 7. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV-1) Transmission

<table>
<thead>
<tr>
<th>Mode of Delivery Clinical Scenario</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario A</strong>&lt;br&gt;HIV-1-infected women presenting in late pregnancy (after about 36 weeks of gestation), known to be HIV-1-infected but not receiving antiretroviral therapy, and who have HIV-1 RNA level and lymphocyte subsets pending but unlikely to be available before delivery.</td>
<td>Therapy options should be discussed in detail. The woman should be started on antiretroviral therapy including at least the PACTG 076 ZDV regimen. The woman should be counseled that scheduled cesarean section is likely to reduce the risk of transmission to her infant. She should also be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and other surgical risks. If cesarean section is chosen, the procedure should be scheduled at 38 weeks of gestation based on the best available clinical information. When scheduled cesarean section is performed, the woman should receive continuous intravenous ZDV infusion beginning three hours before surgery and her infant should receive six weeks of ZDV therapy after birth. Options for continuing or initiating antiretroviral therapy after delivery should be discussed with the woman as soon as her viral load and lymphocyte subset results are available.</td>
</tr>
<tr>
<td><strong>Scenario B</strong>&lt;br&gt;HIV-1-infected women who initiated prenatal care early in the third trimester, are receiving highly active combination antiretroviral therapy, and have an initial virologic response, but have HIV-1 RNA levels that remain substantially over 1,000 copies/mL at 36 weeks of gestation.</td>
<td>The current combination antiretroviral regimen should be continued as the HIV-1 RNA level is dropping appropriately. The woman should be counseled that although she is responding to the antiretroviral therapy, it is unlikely that her HIV-1 RNA level will fall below 1,000 copies/mL before delivery. Therefore, scheduled cesarean section may provide additional benefit in preventing intrapartum transmission of HIV-1. She should also be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and surgical risks. If she chooses scheduled cesarean section, it should be performed at 38 weeks’ gestation according to the best available dating parameters, and intravenous ZDV should be begun at least three hours before surgery. Other antiretroviral medications should be continued on schedule as much as possible before and after surgery. The infant should receive oral ZDV for six weeks after birth. The importance of adhering to therapy after delivery for her own health should be emphasized.</td>
</tr>
<tr>
<td><strong>Scenario C</strong>&lt;br&gt;HIV-1-infected women on highly active combination antiretroviral therapy with an undetectable HIV-1 RNA level at 36 weeks of gestation.</td>
<td>The woman should be counseled that her risk of perinatal transmission of HIV-1 with a persistently undetectable HIV-1 RNA level is low, probably 2% or less, even with vaginal delivery. There is currently no information to evaluate whether performing a scheduled cesarean section will lower her risk further. Cesarean section has an increased risk of complications for the woman compared to vaginal delivery, and these risks must be balanced against the uncertain benefit of cesarean section in this case.</td>
</tr>
<tr>
<td><strong>Scenario D</strong>&lt;br&gt;HIV-1-infected women who have elected scheduled cesarean section but present in early labor or shortly after rupture of membranes.</td>
<td>Intravenous ZDV should be started immediately since the woman is in labor or has ruptured membranes. If labor is progressing rapidly, the woman should be allowed to deliver vaginally. If cervical dilatation is minimal and a long period of labor is anticipated, some clinicians may choose to administer the loading dose of intravenous ZDV and proceed with cesarean section to minimize the duration of membrane rupture and avoid vaginal delivery. Others might begin pitocin augmentation to enhance contractions and potentially expedite delivery. If the woman is allowed to labor, scalp electrodes and other invasive monitoring and operative delivery should be avoided if possible. The infant should be treated with six weeks of ZDV therapy after birth.</td>
</tr>
</tbody>
</table>
REFERENCES


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### Appendix: Perinatal Antiretroviral Guidelines Working Group Conflict of Interest Disclosure – October 12, 2006

<table>
<thead>
<tr>
<th>Name</th>
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<th>Relationship</th>
</tr>
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<tr>
<td>Erika Aaron</td>
<td>NONE</td>
<td>N/A</td>
</tr>
<tr>
<td>Elaine Abrams</td>
<td>Johnson &amp; Johnson</td>
<td>Stockholder</td>
</tr>
<tr>
<td>Jean Anderson</td>
<td>Pfizer Inc.</td>
<td>Advisory Board member</td>
</tr>
<tr>
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<td>Speaker with honoraria</td>
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<td>Educational program support</td>
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<tr>
<td>Magda Barini-Garcia</td>
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<td>N/A</td>
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<tr>
<td>Dawn Averitt Bridge</td>
<td>NONE</td>
<td>N/A</td>
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<td>Susan Cohn</td>
<td>Applera Corp/Celera Genomics</td>
<td>Stockholder</td>
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<tr>
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<td>Quest Diagnostics</td>
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<tr>
<td></td>
<td>STERIS Corporation</td>
<td>Think tank member</td>
</tr>
<tr>
<td></td>
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<td>Consultant</td>
</tr>
<tr>
<td>Susan Cu-Uvin</td>
<td>HIVMA</td>
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</tr>
<tr>
<td>Brian Feit</td>
<td>Medtronic, Inc.</td>
<td>Stockholder</td>
</tr>
<tr>
<td>Patricia Flynn</td>
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<tr>
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</tr>
<tr>
<td>Edward Handelsman</td>
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</tr>
<tr>
<td>Jane Hitti</td>
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<td>Think tank member</td>
</tr>
<tr>
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<td>(Ad hoc) Consultant</td>
</tr>
<tr>
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</tr>
<tr>
<td>Denise Jamieson</td>
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<td>Robert Maupin</td>
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## Appendix: Perinatal Antiretroviral Guidelines Working Group Conflict of Interest Disclosure – October 12, 2006

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<tr>
<th>Name</th>
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<th>Relationship</th>
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<td>Lynne Mofenson</td>
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<td>Gwen Scott</td>
<td>Abbott Laboratories</td>
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<td>Steve Spector</td>
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<td>Ruth Tuomala</td>
<td>Bristol-Myers Squibb</td>
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<td>Heather Watts</td>
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