I. INTRODUCTION

The ability to become pregnant and to bear children is uniquely female. With increasing numbers of HIV-infected women, 80% of whom are of childbearing age, and concerns about perinatal transmission of HIV, pregnancy in the setting of HIV infection has been a focus of much interest, research, and often discrimination. From 1989 to 1994 it was estimated that 1.5 to 1.7/1000 U.S. childbearing women were HIV-positive (Davis, 1998); however, this number may grow as more women become infected through sexual exposure, often unaware of their risk, and as more women who know they are infected choose to become pregnant because of therapeutic advances in care and prevention of vertical transmission. Almost one-third of HIV-infected men and women receiving medical care in the US desire children in the future (Chen, 2001). Furthermore, 20% of serodiscordant couples would practice unsafe sex in order to conceive (Klein, 2003).

This chapter will review issues related to contraception and pregnancy and will discuss guidelines for care during pregnancy to optimize the health of both the mother and the fetus and infant.

II. COUNSELING

The American College of Obstetricians and Gynecologists (ACOG) advocates reproductive counseling for all women of child bearing age as a part of primary care. For women known to be HIV-infected, education and counseling about pregnancy and HIV should be done early in the course of HIV care, not delayed until the woman is pregnant, so that decisions about contraception and if or when to get pregnant can be most informed and carefully considered. Discussions about pregnancy should be repeated at intervals throughout care, especially when personal circumstances change (e.g. new sexual partner, postpartum); when there is nonuse of effective contraception; where therapies are considered which may have adverse effects in pregnancy; or when the woman expresses a desire to become pregnant. Over one half of pregnancies in U.S. women are unplanned, and many of the risk factors for unintended pregnancy also place women at increased risk for HIV. These include:

- substance abuse (patient or partner)
- mental illness
- domestic violence
Adolescents are at an increased risk of unintended pregnancy and may also be at increased risk for HIV because of frequent unstable sexual relationships and unsafe sexual practices. Women with advanced HIV disease and HIV dementia may be at increased risk for unintended pregnancy if they are dependent on a contraceptive method (such as condom use or oral contraceptives) that requires negotiation with a sexual partner or other ongoing patient action (i.e., remembering to take pills). Issues to discuss when counseling about reproductive issues are listed in Table 7-1.

### Table 7-1: HIV and Pregnancy Counseling Issues

- Impact of HIV on pregnancy course/outcome
- Impact of pregnancy on HIV progression
- Other reproductive issues based on maternal factors
  - coexisting drug/alcohol use
  - advanced maternal age
  - hypertension, diabetes, etc.
- General preconception issues
  - nutritional counseling (e.g. folic acid)
  - importance of early and intense prenatal care
- Long term health of mother and care for children (guardianship issues)
- Perinatal transmission
- Use of antiretrovirals and other medications in pregnancy
- Safe conception if partner HIV-negative

### III. CONTRACEPTION

The majority of HIV-infected U.S. women use some form of contraception, most commonly condoms (Wilson, 1999; Watts, 1999). Women using no form of contraception do not necessarily intend to become pregnant but may lack significant power in their sexual relationship, be under pressure from partner or family to have children, may not have disclosed their HIV status to their partner, be unaware of their options concerning contraception or believe they cannot become pregnant, have a disorganized lifestyle that precludes consistent use of contraception, or simply have decided to take their chances. Unplanned also does not necessarily mean unwanted; several studies show low rates of elective pregnancy termination in HIV-positive women (Smits, 1999; Greco, 1999) and no significant difference in repeat pregnancy rates in HIV-positive compared with HIV-negative women from an inner-city population (Lindsay, 1995). Table 7-2 outlines currently available methods of contraception, their effectiveness, side effects and contraindications, and noncontraceptive benefits.
### Table 7-2: Contraceptive Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Failure Rates (% Pregnancies) in First Year of Typical and Perfect Use</th>
<th>Contraindications</th>
<th>Benefits</th>
<th>Potential Side Effects</th>
<th>Convenience</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Combined oral contraceptive pill (OC)</td>
<td>3 0.1</td>
<td>History of CVD, DVT, stroke; Hypertension; High LDL/HDL ratio; &gt;35 and heavy smoker; Markedly impaired liver function; Hepatocellular adenoma; Headache with focal neurologic symptoms; Diabetes with nephropathy, retinopathy, neuropathy, or vascular disease; Breast cancer; Major surgery with immobilization</td>
<td>Decreased menstrual pain, PMS, and blood loss; May reduce acne; Decreased benign breast disease; Decreased functional ovarian cysts; Decreased ovarian and endometrial cancers; Decreased PID</td>
<td>Nausea; Headache; Weight gain; Dizziness; Breast tenderness; Vaginal spotting; Chloasma; Depression</td>
<td>Use independent from sexual intercourse</td>
<td>No STI protection; May increase susceptibility to some STIs; Must remember to take pill daily</td>
</tr>
<tr>
<td>Combined estrogen-progestin injection (Lunelle)</td>
<td>0.03-0.1 0.03-0.1</td>
<td>Same as for OCs</td>
<td>Same as for OCs</td>
<td>Similar to OCs; more spotting/irregular bleeding than with OCs</td>
<td>Use independent from sexual intercourse; Daily action not required</td>
<td>No STI protection; May increase susceptibility for some STIs; Must have IM injection monthly in medical office (5 day &quot;grace&quot; period)</td>
</tr>
<tr>
<td>Combined estrogen-progestin vaginal ring (Nuva Ring)</td>
<td>N/A 0.6</td>
<td>Same as for OCs</td>
<td>Same as for OCs</td>
<td>Similar to OCs; possible increased vaginal discharge</td>
<td>Use independent from sexual intercourse; Vaginal ring inserted for 3 wks out of every mo – precise placement not required</td>
<td>No STI protection; May increase susceptibility for some STIs</td>
</tr>
<tr>
<td>Method</td>
<td>Failure Rates (% Pregnancies) in First Year of Typical and Perfect Use</td>
<td>Contraindications</td>
<td>Benefits</td>
<td>Potential Side Effects</td>
<td>Convenience</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>-------------------</td>
<td>----------</td>
<td>------------------------------------------------------------</td>
<td>-------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Hormonal (continued)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined estrogen-progestin patch (Ortho Evra)</td>
<td>0.6–0.8 (may be higher with wt &gt; 90kg) 0.6</td>
<td>Same as for OCs</td>
<td>Same as for OCs; improved user compliance</td>
<td>Similar to OCs; Skin irritation</td>
<td>Use independent from sexual intercourse; Patch applied weekly 3 of 4 weeks</td>
<td>No STI protection; May increase susceptibility for some STIs</td>
</tr>
<tr>
<td>Depo-medroxyprogesterone acetate (DMPA)</td>
<td>0.3 0.3</td>
<td>Unexplained vaginal bleeding; Breast cancer</td>
<td>Decreased risk of seizures; May have protective effects against PID, ovarian and endometrial cancer; Decreased blood loss, anemia Amenorrhea</td>
<td>Menstrual changes (spotting, irregular bleeding, amenorrhea); Weight gain Breast tenderness; Headache; Adverse effect on lipids; Depression</td>
<td>Often causes amenorrhea; Requires only 4 injections/yr; Requires no ongoing action by user; Use independent from sexual intercourse</td>
<td>No STI protection</td>
</tr>
<tr>
<td>Norplant</td>
<td>0.9 0.9</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Tenderness or infection at site; Menstrual changes; Hair loss; Weight gain; Breast tenderness; Depression</td>
<td>Provides 5 yr of contraception; Requires no ongoing action by user; Use independent from sexual intercourse</td>
<td>No STI protection</td>
</tr>
<tr>
<td>Progestin-only pill</td>
<td>1.1–13.8 0.5</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Menstrual changes (spotting, irregular bleeding, amenorrhea); Breast tenderness; Depression; Weight gain</td>
<td>Use independent from sexual intercourse</td>
<td>No STI protection; Ectopic pregnancy more likely among progestin-only pills than other forms of hormonal contraception; Must remember to take pill daily</td>
</tr>
</tbody>
</table>
### Barrier Methods

| Method                          | Allergy or Sensitivity | Limited STI Protection | Pelvis Pressure | Vaginal Irritation | Allergy or Sensitivity to Polyurethane | Woman Controlled | Can be Inserted Ahead of Time | Same as Above | Woman Controlled | Can be Inserted up to 6 hr Before Intercourse | Same as Above, Except May Be Used During Menses | Efficacy Based on High Motivation | Spermicide Re-application Required with Each Act of Coitus | Should Not Be Used During Menses | Efficacy Reduced When Used Without a Barrier Method | May Increase Susceptibility to HIV With Frequent Sexual Activity | No Protection Against HIV |
|--------------------------------|------------------------|-------------------------|-----------------|-------------------|----------------------------------------|------------------|-------------------------------|---------------|------------------|---------------------------------------------|--------------------------------|---------------------------|-----------------------------------------------------|-----------------------------|-----------------------------------------------------------------|-----------------------------------------------------------|
| Condom, male (latex, polyurethane, natural membrane) | (except for natural membrane) | Protects against STIs, including HIV | | | Protects against STIs, including HIV | Woman controlled; Less likelihood of breakage; Can be inserted up to 8 hr before intercourse; Does not require a prescription | Requires partner possible cooperation; Possible loss of spontaneity during sex | | | |
| Condom, female | Polyurethane allergy | Protects against STIs, including HIV | | | Allergy or sensitivity to polyurethane; Possible decreased sensitivity | Woman controlled; Can be inserted ahead of time | May be awkward to use; Aesthetically unappealing to some | | | |
| Cervical cap — parous/nonparous | Latex allergy; Abnormal cervical/vaginal anatomy; History of TSS or recurrent UTIs; Known or suspected cervical/uterine malignancy; Abnormal Pap; Vaginal or cervical infection; Recent delivery or spontaneous/induced abortion | Limited STI protection | Pelvis pressure; Vaginal irritation; Allergy or sensitivity to latex; Vaginal or urinary tract infections | Woman controlled; Can be inserted up to 6 hr before intercourse | Same as above | Same as above, except may be used during menses | Efficacy based on high motivation; Spermicide re-application required with each act of coitus; Should not be used during menses | | | |
| Diaphragm | Latex allergy; Abnormal vaginal anatomy; History of TSS or recurrent UTIs | Limited STI protection; Reduces risk of PID | Same as above | Woman controlled; Can be inserted up to 6 hr before intercourse | Same as above | | | | | | |
| Spermicides | Allergy to nonoxynol-9 | Protection against some STIs, significant against gonorrhea/chlamydia; In vitro activity against HIV | Vaginal irritation; Allergy; Vaginal and urinary tract infection | Woman controlled; Does not require a prescription; Easily available and inexpensive | Efficacy reduced when used without a barrier method; May increase susceptibility to HIV with frequent sexual activity; No protection against HIV | | | | | | | |
| IUD (Copper-Paar) | Recent (within 3 mo) or recurrent pelvic infection; Postpartum, postabortion endometritis; Active STI; Women at increased risk for STIs; Severely distorted uterine cavity | None | Menstrual cramping; Increased bleeding; Risk of PID and uterine perforation following insertion; Anemia | Provides contraception for 10 yrs; Requires no ongoing user action | No STI protection; Increased risk of PID | | | | | | | | |
### Table 7-2: Contraceptive Methods (continued)

<table>
<thead>
<tr>
<th>Method</th>
<th>Failure Rates (% Pregnancies in First Year of Typical and Perfect Use)</th>
<th>Benefits</th>
<th>Contraindications</th>
<th>Potential Side Effects</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonorgestrel intrauterine system (Mirena)</td>
<td>0.1–0.3</td>
<td>Same as for Copper IUD</td>
<td>Increased incidence in menstrual blood loss (20% compared to Copper IUD), decreased risk of PID</td>
<td>Pain at surgical site, possible decreased risk of ectopic pregnancy if failure</td>
<td>Provides contraception for 5 yr; Requires no ongoing user action; No STI protection</td>
</tr>
<tr>
<td>Female surgical sterilization</td>
<td>0.4</td>
<td>Desire for future fertility, active sexual infection</td>
<td>None</td>
<td>Subsequent regret, increased risk of ectopic pregnancy if failure; Cramping, nausea/vomiting with placement; Expulsion or uterine perforation (&lt;3%)</td>
<td>Provides permanent contraception; Requires no ongoing user action; Lower cost, does not require surgery or general anesthesia as compared to surgical sterilization</td>
</tr>
<tr>
<td>Nonsurgical female sterilization (Essure)</td>
<td>0.2–0.4</td>
<td>Desire for future fertility, active sexual infection</td>
<td>Probably similar to surgical sterilization (experience limited)</td>
<td>Subsequent regret; Increased risk of ectopic pregnancy if failure; Cramping, nausea/vomiting with placement; Expulsion or uterine perforation (&lt;3%)</td>
<td>Provides permanent contraception; Requires no ongoing user action; Lower cost, does not require surgery or general anesthesia as compared to surgical sterilization</td>
</tr>
<tr>
<td>Male sterilization</td>
<td>0.15</td>
<td>Desire for future fertility</td>
<td>None</td>
<td>Pregnancy Rate</td>
<td>Should be used within 72 hrs of intercourse; No STI protection; Failure rate higher if intercourse during fertile phase of cycle</td>
</tr>
</tbody>
</table>

Established pregnancy rate: 3.2% (57% expected pregnancies prevented)

Emergency contraception:
- Levonorgestrel 0.75mg (Plan B)
- Ethinylestradiol 50µg (Preven)

Pregnancy Rate: 0.02

CVD, cardiovascular disease; DVT, deep vein thrombosis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PID, pelvic inflammatory disease; PMS, premenstrual syndrome; TSS, toxic shock syndrome; UTI, urinary tract infection; Source: Hatcher, 1998; Johannson, 2004.

Emergency contraception:
- Levonorgestrel 0.75mg (Plan B)
- Ethinylestradiol 50µg (Preven)
Hormonal methods of contraception, particularly combined estrogen-progestin oral contraceptives (OCs), can have significant drug interactions, resulting in either decreased contraceptive effectiveness or increased or decreased concentrations of the coadministered drug. Use of nelfinavir, ritonavir, lopinavir, and nevirapine are associated with decreases in ethinyl estradiol (estrogen component of OCs) with possible decrease in effectiveness (and possible increase in breakthrough bleeding); an alternative or additional method should be used. Indinavir, atazanavir and efavirenz are associated with increases in ethinyl estradiol and indinavir and atazanavir are associated with increases in norethindrone (progestin component in many OCs). Norethindrone levels are increased over 100% with atazanavir. The clinical significance of these increases in hormonal blood levels is unclear, but they raise concerns about potential increase in estrogen- or progestin-related side effects. Alternative methods of contraception should be considered; if OCs are used, lowest effective doses of affected hormonal components should be prescribed and an additional method is recommended. Amprenavir (and probably fos-amprenavir) not only increases blood levels of ethinyl estradiol and norethindrone, but OCs decrease amprenavir levels as well; these drugs should not be co-administered and an alternative contraceptive method should be used. Other medications known to interact with oral contraceptives (and in some cases with progestin-only contraceptives) include tetracyclines, penicillin, oral hypoglycemic agents, rifampin, tricyclic antidepressants, oral anticoagulants, β-blockers, methyldopa, vitamin C, benzodiazepines, and seizure medications. Clinicians treating women who are at risk for drug interactions should review the need for possible use of alternative methods of contraception or dose adjustment for the interacting agent. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (patch, vaginal ring, estrogen-progestin injection).

Concerns have been raised about possible increased risk of HIV transmission or acquisition in hormonal contraceptive users. There is evidence that both combined oral contraceptives and progestin-only contraceptives may increase genital tract HIV shedding; furthermore, oral contraceptives have been associated with increased cervical ectopy, which has also been linked with genital tract HIV shedding. Similarly, ectopy or other epithelial changes secondary to hormonal contraception or associated effects on immune response may increase susceptibility to HIV, and animal studies have suggested a link between progesterone implants and vulnerability to simian immunodeficiency virus (Mostad, 1998; Plummer, 1998). Data from epidemiologic studies are conflicting and inconclusive regarding the relationship of these methods of contraception and HIV transmission (Martin, 1998; Stephenson, 1998; Kiddugavu, 2003; Wang, 1999; Kapiga, 1998). At the current time, given their effectiveness, overall safety, and ease of use, hormonal methods of contraception remain an appropriate option for HIV-infected or at-risk women. These women should be advised that these contraceptives do not protect against HIV transmission and consistent condom use should be emphasized.
Use of the intrauterine device (IUD) has been accompanied by concerns about a potential increased risk for HIV susceptibility. However, a recent large prospective cohort study of almost 2500 HIV-uninfected women found no association between IUD use and HIV transmission; there was also no increased risk associated with increasing duration of use (Kapiga, 1998). Furthermore, another study from Kenya found no increase in overall complications or infection-related complications in HIV-positive IUD users as compared to HIV-negative IUD users and complications did not differ by CD4 count (Morrison, 2001). Use of the IUD was not associated with increased rate of cervical HIV shedding 4 months after insertion over baseline pre-insertion shedding rates (Richardson, 1999). However, risk of pelvic inflammatory disease is increased in IUD users who are at increased risk for acquiring other sexually transmitted infections (STIs) and a recent study found an association between IUD use and bacterial vaginosis, also a risk factor for PID (Joesoef, 2001). Furthermore, copper IUDs are associated with increased menstrual flow and duration, possibly contributing to transmission risk and anemia in HIV-positive women. The IUD should be used cautiously in the setting of HIV infection.

Spermicides have in vitro activity against HIV; however, standard spermicidal doses of nonoxynol-9 (N-9) have been associated with an increase in irritation, colposcopic and histologic evidence of inflammation, and decreased numbers of vaginal lactobacilli in N-9 users, compared with placebo recipients (Stafford, 1998). In a randomized placebo-controlled clinical trial of N-9 conducted among commercial sex workers with high rates of sexual activity, N-9 did not protect against HIV infection, resulted in increased vaginal lesions, and possibly caused increased transmission (Richardson, 2002). Although these adverse effects might not occur with less frequent use, given current evidence, spermicides containing N-9 should not be recommended as an effective means of HIV prevention. A meta-analysis of randomized controlled trials using N-9 also found no evidence of protection against HIV acquisition (Wilkinson, 2002) and N-9 appears to offer no protection against sexually transmitted infections such as gonorrhea or chlamydia (WHO, 2002).

Condoms — used consistently — reduce HIV transmission risk by 80% and provide the best known protection against sexual transmission of HIV. They should be emphasized for all HIV-infected and at-risk women to decrease risk of HIV transmission/acquisition and transmission/acquisition of other STIs. Other barrier contraceptive methods provide limited STI protection and have not been shown to offer significant protection against HIV transmission.

Because male and female condoms are used for both prevention of infection and prevention of pregnancy, these two separate issues should be distinguished when counseling patients. There is some evidence that condom use is less likely in HIV-infected women using other methods of contraception. Condom use should be reinforced for HIV-positive or at-risk women when prevention of pregnancy is not a concern: postmenopausal
women, during pregnancy, despite infertility, and with the use of other methods of contraception. As with use of contraception in general, use of condoms for HIV prevention is related to education, relationship to sexual partner, and chaos in life. There is some indication that use of HAART and decrease in viral load may lead to drop-off in condom use.

**IV. PREGNANCY TESTING**

Indications for pregnancy testing in currently or recently sexually active women:

- missed menses (unless on Norplant or Depo-Provera)
- irregular bleeding (unless on Norplant or Depo-Provera)
- new onset of irregular bleeding after prolonged amenorrhea on Norplant/Depo-Provera
- new onset pelvic pain
- enlarged uterus or adnexal mass on exam
- consider before instituting new therapies

Pregnancy tests are performed on blood or urine and may be qualitative (positive/negative) or quantitative. Quantitative tests are useful in early pregnancy when ectopic pregnancy or abnormal intrauterine pregnancy (e.g., missed abortion) is suspected. Several qualitative urine pregnancy tests are available over the counter. Most pregnancy tests in current use are positive before the first missed menses with normal intrauterine pregnancy. Table 7-3 lists types of available pregnancy tests and their sensitivity.

<table>
<thead>
<tr>
<th>Table 7-3: Pregnancy Tests</th>
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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Radioimmunoassay - blood</td>
</tr>
<tr>
<td>Enzyme immunoassay - blood - urine</td>
</tr>
<tr>
<td>Antibody agglutination inhibition - urine</td>
</tr>
</tbody>
</table>

**V. HIV AND FERTILITY**

Recent studies in Africa, as well as in developed countries, have suggested that HIV may have an adverse effect on fertility in both symptomatic and asymptomatic women (Desgrees, 1999; L.M. Lee, 2000; Zaba, 1998). A cross-sectional study from Uganda found likelihood of pregnancy lower in HIV-positive women compared with HIV-negative women and lowest
in women who were symptomatic from HIV or were coinfected with syphilis. A prospective study in the same population found that pregnancy rates were lower and pregnancy loss was more common in HIV-infected women (Gray, 1998). There are longer intervals between births for HIV-positive women compared to HIV-negative women (Glynn, 2000) and higher HIV viral loads have been associated with longer times to achieve pregnancy in women trying to conceive (Nguyen, 2003). In addition, both advanced disease stage and HIV-related therapies may be associated with abnormal sperm counts in HIV-infected men and menstrual dysfunction in HIV-infected women.

VI. EFFECTS OF PREGNANCY ON HIV INFECTION

A. CD4 COUNT AND HIV RNA LEVELS IN PREGNANCY

In both HIV-positive and HIV-negative women the response of CD4 cell counts to pregnancy is variable (Tuomala, 1997). Many studies have suggested that there is a decline in absolute CD4 cell counts in pregnancy, which return to baseline at the end of pregnancy or during the postpartum period. The decline in CD4 count is thought secondary to hemodilution; on the other hand, percentage of CD4 cells remains relatively stable. Therefore, percentage, rather than absolute number, may be a more accurate measure of immune function for HIV-infected pregnant women (Brettle, 1995; European Collaborative Study and the Swiss HIV Pregnancy Cohort, 1997; Miotti, 1992). When comparing changes in CD4 count/percentage over time, there is no difference between HIV-positive pregnant and nonpregnant women (O'Sullivan, 1995), suggesting that pregnancy does not accelerate decline in CD4 cells. HIV RNA levels (viral load) remain relatively stable throughout pregnancy in the absence of treatment (Burns, 1998). However, recent data suggest that HIV-RNA levels increase during the postpartum period regardless of ARV treatment (although use of HAART appears to blunt the effect), possibly due to immune activation associated with hormonal changes or to unmasking of a pregnancy-related viral load suppression. The implications for risk of transmission and treatment recommendations in the early postpartum period are unclear (Cao, 1997; Truong, 2003; Watts, 2003). The increase in viral load postpartum does not appear to reflect a long-lasting effect of pregnancy on viral load (Minkoff, 2003).

B. CLINICAL COURSE OF HIV IN PREGNANCY

Most studies to date examining the impact of pregnancy on HIV disease have been small but have not shown significant differences in HIV progression or survival between pregnant women and nonpregnant women with HIV infection. A recent meta-analysis of seven prospective cohort studies found no overall significant differences in death, HIV disease progression, progression to an AIDS-defining illness, or fall in CD4 count to below 200/mm³ between cases and controls (French,
A subsequently reported prospective study of 331 women with known dates of seroconversion were followed for a median of 5.5 years; during this time 69 women were pregnant. There were no differences in progression between those who were and were not pregnant during follow-up (Alliegro, 1997). In addition, a long-term observational study showed no difference in viral load, CD4, or clinical disease progression in women with repeat pregnancy, compared to those with only one pregnancy (Minkoff, 2003).

VII. EFFECT OF HIV ON PREGNANCY COURSE AND OUTCOME

Adverse pregnancy outcomes may occur secondary to underlying disease processes (or their treatment), as well as for unknown reasons. Approximately 10% of U.S. pregnancies end prematurely, and preterm birth is the leading cause of perinatal morbidity and mortality. Data have accumulated that HIV, especially when more advanced, may result in increases in certain pregnancy complications. However, results of studies are conflicting. Some studies suggest that HIV-infected women have an increase in other risk factors for adverse pregnancy outcome (such as smoking, drug use, poor prenatal care) and if these risk factors are controlled for, there is no independent effect of HIV on adverse outcomes (Lambert, 2000). Furthermore, concerns have been raised that antiretroviral treatment itself may increase some adverse outcomes in pregnancy (see discussion under Antiretroviral Treatment). A recent study of 497 HIV-infected pregnant women enrolled in a perinatal clinical trial found that risk factors for adverse pregnancy outcomes (preterm birth, low birth weight, and intrauterine growth retardation) in antiretroviral-treated women are similar to those reported for uninfected women (Lambert, 2000). Table 7-4 summarizes the relationship between common pregnancy-related complications and HIV (Brocklehurst, 1998a; D’Ubaldo, 1998; van Bentham, 2000; Ngweshemi, 2003; Dreyfuss, 2003; Coley, 2001; Ladner, 1998).

Both HIV and pregnancy may affect the natural history, presentation, treatment, or significance of certain infections, and these, in turn, may be associated with pregnancy complications or perinatal infection.

A. VULVOVAGINAL CANDIDIASIS

Pregnancy is associated with both increased rates of colonization and an increase in symptomatic infections with species of *Candida*. HIV infection is also associated with an increase in colonization and possible increased infection rates, especially with declining immune function (Burns, 1997; Cu-Uvin, 1999; Duerr, 1997; Schuman, 1998; Spinillo, 1994). Therefore, pregnant women with HIV infection may be particularly susceptible to yeast infections. Only topical azole agents should be used during pregnancy and should be given for at least 7 days. Prophylactic topical therapy should be considered during courses of systemic, especially broad-spectrum, antibiotics.
Table 7-4: Adverse Pregnancy Outcomes and Relationship to Untreated HIV Infection

<table>
<thead>
<tr>
<th>Adverse Pregnancy Outcome</th>
<th>Relationship to HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion</td>
<td>evidence of possible increased risk</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>evidence of increased risk in developing countries</td>
</tr>
<tr>
<td>Perinatal/infant mortality</td>
<td>evidence of increased risk in developing countries</td>
</tr>
<tr>
<td>Intrauterine growth restriction</td>
<td>evidence of possible increased risk</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g)</td>
<td>evidence of possible increased risk, especially with more advanced disease</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>evidence of possible increased risk, especially with more advanced disease</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>no data</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>no data</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>no data</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>no data</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>most recent studies do not suggest an increased risk in clinical or histologic chorioamnionitis; however, evidence of possible increased risk in developing countries</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>no data</td>
</tr>
<tr>
<td>Group B strep infection</td>
<td>no data</td>
</tr>
<tr>
<td>Fetal malformation</td>
<td>no evidence of increased risk</td>
</tr>
</tbody>
</table>

B. BACTERIAL VAGINOSIS

Bacterial vaginosis (BV) has been associated with several adverse pregnancy outcomes, including preterm labor and birth, premature rupture of membranes, low-birth-weight infants, chorioamnionitis and amniotic fluid infection, postpartum and postabortal endometritis, and perinatal HIV transmission. HIV infection has been associated with increased prevalence and persistence of BV, and prevalence, persistence, and severity increase with lower CD4 cell counts (Jamieson, 2001). If BV is diagnosed during pregnancy, preferred therapies are metronidazole 250 mg po tid x 7 days or clindamycin 300 mg po bid x 7 days, since only oral agents have been shown to reduce preterm births in women with BV (Hauth, 1995; McGregor, 1995; Morales, 1994). Because BV is more common in the setting of HIV, and because both BV and HIV have been linked to increased risk of preterm birth, pregnant women with HIV should be regularly asked about signs or symptoms of vaginal infection and, if present, evaluated for possible BV. Infection should be treated if identified. Currently, there are insufficient data to suggest that screening for and treating BV during pregnancy in the general population reduces the overall rate of preterm birth (Berg, 2001). A recent meta-analysis (Caro-Paton, 1997) found no relationship between metronidazole exposure during the first trimester of pregnancy and birth defects.
C. GENITAL HERPES SIMPLEX

Primary herpes simplex virus (HSV) infection during pregnancy has been associated with spontaneous abortion and prematurity. Congenital or intrauterine infection is uncommon but maternal HSV shedding at delivery is associated with neonatal HSV infection, which is almost always symptomatic (including skin, eye, and central nervous system involvement, or disseminated infection involving multiple organ systems) and frequently lethal. The risk of neonatal herpes is greatest with primary HSV, especially when acquired close to delivery (30–50%), whereas only 0–3% of neonates become infected with recurrent maternal disease at delivery; however, because recurrent HSV is more common than primary disease, most neonatal infections are associated with recurrent HSV. Two thirds or more of mothers with infected infants are asymptomatic during pregnancy; only one third have a history of HSV in themselves or their sexual partner. Because most neonatal infection occurs during vaginal delivery, if genital lesions or prodromal symptoms are present at the time of labor or membrane rupture, cesarean section should be performed. Cesarean section is not indicated for recurrent HSV distant from the genital tract (e.g., thigh, buttocks) (ACOG, 1999b).

HIV infection, particularly with evolving immune compromise and higher plasma HIV viral load (Wright, 2003), is associated with increased HSV shedding and more frequent, severe, and prolonged episodes of genital or perianal herpes (Augenbraun, 1995). Higher doses and/or longer courses of antiviral agents may be required and suppressive therapy is often beneficial in nonpregnant individuals. Infection with HSV-2 is common among pregnant HIV-infected women and reactivation of herpes in labor occurs more frequently in the setting of HIV infection (Hitti, 1997).

Treatment of symptomatic HSV infections and suppressive therapy for frequent recurrences should be offered during pregnancy to HIV-infected women (USPHS/IDSA, 2003). The risk for herpes is high in infants of women who acquire genital HSV in late pregnancy and such women should be managed in consultation with an expert. The use of oral acyclovir prophylactically in late pregnancy has been shown to suppress genital HSV outbreaks and HSV shedding in HIV- women and may reduce the need for cesarean section for recurrent HSV (Brocklehurst, 1998a; Watts, 2001; Scott, 2001); however, this strategy has not been evaluated in HIV+ women, who are more likely to have HSV-2 antibodies and to have both symptomatic and asymptomatic reactivation of genital HSV. Therefore, use of acyclovir for the purpose of reducing the need for cesarean section in all HIV+ women is not recommended (USPHS/IDSA, 2003).

Acyclovir is the drug of choice for HSV therapy during pregnancy and there is no current evidence for increased risk for major birth defects or other adverse pregnancy outcomes (Reiff-Eldridge, 2000). While experience with valacyclovir is more limited, its safety profile is expected to be similar to acyclovir, since it is the prodrug of acyclovir. Experience with use of famciclovir in pregnancy is limited and exposures to this
drug should be reported to the Famciclovir Registry at 1-888-669-6682. Documented HSV infections during pregnancy which do not respond to these agents should be managed with expert consultation.

Prevention of neonatal herpes should also emphasize prevention of acquisition of herpes in susceptible women in pregnancy. If her sexual partner has a history of oral or genital HSV infection, serologic evidence of HSV infection, or infection status is unknown, the pregnant woman should be counseled to avoid unprotected genital and oral sexual contact during pregnancy. Type-specific HSV serology may be useful to identify the pregnant woman at risk for HSV and to guide counseling, especially if her sexual partner has HSV infection. At the onset of labor, all women should be questioned carefully about HSV symptoms, including prodromal symptoms, and all women should be examined carefully for herpetic lesions, in order to make judicious decisions about the use of cesarean section.

D. HUMAN PAPILLOMAVIRUS

Genital warts may be more frequently seen and often enlarge and become friable during pregnancy and in some cases may mechanically obstruct the vaginal canal in labor; perinatal exposure can result in laryngeal papillomatosis in infants and children, although a recent prospective study suggests that the risk of perinatal transmission of human papillomavirus (HPV) is low (Watts, 1998). Both HPV infection in general and genital warts are more common in HIV-infected individuals, correlated with level of immunosuppression. Imiquimod, podophyllin, and podofilox should not be used in pregnancy. In women with large volume or bulk of genital warts treatment in late pregnancy with laser, excision, or cavitronic ultrasonic aspiration may be considered. Cesarean section is not currently recommended to prevent neonatal exposure to HPV, although in rare instances cesarean section may be indicated when extensive lesions obstruct the vagina. Pregnant women with abnormal Pap smears should undergo colposcopy and cervical biopsy, if indicated; increased bleeding may occur with biopsy during pregnancy. Endocervical curettage should not be performed during pregnancy. Pap smear should be repeated with or without colposcopy at 34–36 weeks gestation in women with initial abnormal Pap smear to rule out progression of dysplasia. Women with preinvasive cervical lesions can deliver vaginally, if otherwise appropriate; women with suspected invasive cervical cancer should be referred to a gynecologic oncologist.

E. SYPHILIS

Syphilis is more prevalent in HIV-infected populations and HIV may affect clinical manifestations, serologic response, or response to treatment for syphilis. Pregnancy does not alter the clinical manifestations of syphilis but untreated primary or secondary syphilis during pregnancy affects essentially all fetuses, with 50% rate of prematurity, stillbirth, or neonatal death (Radolf, 1999). Even with later stages of syphilis, there
is a significant increase in adverse pregnancy outcomes, although the frequency and severity of fetal disease decrease with longer duration of untreated maternal infection. Manifestations of congenital syphilis in the newborn include mucocutaneous lesions, hepatosplenomegaly, osteochondritis/periostitis, jaundice, petechiae/purpura, and meningitis.

Congenital syphilis can generally be prevented by identification and appropriate treatment of syphilis during pregnancy. All pregnant women should have serologic testing for syphilis at the beginning of prenatal care and testing should be repeated at 28 wk gestation and at delivery, particularly in women who remain at risk for infection. Any woman with stillbirth after 20 wk gestation should be tested for syphilis. Development of neurologic symptoms mandates evaluation for possible neurosyphilis. Treatment of syphilis during pregnancy should be the penicillin regimen appropriate for the stage of syphilis, although a second injection one week after the first in cases of primary, secondary, or early latent syphilis should be considered, because of concerns about effectiveness of standard therapy in pregnant women and in the setting of HIV infection (USPHS/IDSA, 2003). HIV-positive women with late latent syphilis or syphilis of unknown duration should have cerebrospinal fluid examination before treatment. If there is concern for neurosyphilis, treatment should be with 7–10 days of IV penicillin (CDC, 2002).

Ultrasound evidence of hydrops or hepatosplenomegaly suggesting fetal syphilis increases risk for treatment failure and should be managed with expert consultation. Treatment in the second half of pregnancy is associated with the Jarisch-Herxheimer reaction in up to 40% of cases, with resulting premature labor and/or fetal distress (Myles, 1998); fetal and contraction monitoring for 24 hrs should be considered, especially in the setting of abnormal ultrasound findings, or, alternatively, patients should be advised to seek immediate attention after treatment if contractions or decrease in fetal movements occur (USPHS/IDSA, 2003). Pregnant women with a history of penicillin allergy should be skin tested and, if necessary, desensitized and treated with penicillin, because there are no proven effective alternatives to penicillin for treatment and prevention of congenital syphilis. Even with appropriate treatment of the pregnant woman with syphilis, fetal infection may still occur and neonates should be carefully evaluated for evidence of congenital infection.

Clinical and serologic follow-up should be performed in the third trimester and at delivery and at 3, 6, 9, 12, and 24 mo after treatment. Treatment failure should be managed with cerebrospinal fluid examination and retreatment. Some experts recommend monthly serologic testing after treatment after pregnancy with retreatment if there is a rise in titer.

F. CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is the most common cause of congenital viral infection in the United States: 2–2.2% of liveborn infants acquire this infection perinatally (ACOG, 1993a). Most maternal CMV infections are asymptomatic but may cause a mononucleosis-like illness. Transmission
can occur sexually or with injection drug use, because CMV has been recovered from virtually all body fluids. Transmission can also occur with oral contact with infected secretions (i.e. from children). Transmission of CMV from mother to infant may occur in utero (1–2% of infants born to women with CMV prior to pregnancy and up to 50% of infants born to women with primary infection during pregnancy), intrapartum (25–50% of exposed infants), and through breastfeeding (40–60% of exposed infants) (USPHS/IDSA, 2003). In general, it is in utero infection that results in significant neonatal/infant effects. Ninety percent of infected infants are asymptomatic at birth, but symptomatic infection is more likely with maternal infection acquired early in pregnancy. Even if asymptomatic, many infected infants subsequently develop deafness, mental retardation, or delayed psychomotor development. More severe clinical manifestations include symmetric growth restriction, hepatosplenomegaly, chorioretinitis, microphthalmia, hydrocephaly, microcephaly, and cerebral calcifications.

In the setting of HIV infection, in utero infection was detected in 4.5% of infants, compared to 1–2% transmission noted in previous studies of CMV-seropositive HIV-negative women. By six months of age, 40% of HIV-infected infants were CMV-seropositive compared to 15% of HIV-uninfected infants born to HIV-infected mothers (Kovacs, 1999). Because symptomatic infection in the newborn is usually associated with primary CMV infection of the mother during pregnancy, and because >90% of HIV-infected pregnant women are CMV seropositive in most studies, the risk of symptomatic infection in the newborn is low (Kovacs, 1999; Mussi-Pinhata, 1998; Quinn, 1987), and treatment of asymptomatic maternal CMV infection in order to prevent infant infection is not indicated (USPHS/IDSA, 2003). There have been some reports that cotransmission of HIV and CMV may be related to more rapid HIV progression (Kovacs, 1999; Mussi-Pinhata, 1998).

Testing for antibody to CMV should be considered in pregnancy, especially if the CD4 count is <100/mm$^3$ for reasons of maternal health evaluation; however, seropositivity is common and does not preclude viral shedding during pregnancy and perinatal transmission. Methods to reduce risk of exposure to CMV include safer sexual practices, careful handwashing, and transmission of only CMV antibody-negative blood products. Primary prophylaxis is not routinely recommended; however, after CMV disease (retinal or invasive CMV disease), chronic suppression is indicated in pregnancy and should be continued with expert consultation concerning choice of agents. (See Opportunistic Infection Prophylaxis below.)

G. TOXOPLASMOSIS

Approximately one third of U.S. women have toxoplasma antibodies, reflecting prior infection. Primary infection occurs in approximately 0.1–0.5% of pregnancies and places the fetus at risk for congenital toxoplasmosis. Congenital infection is more common when infection in the mother occurs during the third trimester (59% in third trimester vs. 9% in first trimester)
but is generally more severe when occurring in the first trimester. Although
the majority of infected infants are asymptomatic at birth, most will develop
some sequelae of congenital toxoplasmosis; two thirds of infants infected
after maternal first trimester infection have severe manifestations and 5% are
stillborn or die in the perinatal period (ACOG, 1993a).

Congenital toxoplasmosis may affect all systems, but the most common
findings are chorioretinitis, microcephaly, hydrocephaly, and cerebral
calcifications.

Transmission of toxoplasmosis from a mother with antibody evidence of
prior infection can occur in the setting of HIV infection (as opposed to
in HIV-uninfected women), but does not seem to be common (0–3.7% in
two studies), although there are limited data in more immunosuppressed
mothers (European Collaborative Study and Research Network in
Congenital Toxoplasmosis, 1996; Minkoff, 1997b).

Testing for IgG antibodies to toxoplasma is recommended for all HIV-
infected individuals soon after the diagnosis of HIV is made and should
be considered as part of prenatal testing in HIV-positive pregnant women.
Primary prophylaxis and prophylaxis against recurrent disease in pregnancy
are discussed below (See Opportunistic Infection Prophylaxis). Pregnant
women with symptoms including fever, chills, malaise, lymphadenopathy,
myalgias, and headache should be evaluated serologically for possible
primary toxoplasmic infection. Evidence of primary infection or active
toxoplasmosis should be evaluated and managed with expert consultation.
Detailed ultrasound examination of the fetus should be performed in this
situation to look for evidence of congenital toxoplasmosis. Infants born to
women infected with HIV and seropositive for toxoplasma should also be
evaluated for evidence of congenital toxoplasmosis if suspected by clinical
presentation of the infant.

To prevent exposure to toxoplasmosis, pregnant women should be
counseled to avoid raw or undercooked meat, wash hands after contact
with raw meat or with soil, and wash fruits and vegetables well before
eating them raw. Cats should preferably be kept inside and fed only
canned or dried commercial food; litter boxes should be changed daily,
preferably by someone who is not HIV-positive or pregnant.

H. HEPATITIS B

Approximately 300,000 new cases of hepatitis B virus (HBV) infection
occur each year and more than 1 million Americans are chronic
carriers. Most patients who become infected have complete resolution
of infection and develop protective levels of antibody (anti-HBs). Chronic
HBV infection develops in 1–6% of persons who are infected
as adults; they are chronically HBsAg+ and are at risk of chronic liver
disease, including cirrhosis and hepatocellular carcinoma (CDC, 1991).
The presence of HBeAg indicates active viral replication and increased
infectivity. HBV is transmitted parenterally, sexually, perinatally, and
through household or institutional contact. Approximately one quarter of
regular sexual contacts of infected individuals will become seropositive and sexual transmission accounts for 30–60% of new infections. Perinatal transmission, usually with intrapartum contact with maternal blood and genital secretions, occurs in 10–20% of women who are HBsAg+, but increases to approximately 90% if the mother is also HBeAg+. Chronic HBV infection develops in about 90% of infected newborns, who are at high risk of chronic liver disease (ACOG, 1998).

All pregnant women should be screened for HBsAg. Symptomatic acute HBV infection should be treated supportively, with special attention to maintaining blood glucose levels and clotting function. Risk of preterm labor and birth may be increased with acute HBV infection in pregnancy. Treatment of chronic HBV infection is generally not indicated in pregnancy. Antiretroviral therapy containing lamivudine (3TC) may potentially decrease risk of perinatal HBV transmission in women with high HBV DNA levels, although this has not been examined in the setting of HIV infection.

Infants born to women who are HBsAg+ should receive hepatitis B immune globulin and initiate HBV vaccination within 12 hr after birth. HBV vaccine can be safely administered during pregnancy and should be considered in women who are high risk (injection drug use, STIs, multiple sexual partners, household or sexual contact of HBV carrier) and are anti-HBs- or anti-HBc-negative, indicating susceptibility. Some experts argue for more liberal use of vaccination in HIV-infected individuals, because HBV infection in the setting of HIV infection increases risk for chronic HBV infection. HIV can impair response to HBV vaccine; therefore, testing for hepatitis B surface antibody is recommended 1–2 mo after the third vaccine dose. Full revaccination should be considered for those who are nonresponders (ACOG, 1998; Bartlett, 1999).

I. HEPATITIS C

Hepatitis C virus (HCV) infection is primarily transmitted by injection drug use, but may also be transmitted sexually. Approximately 50% of those with acute HCV infection develop biochemical evidence of chronic liver disease, and 20% or more ultimately have chronic active hepatitis or cirrhosis and are at risk for hepatocellular carcinoma (CDC, 1998). Coinfection with HIV increases the risk and speeds the rate of development of progressive liver disease (Graham, 2001; Soto, 1997). Cofactors influencing disease progression include age, low CD4 cell count, and history of alcoholism. There is evidence that HCV infection may also hasten progression of HIV infection (Piroth, 2000).

Women newly diagnosed with HIV in pregnancy should have testing for antibody to HCV by enzyme immunoassay; positive results should be confirmed with HCV polymerase chain reaction (PCR) and liver function abnormalities should be documented. Negative serologic screening associated with history of risk factors for HCV transmission or unexplained liver function abnormalities is an indication for performance of HCV viral RNA testing, especially with low CD4 cell counts. Studies
have shown that serum transaminases tend to decrease during pregnancy in HCV-infected women, but may rise transiently postpartum, while HCV-RNA levels tend to increase during pregnancy (Gervais, 2000; Conte, 2000). Treatment of HCV infection aims to eradicate infection and prevent the long-term complications of progressive liver disease and generally includes combination therapy with interferon plus ribavirin. However, treatment is generally not recommended during pregnancy (USPHS/IDSA, 2003) and evaluation for treatment, including liver biopsy, can be delayed until three months or more after delivery to allow pregnancy-related changes in disease activity to resolve. Ribavirin is teratogenic at low doses in multiple animal species and both women and men of childbearing potential receiving ribavirin should be counseled regarding the need for effective contraception during and for six months after completion of therapy.

Women coinfected with HIV and HCV should avoid alcohol, both during and after pregnancy, because alcohol use increases risk of cirrhosis. Vaccination against hepatitis A, if the woman is anti-HAV-negative, is recommended because the risk for fulminant hepatitis associated with hepatitis A is increased in HCV-infected individuals; this vaccination may be given safely during pregnancy (ACOG, 1998; Bartlett, 1999).

The risk of perinatal transmission of HCV is significantly higher among HIV-infected compared to HIV-uninfected women and has been reported to be approximately 22% or an increase in relative risk of 1.7–7.5-fold (European Paediatric Hepatitis C Virus Network, 2001). This may be related to higher HCV RNA levels seen in the setting of HIV infection, since perinatal transmission in both HIV-infected and –uninfected women is related to higher plasma HCV RNA levels (Yeung, 2001), although HCV transmission is highest with higher HCV RNA levels in the setting of HIV (Thomas, 1998). Furthermore, maternal coinfection with HIV and HCV may also increase risk for perinatal HIV transmission (Hershow, 1997). Scheduled cesarean section may reduce the risk of HCV transmission among HIV-coinfected women; in one large study scheduled C-section was associated with a reduction in transmission of almost two-thirds compared to other modes of delivery, although concomitant mother-to-child transmission of HIV was not controlled for (European Paediatric Hepatitis C Virus Network, 2001). Perinatal HCV transmission may be more likely in HIV-infected infants born to dually infected mothers (Papaevangelou, 1998).

VIII. PERINATAL TRANSMISSION

The baseline rate of perinatal HIV transmission without prophylactic therapy is approximately 25%. The timing of transmission is a critical factor impacting on development of preventive interventions. There is evidence that transmission can occur during the course of pregnancy, around the time of labor and delivery, or postpartum through breastfeeding; however, two thirds to three quarters of transmission appears to occur during or close to the intrapartum period, particularly in non-breast-feeding populations (Mofenson, 1997).
POTENTIAL VARIABLES IN TRANSMISSION

A. HIV-RELATED FACTORS

- **Plasma HIV RNA level**: HIV RNA levels correlate with risk of transmission in both antiretroviral-treated and untreated women. The risk of perinatal transmission appears to be extremely low in women with undetectable plasma viral loads, but transmission has been reported at all levels of maternal HIV RNA. There is no upper limit of HIV RNA above which perinatal transmission always occurs (Garcia, 1999; Mofenson, 1999; Shaffer, 1999; Cooper, 2002).

- **Strain variation (genotype)**: Each HIV-infected individual's viral pool is composed of a variety of HIV quasispecies. One recent study found that in utero transmission was associated with transmission of major maternal viral variants, whereas intrapartum transmission was associated with transmission of minor maternal viral variants, suggesting that different selective pressures may be involved in determining the pattern of viral strain transmission depending on timing of transmission (Dickover, 2000). HIV in vaginal secretions can be derived from local expression and may have significant genotypic differences from plasma virus, with possible implications for perinatal transmission (Subbarao, 1998).

- **Biologic growth characteristics (phenotype)**: Fetal blood mononuclear cells may be more susceptible to macrophage-tropic, non-syncytium-inducing HIV phenotypes and this may influence mother-to-infant HIV transmission (Palasanthiran, 1994; Reinhardt, 1995).

- **Genital tract viral load**: There is general correlation between plasma and genital tract viral load but discordance has been reported and may help explain some cases of transmission with undetectable plasma HIV RNA. In the Thai short-course zidovudine (ZDV) clinical trial, both plasma and cervicovaginal HIV RNA levels were suppressed by ZDV treatment and both were independently correlated with transmission (Chuachoowong, 2000). The female genital tract can also be a reservoir for virus with a different drug-resistance pattern than that observed in plasma (Fang, 1998). The use of HAART has been associated with undetectable HIV RNA levels in the genital tract and viral suppression in the genital tract may occur rapidly after initiating therapy (Cu-Uvin, 2000). It is possible that intra-cellular HIV in the genital tract can lead to transmission, even in the presence of antiretroviral treatment (Tuomala, 2003).

- **Antiretroviral resistance**: Special concerns have been raised about a possible increased risk for mother-to-child transmission associated with the potential development of antiretroviral resistance related to the use of single agents (i.e., ZDV or nevirapine) or dual nucleosides during pregnancy for perinatal prophylaxis. These regimens do not totally suppress viral replication, a common denominator in the development
of antiretroviral drug resistance, since the process of reverse transcription necessary for viral replication is mutation prone. In addition, the increasing prevalence of resistance in both ARV treatment-experienced and newly-infected and treatment-naïve individuals (implying transmission of resistant strains) makes the relationship between drug resistance and perinatal transmission even more critical to understand.

The presence of resistance mutations has been described in pregnant women and mother-to-child transmission of resistant virus has been reported, although it appears to be rare (Frenkel 1995; Johnson 2001). Studies to date of resistance mutations in the setting of ZDV monotherapy during pregnancy have shown increasing prevalence of ZDV mutations over time and an association with length of drug exposure and more advanced disease (Eastman, 1998; Welles, 2000; Sitnitskaya, 2001; Palumbo, 1999). Most studies, including PACTG 076, PACTG 185, Swiss cohort, or the PACTS, have not shown an increased risk of perinatal transmission associated with the detection of ZDV or other resistance mutations (Eastman, 1998; Kully, 1999; Palumbo 1999; Mofenson, 2002). However, in a recent Women and Infants Transmission Study (WITS) substudy, 25% of 142 maternal isolates from women receiving ZDV in pregnancy had at least one ZDV-associated resistance mutation and, on multivariate analysis, the presence of resistance mutations was independently associated with perinatal transmission (Welles, 2000). It has been pointed out that the characteristics of women in this cohort (mean CD4 count at delivery 315 cells/mL, usually did not receive ZDV in labor or for the neonate) and the factors associated with development of resistance (use of ZDV prior to pregnancy, higher HIV-RNA level, and lower CD4 count) illustrate the importance of current USPHS guidelines (discussed under Antiretroviral Therapy below) which advise the use of HAART in these circumstances, both for the woman’s health and for prophylaxis against perinatal transmission. There is also some evidence that ARV-resistant virus may have decreased fitness for transmission; in the WITS substudy, when a transmitting mother had a mixed viral population of wild-type and low-level resistant virus, only the wild-type virus was found in the infant, suggesting that virus with low-level ZDV resistance may be less transmissible (Colgrove, 1998).

Selection of nevirapine-resistant virus has also been detected in women who received a single dose of nevirapine for prevention of perinatal transmission. In the HIVNET 012 clinical trial, ARV-naïve Ugandan women received one dose of nevirapine during labor and in 111 women who had detectable viral replication, 21 (19%) had genotypic mutations associated with nevirapine resistance at 6 weeks (Eshleman, 2001). However, maternal drug resistance was not associated with increased risk of perinatal transmission: rates of resistance were similar among mothers whose children were or were not infected.
• **CD4 cell count:** Lower CD4 count or decreased CD4:CD8 ratio have been consistently associated with increased risk of transmission.

• **Maternal immune response:** Studies have been inconsistent when evaluating the role of maternal antibodies, including anti-gp120, anti-gp41, anti-p24, and autologous neutralizing antibody titers. ß-chemokine and cytokine responses may affect risk of transmission (Pitt, 2000; Rich, 1998).

### B. MATERNAL/OBSTETRIC FACTORS

• **Clinical stage:** Maternal symptomatic disease or AIDS-defining illness are consistently associated with higher risk for transmission. Women with primary HIV infection in pregnancy, at which time plasma viremia is high, are also at increased risk for transmission (Nesheim, 1996).

• **STIs/other coinfections:** STIs have been shown to increase genital tract HIV shedding and also increase plasma viremia (Plummer, 1998), both of which may increase risk for perinatal transmission. STIs (Mandelbrot, 1996), syphilis (M.J. Lee, 1998), bacterial vaginosis (Taha, 1998), and placental malaria have been associated with increased risk for vertical transmission, as have increased levels of genital tract inflammatory cells (Panther, 2000; Chandramohan, 1998).

• **Vitamin A deficiency:** Vitamin A deficiency has been associated with increased risk of perinatal HIV transmission and increased genital tract HIV shedding (Nimmagadda, 1998). However, a recent randomized trial of vitamin A supplementation in South Africa found no overall reduction in mother-to-child transmission of HIV, although vitamin A recipients were less likely to have a preterm delivery, and in preterm deliveries, those infants assigned to the vitamin A group were less likely to be infected (Coutsoudis, 1999). A controlled clinical trial in Malawi of vitamin A supplementation combined with iron and folate vs iron and folate alone also found no effect on HIV perinatal transmission (Kumwenda 2002), although vitamin A did improve pregnancy outcome (increased birth weight and decreased infant anemia). In another randomized trial of vitamin A or multivitamins (B, C, E) from 20 weeks gestation through completion of lactation, vitamin A was actually associated with increased risk of HIV MTCT. Multivitamin supplementation was associated with reduced child mortality and MTCT through breastfeeding among women with immunologic or nutritional compromise (Fawzi, 2002).

• **Substance abuse:** Illicit drug use during pregnancy has been associated with increased risk for perinatal transmission (Landesman, 1996; Lyman, 1993; Rodriguez, 1996).
• **Cigarette smoking:** Cigarette smoking has been associated with an increased risk of perinatal transmission (Burns, 1994; Turner, 1997).

• **Antiretroviral therapy:** Monotherapy with ZDV or with nevirapine, as well as dual nucleoside agents, have demonstrated effectiveness in reducing perinatal transmission in randomized clinical trials (see page 284 Table 7-8). In the PACTG 076 study (ZDV given antepartum/intrapartum/neonatal), reduction in plasma viral load accounted for only 17% of ZDV's effectiveness, suggesting pre- and/or post-exposure prophylaxis as other possible mechanisms of action (Sperling, 1996). Although there are no completed clinical trials examining effectiveness of HAART regimens in reducing perinatal transmission, prospective cohort data from the WITS found that the protective effect of antiretroviral therapy increased with the complexity and duration of the regimen, and the use of HAART was associated with the lowest rates of transmission, 1.2% of 250 women (Cooper, 2002). Preliminary results from the PACTG 367 study, a combined retrospective and prospective chart analysis of over 2000 HIV-infected pregnant women at 67 U.S. clinical sites, found that in all subgroups of viral load, lowest transmission rates were seen with multiagent ARV therapy (Shapiro, 2004), both dual therapy and HAART.

• **Sexual behavior:** Unprotected sex with multiple partners has been associated with increased risk for perinatal transmission (Bultery, 1997).

• **Preterm delivery:** Delivery at preterm gestational age has been associated with increased risk for perinatal transmission (Kuhn, 1997, 1999).

• **Duration of membrane rupture:** A recent metaanalysis from 15 prospective cohort studies, including almost 5000 deliveries, examined the role of duration of ruptured membranes in perinatal transmission (International Perinatal HIV Group, 2001). The likelihood of transmission increased linearly with increasing duration of ruptured membranes, with a 2% increase in risk for each hour increment. Women with clinical AIDS had the most pronounced increase in risk, with a 31% probability of vertical transmission after 24 hr of ruptured membranes. This study did not include women receiving HAART and did not control for viral load. The effect of duration of membrane rupture with very low viral loads is not clear.

• **Placental disruption-abruption, chorioamnionitis:** Clinical and histologic chorioamnionitis (Goldenberg, 1998; Mwanyumba, 2002) has been associated with increased risk of transmission. Placental abruption causing disruption of fetal-placental barrier and possible increased exposure of the fetus to maternal blood has also been suggested as a risk factor for transmission.
• **Invasive fetal monitoring:** Use of fetal scalp electrodes or fetal scalp sampling increases exposure of the fetus to maternal blood and genital secretions and may increase risk of vertical transmission (Maiques, 1999). Amnioscopy and amniocentesis increased risk in the French Perinatal Cohort (Mandelbrot, 1996).

• **Episiotomy, forceps:** Use of episiotomy or vacuum extraction or forceps may potentially increase risk of transmission by increasing exposure to maternal blood/genital secretions with trauma to maternal or neonatal tissue. On the other hand, judicious use of these techniques to shorten duration of labor or ruptured membranes with vaginal delivery may decrease likelihood of transmission.

• **Vaginal vs. cesarean delivery:** Several studies (done before routine use of viral load testing and use of combination antiretroviral therapy in pregnancy) indicate that cesarean delivery performed before the onset of labor and rupture of membranes significantly reduces the risk of perinatal HIV transmission by 55–80% (European Mode of Delivery Collaboration, 1999; International Perinatal HIV Group, 1999; Kind, 1998; Mandelbrot, 1998). Whether cesarean delivery offers any benefit when the mother is receiving HAART and/or if she has low or undetectable viral load is unknown, and cesarean section is not recommended in those circumstances (ACOG, 2000).

C. **FETAL/NEONATAL FACTORS**

Fetal/neonatal factors, including an immature immune system (particularly in the premature infant) and genetic susceptibility, as expressed by human lymphocyte antigen (HLA) genotype (Just, 1995) or CCR-5 receptor (a coreceptor for macrophage-tropic strains of HIV; a homozygous deletion in this gene confers a high degree of natural resistance to HIV sexual transmission) mutations may play a role in perinatal transmission (Kostrikis, 1999; Mangano, 2000; Philpott, 1999). A recent study from South Africa (Kuhn, 2000) found that early acquired cellular immune responses to HIV, presumably from in utero exposure, were present in over one third of 86 uninfected infants born to HIV-infected mothers. These detectable immune responses appeared to provide complete protection against subsequent HIV transmission at delivery and through breast-feeding.

D. **BREAST-FEEDING**

Overall breastfeeding appears to increase the risk of perinatal transmission by 5–20% (DeCock, 2000). In 1998 breastfeeding is estimated to have accounted for up to 50% of newly infected children globally (Fowler, 1999). Factors that have been associated with an increased risk of breast milk transmission include the following:
• Maternal factors:
  - acute HIV infection or recent seroconversion (Dunn, 1992), most likely related to high HIV viral loads
  - advanced HIV infection clinically or with low CD4 counts
  - high plasma or breast milk viral load
  - inflammatory breast conditions, such as mastitis or breast abscess
  - cracked nipples
  - vitamin A deficiency
  - colostrum

• Newborn factors:
  - Oral thrush
  - Other mucosal lesions due to trauma or infection
  - Preterm birth or low birthweight
  - Nutritional deficiencies

• Breastfeeding characteristics:
  - Timing – highest in first months, increases with longer duration of breastfeeding (Miotti, 1999)
  - Pattern of breastfeeding-mixed feeding (addition of other solids or liquids to breastmilk) associated with increased risk over exclusive breastfeeding (Coutsoudis, 2000)

A recent randomized clinical trial of breastfeeding vs. formula feeding in Kenya (Nduati, 2000) found that formula feeding prevented 44% of infant infections and was associated with a significantly improved survival.

**STRATEGIES FOR PREVENTION OF PERINATAL TRANSMISSION**

Based on the potential factors impacting perinatal HIV transmission discussed above, several basic approaches to prevention have been suggested. These include:

• Identification and treatment of modifiable risk factors

• Decreasing viral load

• Decreasing viral exposure

• Stimulation of the immune system (passive or active immunization)

Currently, most major efforts at prevention are aimed at decreasing viral load.
IX. GUIDELINES FOR CARE

A. ANTEPARTUM

HISTORY/PHYSICAL EXAMINATION

(See also Chapter IV on Primary Medical Care.)

• **HIV history:** date of diagnosis; history of HIV-related symptoms or opportunistic infections or malignancies; lowest CD4 cell count; highest and current viral load; complete antiretroviral history, including specific drugs, side effects or toxicity, length of treatment, adherence, results of resistance testing (if performed), and response to treatment

• **Pregnancy history:** previous pregnancies and outcomes, complications, mode of delivery, use of antiretroviral prophylaxis, and HIV status of other children

• **Signs or symptoms of HIV/AIDS:** (initial and follow-up evaluations) assess signs or symptoms that suggest symptomatic HIV infection or AIDS (e.g., generalized lymphadenopathy, thrush, constitutional symptoms such as fever [38.5°C] or diarrhea >1 mo, herpes zoster involving two episodes or >1 dermatome, peripheral neuropathy, wasting, dysphagia, shortness of breath, persistent mucocutaneous herpetic ulcerations, cognitive dysfunction, etc.).

• **Signs or symptoms of pregnancy-related complications:** (the initial and follow-up evaluations) elevated blood pressure, significant edema, severe headache, vaginal bleeding or leakage of fluid, intractable nausea and vomiting, dysuria, abnormal vaginal discharge, persistent abdominal or back pain or cramping, decrease in fetal movement, etc. Gingival disease has recently been identified as a risk factor for preterm labor (Hill, 1998).

• **Signs or symptoms of ARV toxicity:** (initial and follow-up evaluations) nausea/vomiting, abdominal pain, jaundice, extreme fatigue, skin rash.

  Certain symptoms of HIV disease, antiretroviral toxicity, and normal or abnormal pregnancy may overlap, resulting in possible delay in appropriate diagnosis and management.

• **Relevant family history of possible heritable diseases.**

  **LABORATORY EXAMINATION BY TRIMESTER SEE TABLE 7-5.**
<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry into Prenatal Care and Ongoing</strong></td>
<td></td>
</tr>
<tr>
<td>HIV serology</td>
<td>Unconfirmed HIV infection; + test with other techniques; always repeat in the case of a new diagnosis to rule out false+</td>
</tr>
<tr>
<td>CD4 cell count/% HIV RNA</td>
<td>Repeat every 3–4 mo or as indicated to monitor changes with ARV therapy; at milestones for therapeutic decisions, re: ARV therapy/OI prophylaxis</td>
</tr>
<tr>
<td>Viral resistance testing (genotyping)</td>
<td>Acute HIV infection, virologic failure, sub-optimal viral suppression after initiation of ARV therapy, or high likelihood of exposure to resistant virus based on community prevalence or source characteristics</td>
</tr>
<tr>
<td>CBC</td>
<td>Repeat at minimum of every trimester in women on stable ARV therapy; for changes in regimen, repeat q 2–4 wk until stable; in general, consider more frequent testing if low or receiving marrow-toxic drugs (e.g., ZDV)</td>
</tr>
<tr>
<td>Serum chemistry panel (liver enzymes, electrolytes, +/- amylase)</td>
<td>Repeat at minimum of every trimester in women on stable ARV therapy; for changes in regimen, repeat q 2–4 wk until stable. Repeat as indicated with abnormal results or use of hepatotoxic/nephrotoxic drugs</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td></td>
</tr>
<tr>
<td>Hepatitis serology: HBsAg, anti-HCV, anti-HAV</td>
<td>Order anti-HBs or anti-HBc and anti-HAV to screen for hepatitis B and A vaccine candidates. If anti-HCV+, order HCV-RNA</td>
</tr>
<tr>
<td>Rubella, Blood type and Rh, Antibody screen, Urine culture, GC/chlamydia testing, Pap smear</td>
<td>Cytobrush can be used</td>
</tr>
<tr>
<td>PPD</td>
<td>+ skin test = ≥5 mm induration; anergy testing not indicated; obtain CXR if at high risk for TB exposure</td>
</tr>
<tr>
<td>Hemoglobin electrophoresis, red blood cell indices</td>
<td>Perform in women at increased risk for hemoglobinopathies</td>
</tr>
<tr>
<td>G6PD</td>
<td>Optional — may consider screening black women or those receiving oxidant drugs (e.g., dapsone, sulfonamides)</td>
</tr>
<tr>
<td>Test</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>CMV IgG</td>
<td>Consider especially with CD4 &lt;100 mm$^3$ or in patients at low risk for CMV (non-IDU)*</td>
</tr>
<tr>
<td>Toxoplasmosis IgG</td>
<td>Screen all patients with initial HIV diagnosis; repeat with CD4 &lt;100/ mm$^3$ and not on TMP-SMZ, or with symptoms suggestive of toxoplastic encephalitis</td>
</tr>
<tr>
<td>Urine toxicology screen</td>
<td>As indicated</td>
</tr>
<tr>
<td>Serum screening for Tay-Sachs disease</td>
<td>Consider screening both partners if at increased risk (Ashkenazi Jews, French-Canadian, or Cajun descent)</td>
</tr>
<tr>
<td>Bacterial vaginosis screening</td>
<td>Consider in women at high risk for preterm labor (previous preterm birth); women with signs/symptoms of vaginitis</td>
</tr>
<tr>
<td><strong>16–20 wk</strong></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Gestational dating, anomaly screen; repeat as indicated to monitor fetal growth</td>
</tr>
<tr>
<td>Maternal serum $\alpha$-fetoprotein**</td>
<td>Voluntary; requires counseling; screening test for neural tube and abdominal wall defects; abnormal result (usually &gt;2.5 multiple of the median) requires further evaluation</td>
</tr>
<tr>
<td>Triple screen (HCG, unconjugated estriol, $\alpha$-fetoprotein)**</td>
<td>Voluntary; requires counseling; noninvasive test to determine risk of neural tube &amp; abdominal wall defects, Down syndrome, and trisomy 18</td>
</tr>
<tr>
<td><strong>24–28 wk</strong></td>
<td></td>
</tr>
<tr>
<td>CBC, Syphilis serology, Antibody screen</td>
<td></td>
</tr>
<tr>
<td>Diabetes screen</td>
<td>Glucose 1 hr after 50 g glucola — 3 hr oral GTT if abnormal; may need additional glucose monitoring in women on protease inhibitors (consider 20 wk screening and repeat at 24–28 wk if on PIs)</td>
</tr>
<tr>
<td><strong>32–36 wk</strong></td>
<td></td>
</tr>
<tr>
<td>GC/chlamydia testing</td>
<td></td>
</tr>
<tr>
<td>Group B streptococcus culture (35–37 wk) (vaginal and rectal)</td>
<td>Recommend intrapartum chemoprophylaxis with IV PCN G (2.5 million units q 4 hr) if positive (or if GBS bacteriuria during current pregnancy or with previous infant with invasive GBS disease; if unknown GBS status, IP prophylaxis with delivery &lt;37 wk gestation, membrane rupture ≥ 18 hr or IP temperature ≥ 100.4°F/38.0°C (Schrag, 2002).</td>
</tr>
</tbody>
</table>
### Table 7-5: Laboratory Evaluation in the HIV-Infected Pregnant Woman (continued)

<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4, HIV-RNA</td>
<td>Results may influence decisions about mode of delivery</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>Consider in high-risk patients or populations</td>
</tr>
</tbody>
</table>

**Other Considerations**

<table>
<thead>
<tr>
<th>Test</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver enzymes, electrolytes</td>
<td>Assess more frequently in third trimester in setting of NRTI therapy, nevirapine, recent changes in ARV therapy</td>
</tr>
<tr>
<td>Serum lactate, electrolytes, liver enzymes; consider anion gap, CPK, amylase, lipase</td>
<td>Signs or symptoms suggest possible lactic acidosis in setting of NRTI therapy, especially if long-term</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>Consider at baseline and at 3–6 mo after starting PI- or NNRTI-based therapy; subsequent measurements based on initial results and risks</td>
</tr>
<tr>
<td>Liver enzymes (ALT, AST)</td>
<td>Initiation of nevirapine therapy (does not apply to single dose prophylactic therapy in labor)</td>
</tr>
</tbody>
</table>

* Seroprevalence CMV IgG in US adults is 50–60%; IDU patients ≥90%

** Accurate gestational age is essential for interpretation of both tests.

** Though not yet considered standard of care, 1st trimester screening for genetic abnormalities can be done with nuchal lucency assessment on ultrasound and with biochemical markers.

** Antepartum Fetal Surveillance/Testing**

The general purpose of antepartum fetal testing and surveillance is to identify fetal abnormalities or compromise so that appropriate interventions can be undertaken to optimize fetal health and prevent fetal damage or death; or, in some instances, to aid in decisions regarding continuation of pregnancy (ACOG, 1999).

- **Fetal surveillance:** Indications include:
  - maternal conditions in which risk of fetal death is increased. This includes (but is not limited to) hemoglobinopathies, chronic renal disease, systemic lupus erythematosus, hypertension, and diabetes.
  - pregnancy-related conditions in which risk of fetal death is increased. This includes pregnancy-induced hypertension, decreased fetal
movement, oligohydramnios, polyhydramnios, intrauterine growth retardation, postterm pregnancy, mild to moderate isoimmunization, previous fetal death, and multiple gestation.

- HIV considerations: There are no data specifically on the need for and use of fetal surveillance techniques in the HIV-infected woman during pregnancy, and HIV per se is not an indication for fetal testing. However, HIV-infected women who have coexisting medical conditions placing the fetus at increased risk should have fetal surveillance; furthermore, HIV infection, especially when more advanced or associated with substance abuse, may be associated with increased risk for poor fetal growth, which places the fetus at increased risk. May consider in pregnant women on HAART particularly when containing newer agents with little experience of use in pregnancy. Need for fetal surveillance in the HIV-positive pregnancy should be determined on an individual basis.

Fetal surveillance techniques include:

- Fetal movement assessment: “kick-counts” – perception of 10 distinct movements in a period of up to 2 hr is reassuring.

- Nonstress test (NST): reactive or reassuring test is defined as two or more fetal heart rate accelerations (at least 15 beats/min above baseline and lasting at least 15 sec on fetal monitor) within a 20-min period.

- Contraction stress test (CST): negative or reassuring test is absence of late or significant variable fetal heart rate decelerations with at least three contractions (lasting at least 40 sec) within 10 min.

- Biophysical profile: consists of an NST combined with observations of fetal breathing, fetal movements, fetal tone, and amniotic fluid volume by real-time ultrasonography. Each component is given a score of 2 (normal or present) or 0 (abnormal or absent); a composite score of 8 or 10 is normal.

- Modified biophysical profile: combines NST and amniotic fluid index (AFI), which is the sum of measurements of the deepest amniotic fluid pocket in each abdominal quadrant; normal AFI is >5 cm. This test combines a short-term indicator of fetal acid-base status (NST) and an indicator of long-term placental function (AFI); placental dysfunction often leads to poor fetal growth and oligohydramnios.

- Umbilical artery Doppler velocimetry: evaluation of flow velocity wave forms in the umbilical artery; in the normally growing fetus, characterized by high-velocity diastolic flow; of benefit only in pregnancies complicated by intrauterine growth restriction.

Although there is no data from randomized clinical trials, antepartum fetal surveillance has been consistently associated with lower rates of fetal death than in untested pregnancies from the same institution or than historic controls with similar complicating factors. Testing should be initiated at 32–34 wk gestation, but may be started as early as 26–28 wk in pregnancies at very high risk. When the condition prompting testing persists, testing should be repeated periodically (weekly or, in some cases, biweekly) until delivery. Fetal reevaluation should also be repeated with significant deterioration in maternal medical condition or acute decrease in fetal movement, regardless of the time elapsed since the previous test.
NST, CST, biophysical profile, and modified biophysical profile are the most commonly used forms of testing and have a negative predictive value >99%. However, they are not predictive of acute events, such as placental abruption or umbilical cord accidents. On the other hand, the positive predictive value of an abnormal test can be quite low and the response to an abnormal result should be dictated by the individual clinical situation. Any abnormal test result requires further evaluation or action. Maternal perception of decreased fetal movements should be evaluated by NST, CST, biophysical profile, or modified biophysical profile. If normal, the mother can be reassured that the fetus is in no immediate danger. A nonreactive NST or abnormal modified biophysical profile is usually followed by additional testing with a CST or full biophysical profile. Management will be based on results of these tests, gestational age, degree of oligohydramnios (if assessed), and maternal condition. Oligohydramnios should prompt evaluation for membrane rupture. Depending on the degree of oligohydramnios, the gestational age, and the maternal medical condition, oligohydramnios warrants either delivery or close maternal/fetal surveillance.

- **Ultrasound.** Indications for obstetric ultrasound are many. Some of the more common include (ACOG, 1993b):
  - pregnancy dating
  - evaluation of fetal growth
  - evaluation of vaginal bleeding during pregnancy
  - determination of fetal presentation
  - suspected multiple gestation
  - significant uterine size/clinical dates discrepancy
  - pelvic mass
  - suspected ectopic pregnancy
  - document fetal viability/rule out fetal death
  - biophysical profile for antepartum fetal surveillance
  - suspected polyhydramnios/oligohydramnios
  - placental localization
  - abnormal serum $\alpha$-fetoprotein or triple screen
  - evaluation for fetal anomalies
  - evaluation of fetal condition in late registrants for prenatal care

With transvaginal ultrasound, an intrauterine gestational sac can be seen by 5 wk after the last menstrual period and fetal heart activity can be detected by 6 wk. First-trimester bleeding is the most common indication for early ultrasound, when the major differential diagnoses are threatened abortion (miscarriage) and ectopic pregnancy. Accurate pregnancy dating is best accomplished in the late first and second trimesters.
In the setting of HIV infection, an ultrasound should be considered in the second trimester for accurate dating, which is important later in gestation if scheduled cesarean section is planned to avoid premature delivery (see below). This will also allow survey of fetal anatomy and screening for anomalies. A third trimester (or other follow-up) ultrasound(s) should be considered, particularly in women with more advanced disease, those on HAART, and/or with other maternal pregnancy-related factors possibly impacting on fetal growth, in order to monitor growth.

- **Amniocentesis/chorionic villus sampling/percutaneous umbilical blood sampling:** Because of concerns about increasing risk of perinatal transmission with these invasive techniques, they should be performed only for obstetric indications, with careful counseling; attempts to minimize viral load prior to the procedure should be considered.

**ANTIRETROVIRAL TREATMENT**

(See Table 7-6.) Although there are special considerations in using antiretroviral drugs during pregnancy, the basic principle is that therapies of known or possible benefit to the woman should not be withheld during pregnancy unless there are known adverse effects for mother, fetus, or infant that outweigh the potential benefits (Minkoff, 1997a). The goals in the use of antiretroviral drugs during pregnancy are two-fold: (1) treatment of maternal infection and (2) reduction in the risk of perinatal transmission. Pregnant women meeting the criteria outlined for other adults and adolescents should be offered standard combination antiretroviral therapy, generally including two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (excluding efavirenz). (See Chapter IV on Primary Medical Care.) If such criteria are not met, ARV therapy appropriate for prevention of perinatal transmission, including combination treatment, should be offered.
Table 7-6 Preclinical and Clinical Data Relevant to the Use of Antiretrovirals During 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 ratio]</th>
<th>Long-term animal carcinogenicity studies</th>
<th>Animal teratogen studies</th>
</tr>
</thead>
<tbody>
<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>Not completed</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>Antiretroviral drug</td>
<td>FDA pregnancy category†</td>
<td>Placental passage [newborn: mother drug ratio]</td>
<td>Long-term animal carcinogenicity studies</td>
<td>Animal teratogen studies</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------</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 (cynomolgous monkey, rat, rabbit) [-1.0]</td>
<td>Positive (increased hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female but not male mice)</td>
<td>Positive (cynomolgous monkey anencephaly, anophthalmia, micro-ophthalmia)</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 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>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Fosamprenavir (Lexiva)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (increased 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>Not completed</td>
<td>Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)</td>
</tr>
</tbody>
</table>
### Nelfinavir (Viracept)

| B | Minimal (humans) | Positive (thyroid follicular adenomas and carcinomas in rats) | Negative |

### Ritonavir (Norvir)

| B | Minimal (humans) | Positive (rodent, liver adenomas and carcinomas in male mice) | Negative (but cryptorchidism in rodents) |

### Saquinavir (Fortovase)

| B | Minimal (humans) | Not completed | Negative |

### Fusion inhibitors

| Enfuvirtide (Fuzeon) | B | Unknown | Not done | Negative |

---

† 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 there is no evidence 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 based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable 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.

Nevertheless, there are additional issues to consider with treatment in pregnancy:

- **Pharmacokinetics:** (See Table 7-7.) There are potential changes in dosing secondary to the physiologic changes during pregnancy; at the current time, pharmacokinetic information on existing antiretroviral agents during pregnancy is limited, and has not been correlated with clinical efficacy. PK data on the NRTI and NNRTI drugs studied are similar to that in nonpregnant adults and these drugs cross the placenta to a variable extent. In general protease inhibitors have different PK levels during pregnancy and do not cross the placenta. Adequate drug levels are achieved in pregnant women with nelfinavir 1250 mg bid (Bryson, 2002), but levels were low and more variable with dosing 750 mg tid. Small PK studies conducted with non-boosted indinavir and saquinavir, as well as lopinavir/ritonavir, found inadequate drug concentrations in pregnancy using standard dosing; adequate drug levels were achieved with saquinavir 800 mg/ritonavir 100 mg (Acosta, 2004) and a boosted indinavir PK study is underway, as well as a trial of altered dosing of lopinavir/ritonavir. PK parameters of nevirapine are not significantly altered in pregnancy (Aweeka, 2004), but several recent studies show prolonged postnatal drug levels for over 3 weeks in a significant proportion of women after a single-dose of nevirapine given in labor (Jourdain, 2004).

- **Perinatal transmission:** The effect of different drugs and drug combinations on vertical transmission. Current information from clinical trials on the use of antiretroviral agents during the antepartum period and perinatal transmission are summarized in Table 7-8.

Although there are no clinical trial data regarding effectiveness of HAART in reducing perinatal transmission, there is prospective cohort data which suggests that the lowest rates of transmission occur with effective combination ARV therapy and with reductions in viral load to undetectable levels. Both choice of ARV therapy and suppression of viral load to <1000 copies/mL are important and probably additive. An analysis of the WITS (Cooper, 2002) cohort found the transmission rate was 1.2% in women receiving HAART and was 1% when HIV-RNA levels were suppressed below 400 c/mL. Preliminary results of a retrospective/prospective combined analysis (PACTG 367) of over 4000 women found that in all subgroups of viral load, multiagent ARV—both dual nucleoside and HAART—was associated with the lowest rates of perinatal transmission and when viral load was <1000 c/mL in these women, transmission rate was <1% (Shapiro, 2004).
Table 7-7: 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>NRTI/NtRTIs</td>
<td></td>
<td></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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine*</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated</td>
<td>No evidence of human teratogenicity. 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</td>
<td>No evidence of human teratogenicity. 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>
</tbody>
</table>
### Table 7-7: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (continued)

<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 (NRTI/NtRTIs)</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</td>
<td>Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together</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>Emtricitabine</td>
<td>No studies in human pregnancy</td>
<td>No studies in human pregnancy</td>
<td>Alternate NRTI for dual nucleoside backbone of combination regimens.</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated</td>
<td>No evidence of human teratogenicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together</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>Phase I/II study in progress.</td>
<td>Hypersensitivity reactions occur in ~ 5–8% of nonpregnant persons, a much smaller percentage are fatal and 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 (NRTI/NtRTIs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</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. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown.</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>Not recommended (NRTI/NtRTIs)</td>
<td>Zalcitabine</td>
<td>Rodent studies indicate potential for teratogenicity and developmental toxicity</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Recommended agents (NNRTIs)</td>
<td>Nevirapine</td>
<td>Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No evidence human teratogenicity. Increased risk of symptomatic, often rash-associated and potentially fatal liver toxicity among women with CD4+ lymphocyte counts &gt; 250/mm$^3$ when first initiating therapy. Uncertain if pregnancy increases risk.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nevirapine should be initiated in pregnant women who enter pregnancy may continue therapy regardless of CD4+ lymphocyte count.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not recommended (NNRTIs)</th>
<th>Efavirenz</th>
<th>Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Alternative effective regimens should be considered if available. Use after the second trimester of pregnancy can be considered if other alternatives not available and if adequate contraception can be assured postpartum.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>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 are three case reports of neural tube defects in humans after first trimester exposure, relative risk unclear.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No studies in human pregnancy. Pharmacokinetics not significantly altered in pregnancy, no change in dose indicated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No studies in human pregnancy. No significantly altered in pregnancy, no change in dose indicated.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Not recommended (NRTI/NtRTIs)</th>
<th>Zalcitabine</th>
<th>No studies in human pregnancy. No studies in human pregnancy.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rodent studies indicate potential for teratogenicity and developmental toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives not available.</td>
</tr>
</tbody>
</table>

| Recommended agents (NNRTIs)  | Nevirapine | No evidence human teratogenicity. Increased risk of symptomatic, often rash-associated and potentially fatal liver toxicity among women with CD4+ lymphocyte counts > 250/mm$^3$ when first initiating therapy. Uncertain if pregnancy increases risk. |
|                               |            | Nevirapine should be initiated in pregnant women who enter pregnancy may continue therapy regardless of CD4+ lymphocyte count. |
|                               |            | Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated. |

<table>
<thead>
<tr>
<th>Not recommended (NNRTIs)</th>
<th>Efavirenz</th>
<th>No studies in human pregnancy. Pharmacokinetics not significantly altered in pregnancy, no change in dose indicated.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>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 are three case reports of neural tube defects in humans after first trimester exposure, relative risk unclear.</td>
</tr>
<tr>
<td></td>
<td></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. Alternative effective regimens should be considered if available. Use after the second trimester of pregnancy can be considered if other alternatives not available and if adequate contraception can be assured postpartum.</td>
</tr>
<tr>
<td>Antiretroviral drug</td>
<td>Pharmacokinetics in Pregnancy</td>
<td>Concerns in Pregnancy</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>No studies in human pregnancy</td>
<td>Rodent studies indicated potential for carcinogenicity and teratogenicity</td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td></td>
<td>Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs</td>
</tr>
<tr>
<td><strong>Recommended agents (Protease Inhibitors)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Adequate drug levels are achieved in pregnant women with nelfinavir, 1250 mg, given twice daily</td>
<td>No evidence of human teratogenicity. 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>
</tr>
</tbody>
</table>
### Saquinavir-soft gel capsule [SGC] (Fortavase) + ritonavir

**Adequate drug levels are achieved in pregnant women with saquinavir-SGC 800 mg boosted with ritonavir 100 mg given twice daily.**

Recommended adult dosing of saquinavir-SGC 1000 mg plus ritonavir 100 mg may be used.

No pharmacokinetic data on saquinavir-hard gel capsule [HGC] + ritonavir in pregnancy, but better GI tolerance in non-pregnant adults.

Well-tolerated, short-term safety demonstrated for mother and infant. Inadequate drug levels observed in pregnant women when saquinavir-SGC given alone at 1200 mg three times daily.

Given pharmacokinetics data and extensive experience with use in pregnancy, ritonavir-boosted saquinavir-SGC can be considered a preferred PI for combination regimens in pregnant women.

### Alternative agents (Protease Inhibitors)

| Indinavir | Study underway to evaluate pharmacokinetics of indinavir 800 mg with ritonavir 100 mg, given twice daily | Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Two studies including six women receiving indinavir 800 mg three times daily showed marked lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen | Alternate PI to consider if unable to use nelfinavir or saquinavir-SGC/ritonavir. Use of unboosted indinavir during pregnancy is not recommended. Optimal dosing for the combination of ritonavir/indinavir in pregnancy unknown. |
### Table 7-7: Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (continued)

<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>Lopinavir/ritonavir</td>
<td>Phase I/II safety and pharmacokinetic study in progress using twice daily lopinavir 400 mg and ritonavir 100 mg</td>
<td>Limited experience in human pregnancy</td>
<td>Preliminary studies suggest increased dose may be required during pregnancy, though specific dosing recommendations not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result not observed, consider increasing dose in consultation with a specialist with expertise in HIV in pregnancy.</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum</td>
<td>Minimal experience in human pregnancy</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>
</tbody>
</table>

**Insufficient data to recommend use (Protease Inhibitors)**

<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>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>Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use of capsules during pregnancy. Oral solution contraindicated</td>
</tr>
<tr>
<td>Fos-amprenavir</td>
<td>No studies in human pregnancy</td>
<td>No experience in human pregnancy</td>
<td>Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use 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>Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.</td>
</tr>
</tbody>
</table>
### Fusion Inhibitors

**Insufficient data to recommend use (Fusion Inhibitors)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>No studies in human pregnancy</th>
<th>No experience in human pregnancy</th>
<th>Data are insufficient regarding safety and pharmacokinetics in pregnancy to recommend use during pregnancy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NRTI =** nucleoside reverse transcriptase inhibitor; **NtRTI =** 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®, and zidovudine, lamivudine, and abacavir are included as fixed-dose combination in Trizivir®.

# Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based HAART regimens. These regimens should be used only when an NNRTI or PI-based HAART regimen cannot be used (eg, 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>
<thead>
<tr>
<th>Site/sponsor</th>
<th>Antepartum</th>
<th>Intrapartum</th>
<th>Post-partum Mother</th>
<th>Post-partum Infant</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (PACTG 076)</td>
<td>Starting at 14-34 wks</td>
<td>Arm 1: ZDV 100 mg 5x/d</td>
<td>Arm 1: ZDV intravenous infusion</td>
<td>No ARV</td>
<td>Arm 1: ZDV 2 mg/kg qid x 6 wk 7.6% ZDV vs 22.6% placebo, 68% efficacy (Connor, 1994)</td>
</tr>
<tr>
<td></td>
<td>Arm 2: Placebo</td>
<td>Arm 2: Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THAILAND (CDC)</td>
<td>Starting at 36 wks</td>
<td>Arm 1: ZDV 300 mg bid</td>
<td>Arm 1: ZDV 300 mg q 3 hr</td>
<td>No ARV</td>
<td>Arm 2: Placebo 9.4% ZDV vs 18.9% placebo, 50% efficacy (Shaffer, 1999)</td>
</tr>
<tr>
<td></td>
<td>Arm 2: Placebo</td>
<td>Arm 2: Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVORY COAST (CDC)</td>
<td>Starting at 36 wks</td>
<td>Arm 1: ZDV 300 mg bid</td>
<td>Arm 1: ZDV 300 mg q 3 hr</td>
<td>No ARV</td>
<td>Arm 2: Placebo 16.5% ZDV vs 26.1% placebo, 37% efficacy (Wiktor, 1999)</td>
</tr>
<tr>
<td></td>
<td>Arm 2: Placebo (stopped 2/98)</td>
<td>Arm 2: Placebo (stopped 2/98)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### IVORY COAST/BURKINA FASO (DITRAME; ANRS 049a)
- Randomized, placebo-controlled
- After trial completion, continued to enroll into an open-label ZDV regimen cohort
- Breastfeeding
- N=400

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV 300 mg bid x1</td>
<td>Placebo (stopped 2/98)</td>
</tr>
<tr>
<td>ZDV 300 mg bid x1 wk</td>
<td>Placebo (stopped 2/28)</td>
</tr>
</tbody>
</table>

- At 6 mos, tx 18.0% ZDV vs 27.5% placebo, 38% efficacy
- At 15 mos, tx 21.5% ZDV vs 30.6% placebo, 30% efficacy
- At 24 mos (pooled analysis with CDC), tx 22.5% ZDV vs 30.2% placebo, 26% efficacy
- 18 mo mortality: 17.6% ZDV vs 22.1% placebo
- Open-label ZDV cohort (N=209), 15 mo tx with ZDV regimen, 19.6%

(Dabis, 1999; DITRAME ANRS 049 Study Group, 1999; Leroy, 2002)

### THAILAND/PHPT (Harvard)
- Randomized, comparative, factorial
- No placebo (076-like control)
- Formula feeding
- N=1,437

<table>
<thead>
<tr>
<th>Arm 1 (Long-Long, LL)</th>
<th>Arm 2 (Long-Short, LS)</th>
<th>Arm 3 (Short-Long, SL)</th>
<th>Arm 4 (Short-short, SS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV 300 mg bid</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>ZDV 2 mg/kg qid</td>
<td>6 wks</td>
<td>3 d</td>
<td>6 wks</td>
</tr>
</tbody>
</table>

- Interim analysis 3/99 (N=449 enrolled), stopped SS arm due to sig higher tx than LL
  - At 6 mos, tx 10.5% SS vs 4.1% LL
- Final analysis 7/00, no sig differences;
  - At 6 mos, tx 6.5% LS vs 8.6% SL
- In utero tx sig different:
  - 1.6% [LL+LS] vs 5.1% [SL+SS]

(Lallemant, 2000)
### Table 7-8: Overview of Antiretroviral Intervention Trials to Prevent Mother-to-child Transmission of HIV (continued)

<table>
<thead>
<tr>
<th>Site/sponsor</th>
<th>Antepartum</th>
<th>Intrapartum</th>
<th>Post-partum Mother</th>
<th>Post-partum Infant</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOUTH AFRICA, UGANDA, TANZANIA (PETRA)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Randomized, placebo-controlled</td>
<td>Arm 1: ZDV 300 mg bid plus 3TC 150 mg bid</td>
<td>Arm 1: ZDV 300 mg q 3 hr plus 3TC 150 mg q 12 hr</td>
<td>Arm 1: ZDV 300 mg bid plus 3TC 150 mg q 7 d</td>
<td>Arm 1: ZDV 4 mg/kg bid plus 3TC 2 mg/kg bid x 7 d</td>
<td>• At 6 wks, tx:</td>
</tr>
<tr>
<td>• Breastfeeding</td>
<td>Arm 2: Placebo</td>
<td>Arm 2: ZDV 300 mg q 3 hr plus 3TC 150 mg q 12 hr</td>
<td>Arm 2: ZDV 300 mg bid plus 3TC 150 mg q 7 d</td>
<td>Arm 2: ZDV 4 mg/kg bid plus 3TC 2 mg/kg bid x 7 d</td>
<td>— 5.7% AP/IP/PP (63% efficacy)</td>
</tr>
<tr>
<td>• N=1,797</td>
<td>Arm 3: Placebo</td>
<td>Arm 3: ZDV 300 mg q 3 hr plus 3TC 150 mg q 12 hr</td>
<td>Arm 3: Placebo</td>
<td>Arm 3: Placebo</td>
<td>— 8.9% IP/PP (42% efficacy)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>— 15.3% placebo</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>• At 18 mos, tx:</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>— 14.9% AP/IP/PP</td>
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<td></td>
<td></td>
<td></td>
<td>— 18.1% IP/PP</td>
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<td></td>
<td>— 20.0% IP</td>
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<td></td>
<td>— 22.2% placebo</td>
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<td></td>
<td></td>
<td>(Petra Study Team, 2002)</td>
</tr>
<tr>
<td>FRANCE (ANRS 075)</td>
<td>Standard ZDV after 14 wks</td>
<td>Standard intravenous ZDV</td>
<td>Non-study ARV</td>
<td>Standard ZDV x 6 wks</td>
<td>• Tx 1.6% ZDV/3TC vs 6.8% 1994-97 historical, ZDV-alone control</td>
</tr>
<tr>
<td>• Non-randomized, open-label</td>
<td>3TC 150 mg bid added at 32 wks</td>
<td></td>
<td></td>
<td>3TC 2 mg/kg bid x 6 wks</td>
<td>(Mandelbrot, 2001)</td>
</tr>
<tr>
<td>• Formula feeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• N=445</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>THAILAND (Ministry of University Affairs, Bangkok)</td>
<td>Starting at 34 wks</td>
<td>ZDV 300 mg bid plus 3TC 150 mg bid</td>
<td>No ARV</td>
<td>ZDV 2 mg/kg qid x 4 wks</td>
<td>• At 18 mos, tx 2.8% vs 11.7% historical, ZDV-alone control (N=60: 36 wk start, oral IP, 4 wk infant)</td>
</tr>
<tr>
<td>• Non-randomized, open-label</td>
<td></td>
<td>ZDV 300 mg q 3 hr plus 3TC 150 mg q 3 hr</td>
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<tr>
<td>• Formula feeding</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• N=106</td>
<td></td>
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</tbody>
</table>

(Chaisilwattana, 2002)
<table>
<thead>
<tr>
<th>Country/Study</th>
<th>Design</th>
<th>Breastfeeding</th>
<th>Infants</th>
<th>ARV</th>
<th>Tx Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UGANDA (HIVNET 012)</strong></td>
<td>Randomized, originally had 3rd placebo arm, stopped 2/98</td>
<td>Breastfeeding</td>
<td>N=626</td>
<td>Arm 1: No ARV, Arm 2: No ARV, Arm 3: Placebo (stopped 2/98)</td>
<td>• At 14-16 wks, tx 13.1% NVP vs 25.1% ZDV, 47% efficacy&lt;br&gt;• At 18 mos, tx 15.7% NVP vs 25.8% ZDV, 41% efficacy (Guay, 1999)</td>
</tr>
<tr>
<td><strong>US/EUROPE/BAHRAIN (PACTG 316)</strong></td>
<td>Randomized, [NVP] placebo-control</td>
<td>Women and infants received non-study standard ARV</td>
<td>N=1,248</td>
<td>Arm 1: NVP 200 mg x1, Arm 2: ZDV 300 mg q 3 hr, Arm 3: Placebo (stopped 2/98)</td>
<td>• Stopped early due to low 1.5% overall tx (53% in utero)&lt;br&gt;• At 6 mos, tx 1.4% NVP vs 1.6% placebo (Dorenbaum, 2002)</td>
</tr>
<tr>
<td><strong>SOUTH AFRICA (SAINT)</strong></td>
<td>Randomized, comparative</td>
<td>Breastfeeding (42%) and formula feeding</td>
<td>N=1,331</td>
<td>Arm 1: No ARV, Arm 2: No ARV, Arm 1: NVP 200 mg x1, Arm 2: ZDV 300 mg q3 hrs plus 3TC 150 mg q 12 hr</td>
<td>• At 8 wks, tx 12.3% NVP vs 9.3% ZDV/3TC (p&lt;0.01) (Moodley, 2003)</td>
</tr>
<tr>
<td><strong>THAILAND (CDC)</strong></td>
<td>Non-randomized, open-label</td>
<td>Formula feeding</td>
<td>N=195</td>
<td>Starting at 34-36 wks ZDV 300 mg bid, ZDV 300 mg q3 hrs plus NVP 200 mg x1, ZDV 2 mg/kg qid x 4 wks plus NVP 6 mg x1 at 48-72 hr</td>
<td>• Tx 4.6% (Chalermchokcharoenkit, 2004)</td>
</tr>
<tr>
<td>Site/sponsor</td>
<td>Antepartum</td>
<td>Intrapartum</td>
<td>Post-partum Mother</td>
<td>Post-partum Infant</td>
<td>Results</td>
</tr>
<tr>
<td>------------------------</td>
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<tr>
<td><strong>THAILAND/PHPT (Harvard)</strong></td>
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</tr>
<tr>
<td>• Randomized, comparative</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• All women/infant get short-course ZDV</td>
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<tr>
<td>• Formula feeding</td>
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<tr>
<td>• N=1,844</td>
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<tr>
<td>Starting at 28 wks</td>
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<tr>
<td>Arm 1: ZDV 300 mg bid</td>
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<tr>
<td>Arm 2: ZDV 300 mg bid</td>
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<tr>
<td>Arm 3: ZDV 300 mg bid</td>
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<td></td>
</tr>
<tr>
<td>Arm 3: ZDV 300 mg q 3 hr plus NVP 200 mg x 1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No ARV</td>
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<tr>
<td>Arm 1: ZDV 300 mg q 3 hr</td>
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<tr>
<td>Arm 2: ZDV 300 mg q 3 hr plus NVP 200 mg x 1</td>
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<td>No ARV</td>
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<td><strong>MALAWI (Fogarty)</strong></td>
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<td>• Randomized, comparative</td>
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<tr>
<td>• Designed for infants of women 1st identified as HIV+ in labor/PP</td>
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<tr>
<td>• Breastfeeding</td>
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<tr>
<td>• N=1,119</td>
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<td>No ARV</td>
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<td>No ARV</td>
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<td>No ARV</td>
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<tr>
<td>Arm 1: NVP 2 mg/kg x 1 at 48-72 hr</td>
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<tr>
<td>Arm 2: NVP 2 mg/kg x 1 at 48-72 hr plus ZDV 4 mg/kg bid x 7 d</td>
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<tr>
<td>Interim analysis 6/02: --ZDV alone Arm 1 stopped due to higher tx than in ZDV/NVP Arm 3</td>
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<tr>
<td>• Analysis through 3/03: --ZDV alone 6.3% --Arms 2 &amp; 3 combined 1.7% --NVP/placebo 2.8% --NVP/NVP 1.9% (Lallemant, 2004)</td>
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<td><strong>MALAWI (Fogarty)</strong></td>
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<td>• Randomized, open label</td>
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<td>• Breastfeeding</td>
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<td>• N=894</td>
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<td>No ARV</td>
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<td>NVP 200 mg x 1</td>
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<td>No ARV</td>
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<td>Arm 1: NVP 2 mg/kg x 1 at 48-72 hr</td>
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<td>Arm 2: NVP 2 mg/kg x 1 at 48-72 hr plus ZDV 4 mg/kg bid x 7 d</td>
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<tr>
<td>At 6-8 wks, tx rate: NVP 20.9% NVP/ZDV 15.3% (26.8% efficacy); when limited to infants uninfected at birth: NVP 12.9% vs NVP/ZDV 7.7% (36.4% efficacy) (Taha, 2003)</td>
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<td>• Randomized, comparative</td>
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<td>• Designed for infants of women 1st identified as HIV+ in labor/PP</td>
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<td>NVP 200 mg x 1</td>
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<td>No ARV</td>
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<td>Arm 1: NVP 2 mg/kg x 1 at 48-72 hr</td>
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<tr>
<td>Arm 2: NVP 2 mg/kg x 1 at 48-72 hr plus ZDV 4 mg/kg bid x 7 d</td>
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<tr>
<td>At 6-8 wks, tx rate: NVP 14.1% NVP/ZDV 16.3% (p=.36) When limited to infants uninfected at birth: NVP 6.5% vs NVP/ZDV 6.9% (p=.88) (Taha, 2004)</td>
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*Courtesy: Lynne Mofenson, M.D.*
• **Fetal/infant adverse effects:** Potential teratogenicity, carcinogenicity, mutagenicity, or fetal/neonatal side effects/toxicity from transplacentally transferred drugs. The potential for adverse effects may be related to several factors: the drug itself, dose, gestational age at exposure, duration of exposure, interactions with other drugs or agents to which the fetus is exposed, and the genetic make-up of mother and fetus. Potential toxicity of antiretroviral drugs with perinatal exposure applies both to the infected and uninfected fetus and/or infant.

Information about the safety of drugs in pregnancy comes from animal toxicity studies, anecdotal experience, cohort studies, registry data, and clinical trials. Preclinical data do not necessarily correlate with adverse effects in humans. There are approximately 1200 known animal teratogens, but only about 30 are known human teratogens. Of currently available drugs, ZDV is the agent for which there is the most information, and information about other antiretrovirals agents, particularly when used in combination, is more limited. Issues related to specific drugs and their possible impact on fetal safety are addressed below; all antiretroviral drugs are discussed in more detail in Chapter XIV on Pharmacology and the U.S. Public Health Service Task Force Recommendations for the 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, which is updated regularly online at http://www.aidsinfo.nih.gov.

- **Zidovudine (ZDV):** In the PACTG 076 study the only side effect significantly different between ZDV and placebo recipients was the presence of anemia in ZDV-exposed infants; however, the anemia was mild and resolved spontaneously without need for transfusion (Connor, 1994). There has been no evidence of increase in congenital abnormalities in infants exposed to ZDV in utero, compared with the general population. Uninfected children who were participants in the PACTG 076 study have now been followed for nearly 6 years with no evidence of impact of ZDV on growth, neurodevelopment, or immunologic status (Culnane, 1999).

  Two transplacental carcinogenicity studies in mice showed different results: in one study (Olivero, 1997), two very high doses (approximately 25x and 50x daily human therapeutic exposure) were associated with an increase in lung, liver, and female genital tract tumors; in the second study (Ayers, 1997), a much lower dose (approximately 3x human therapeutic exposure) was not associated with an increase in tumors. A consensus conference reviewed all available information and concluded that the known benefits of zidovudine far outweighed the theoretical risks, but recommended long-term follow-up of infants exposed in utero to zidovudine or other antiretrovirals. In a follow-up of over 700 infants with in utero exposure to ZDV, no malignancies were observed in up to 6 yr of age (Hanson, 1999).

- **Efavirenz:** In primate studies efavirenz was associated with anencephaly, anophthalmia, microphthalmia, and cleft palate at doses comparable to human exposure. There have been four reports of central nervous system defects in human infants with early in utero exposure. Efavirenz should be avoided during pregnancy, particularly early
pregnancy, and in women at risk for pregnancy (trying to get pregnant or unsafe sexual practices). Pregnant women who have conceived while on efavirenz should be counseled about possible fetal risks and ultrasound screening should be considered to look for fetal anomalies.

- **Amprenavir:** Amprenavir oral solution contains high levels of propylene glycol (the capsule form does not contain propylene glycol). Pregnant women and infants and children under the age of 4 are unable to adequately metabolize and eliminate propylene glycol, leading to accumulation and potential serious adverse events, including hyperosmolarity, lactic acidosis, seizures, and respiratory depression. Amprenavir oral solution is contraindicated in pregnancy and in children under the age of 4 yr.

- **Indinavir:** Indinavir has been associated with indirect hyperbilirubinemia and increased risk for renal stones. There are theoretical concerns from in utero exposure to indinavir about risk for renal stones in neonates who cannot voluntarily hydrate themselves adequately and possible complications associated with exacerbation of physiologic hyperbilirubinemia (especially in premature infants, who are at greater risk for neonatal jaundice and kernicterus); however, placental passage of indinavir in humans appears to be minimal, which should minimize risk. Third trimester in utero exposure to indinavir in Rhesus monkeys found fetal plasma drug levels only 1–2% of maternal drug levels and no exacerbation of physiologic hyperbilirubinemia in neonates. Nevertheless, neonates exposed to indinavir late in gestation should be closely monitored. Because of its short half-life, these concerns probably do not apply to use of indinavir earlier in pregnancy.

- **Atazanavir:** The most common laboratory abnormality observed with use of atazanavir is hyperbilirubinemia, with 15–24% of subjects receiving atazanavir developing jaundice or scleral icterus. This abnormality was reversible with drug discontinuation and did not appear to be associated with increased risk of liver injury. The degree of placental passage and the potential risk of exacerbation of physiologic hyperbilirubinemia in neonates is unknown.

- **Tenofovir:** Recent studies in animal models suggest potential risks for bone abnormalities with infant (and possibly fetal) exposure to relatively low doses of tenofovir (Castillo, 2002; Tarantal, 2002). No human studies in pregnancy are available.

- **Hydroxyurea:** Although hydroxyurea is not a true antiretroviral drug, it has been used in some antiretroviral regimens in the past; this agent is no longer recommended as part of any antiretroviral regimen. Hydroxyurea has been referred to as a “universal teratogen” with evidence of teratogenicity in every animal species studied and defects involving multiple organ systems. This agent should be avoided during pregnancy and in women at risk for pregnancy.

- **Mitochondrial toxicity:** A large prospective cohort of almost 4400 HIV uninfected or HIV-indeterminant children (2644 with perinatal antiretroviral exposure) born to women with HIV identified 12 cases of mitochondrial dysfunction over 18 months of follow-up (0.26%), all with antiretroviral exposure (Barret, 2003); risk was higher with exposure to combination ARV therapy (primarily ZDV/3TC) than to ZDV alone. All children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or hyperlactatemia, and all had deficit in one of the mitochondrial respiratory chain complexes and/or abnormal muscle biopsy. The same group has reported an increase in febrile seizures during the first 18 months
of life among uninfected infants with antiretroviral exposure (French Perinatal Cohort Study Group, 2002). Other studies have found associations between antiretroviral exposure and markers of mitochondrial dysfunction, including lower mitochondrial DNA quantity (Poirier, 2003) and transient hyperlactatemia (Giaquinto, 2001).

However, a retrospective review of deaths occurring among over 16,000 HIV-exposed but uninfected children (with and without antiretroviral exposure) followed 1986-1999 in five large prospective US cohorts found no deaths felt consistent with mitochondrial dysfunction. In this study most ARV exposure was to ZDV alone (Perinatal Safety Review Working Group, 2000). Neurologic adverse events were reviewed in 1,798 infants exposed to ZDV/3TC or placebo in the PETRA study, an African perinatal prophylaxis trial; no increased risk of neurologic events was observed among children treated with ZDV/3TC compared with placebo, regardless of intensity of treatment (Petra Study Team, 2002). In a review of clinical symptoms in 2414 uninfected children, 1008 with perinatal antiretroviral exposure, and with median follow-up of over 2 years, there was no association between antiretroviral exposure and clinical manifestations (European Collaborative Study, 2003). Mitochondrial toxicity can also manifest as cardiomyopathy and in a study of 382 uninfected infants, serial echocardiograms for the first 5 years of life found no significant differences in ventricular function stratified by ZDV exposure (Lipshultz, 2000).

Although there is conflicting data regarding ARV exposure and mitochondrial dysfunction, the likelihood of severe or fatal manifestations appears to be extremely small. However, mitochondrial dysfunction should be considered in ARV-exposed but uninfected children who present with severe clinical findings of unknown etiology, particularly neurologic findings. Appropriate monitoring should be considered for all exposed infants.

Given the limited and relatively short-term experience with all antiretroviral agents in pregnancy, long-term follow-up of infants exposed to these medications in utero is important.

- **Adverse pregnancy outcomes**: Concerns about possible increased risk for preterm delivery were raised by a small retrospective series of pregnant women receiving combination antiretroviral therapy (Lorenzi, 1998). Subsequently a large European cohort of almost 4000 mother-child pairs (only 323 on combination therapy) found a 2.6-fold (95% CI 1.4-4.8) increase in preterm delivery associated with exposure to combination therapy with or without protease inhibitors compared with no treatment, after adjusting for CD4 count and injection drug use; risk was doubled in women who were on therapy before pregnancy as compared with those initiating therapy in the third trimester (The European Collaborative Study and the Swiss Mother+Child HIV Cohort Study, 2000).

In contrast, a preliminary report from an observational study of pregnant HIV-infected US women found no association between combination ARV therapy and preterm birth in over 3000 women, 82% of whom received combination therapy (Read, 2003). The highest rates of preterm delivery was among women on no ARV therapy. A large meta-analysis of 7 clinical studies including 2,123 pregnant women receiving antenatal ARV therapy and 1,143 women on no therapy found no increased rates of preterm labor,
low birth weight, low Apgar scores, or still birth with exposure to multiple ARV drugs as compared to one drug alone or to no therapy (Tuomala, 2002).

Given this conflicting data, no changes in antiretroviral management are indicated in pregnancy. Several studies have found increased preterm birth rates in women on no ARV therapy, especially with more advanced disease (Brocklehurst, 1998b; Leroy, 1998; Martin, 1997)

- Maternal adverse effects:
  - **Hepatotoxicity/Skin rash:** Women, particularly those with CD4 counts >250/mm$^3$, have an increased risk of developing symptomatic, often rash-associated, nevirapine-related hepatotoxicity (Stern, 2002) and deaths from hepatic failure have been reported in pregnant women receiving HAART regimens including nevirapine (Lyons, 2003; Langlet, 2000). It is not known whether pregnancy increases risk for hepatotoxicity in women receiving nevirapine; however, because some of the early symptoms of hepatotoxicity are relatively nonspecific and can be confused with common symptoms during pregnancy, health care providers for pregnant women receiving nevirapine should be aware of this potential complication and should regularly and frequently monitor clinical symptoms and hepatic transaminases (i.e., ALT and AST), particularly during the first 18 weeks of therapy, when this toxicity is most likely. When suggestive clinical symptoms develop, accompanied by elevation in ALT and/or AST, or when transaminases are significantly elevated in the absence of symptoms, nevirapine should be stopped and should not be restarted in the future. (USPHS Guidelines). When antiretroviral therapy is being started in pregnancy and CD4 counts are greater than 250/mm$^3$, nevirapine should be used as part of the regimen only if benefit clearly outweighs the risk. These toxicities have not been reported in women receiving single dose nevirapine for prevention of perinatal transmission.

  - **Lactic acidosis/steatosis:** Lactic acidosis and hepatic steatosis, clinical disorders linked to mitochondrial toxicity in long-term nucleoside analogue users, may have a female preponderance, and a possible genetic susceptibility has been suggested. Bristol-Myers Squibb has reported several maternal deaths due to lactic acidosis/hepatic steatosis, all in women receiving a combination of d4T/ddI as part of their antiretroviral regimen at the time of conception and for the duration of pregnancy, and other non-fatal cases of lactic acidosis have been reported in pregnant women receiving this combination (Mandelbrot, 2003). All nucleoside analogue drugs can induce mitochondrial dysfunction, but use of ddI and/or d4T carries greater risk than use of ZDV, 3TC, abacavir, or tenofovir because of their greater potential for interfering with mitochondrial replication. Typical initial symptoms are relatively nonspecific and include nausea, vomiting, abdominal pain, dyspnea, and weakness. Metabolic acidosis with elevated serum lactate and liver enzymes is common. It is not known if pregnancy increases the incidence of this syndrome; however, pregnancy itself can mimic some of the early symptoms of lactic acidosis/hepatic steatosis and is also associated with some rare but life-threatening disorders of liver metabolism (acute fatty liver of pregnancy; hemolysis, elevated liver enzymes and low platelets—the HELLP syndrome). Therefore, pregnant women receiving nucleoside analogue drugs should have liver enzymes and electrolytes evaluated
more frequently during the last trimester of pregnancy and any new symptoms should be evaluated promptly and thoroughly. Signs and symptoms of lactic acidosis/hepatic steatosis tend to improve with drug discontinuation; therefore, if this condition is suspected drugs should be stopped promptly. Because of the maternal deaths noted above, clinicians should prescribe the combination of d4T/ddI during pregnancy with caution and generally only when other nucleoside analogue combinations have failed or been associated with unacceptable toxicity or side effects.

- **Interaction of drugs with pregnancy-related side effects/physiologic changes:**

  - Drugs that cause gastrointestinal upset may not be well tolerated in early pregnancy when morning sickness is common and may increase risk for nonadherence or inadequate blood levels from vomiting. In this situation, all ARVs should be discontinued and restarted when the nausea and vomiting is gone or has been effectively treated.

  - Protease inhibitors and hyperglycemia: Protease inhibitors (PIs) have been associated with the development or worsening of existing hyperglycemia or diabetes and pregnancy also increases risk for glucose intolerance. It is unknown whether the use of PIs in pregnancy will exacerbate risk for development of gestational diabetes. Women receiving PIs in pregnancy should have their glucose levels monitored closely and be questioned regularly about symptoms of hyperglycemia.

- **Anemia:** Several antiretroviral agents, in particular ZDV, may cause bone marrow suppression and result in anemia. Pregnant women are at increased risk for anemia because of increased demands on nutritional stores, including iron and folic acid, and the addition of ARV regimens including ZDV may exacerbate anemia. Iron and folate supplementation should generally be given, as well as nutritional counseling to maintain adequate intake of other nutrients. Administration of ZDV is usually associated with macrocytosis; this should be kept in mind when evaluating anemia and should not exclude consideration of causes of microcytic or normocytic anemia, nor should it result in an assumption of causes of macrocytic anemia, such as folate or B12 deficiency. Treatment of anemia, including use of erythropoietin, may be considered in such women, as opposed to discontinuation of drug.

**ANTIRETROVIRAL DRUG RESISTANCE ISSUES**

The development of antiretroviral drug resistance is one of the major factors leading to therapy failure in HIV-infected individuals and there are concerns that resistance may also limit the effectiveness of antiretroviral drugs in providing prophylaxis against perinatal transmission (see IX A above). Resistance emerges under selective pressure, especially when viral replication is not completely suppressed. Women who have been treated in the past with incompletely suppressive regimens (e.g., single or dual nucleosides); have documented clinical, immunologic, or virologic failure with previous regimens (with or without a history of resistance on genotypic or phenotypic testing); or have a history of nonadherence or problems with intolerance are at increased risk for having resistance to one or more antiretroviral agents. These factors should be considered in decisions about choice of ARV regimen during pregnancy.
There is also an increasing prevalence of antiretroviral drug resistance in newly infected and treatment naïve individuals, implying transmission of drug-resistant strains. The prevalence of antiretroviral drug resistance in surveys of U.S. and European newly infected individuals who had never been exposed to therapy has been >10% for primary resistance mutations in the reverse transcriptase gene in the majority of studies and ranged as high as 23%; primary resistance mutations in the protease gene ranged from 1–16% (Wainbert, 1998; Weinstock, 2000; Little, 1999; Boden, 1999). Drug resistance testing is recommended if a woman has acute HIV infection during pregnancy and should be considered in pregnant women who are ARV naïve but have significant probability of having been infected with drug-resistant virus (Perinatal HIV Guidelines Working Group, 2004).

**GENERAL PRINCIPLES FOR ANTIRETROVIRAL TREATMENT IN PREGNANCY**
(Perinatal HIV Guidelines Working Group, 2004)

- Decisions regarding choice of antiretroviral regimens for maternal treatment should be the same in pregnant and nonpregnant women, with the additional considerations outlined above.

- Monitor CD4 count/viral load according to guidelines for nonpregnant adults: in pregnancy, this should be done approximately each trimester, but may be needed more frequently with failing or altered therapy. CD4 percentage may be a more accurate reflection of immune status during pregnancy than absolute CD4 cell count, because of possible variation in absolute CD4 count secondary to dilutional effects associated with hemodynamic changes in pregnancy.

- The three-part ZDV chemoprophylaxis regimen (Table 7-9) should be recommended as a minimum for all HIV-infected pregnant women to reduce the risk of perinatal HIV transmission. Current clinical trial and epidemiologic data confirm the effectiveness of this regimen; no other regimen studied to date in randomized clinical trials has shown superior results. However, cohort studies have suggested additional benefit to decreasing perinatal transmission with use of combination ARV regimens.

In women already receiving antiretroviral therapy when they become pregnant and this regimen does not include zidovudine, ZDV should be included as part of the regimen after 14 wk gestation, if feasible. There is evidence that duration of prior ZDV therapy in women with more advanced disease may not reduce effectiveness of ZDV in decreasing perinatal transmission (Stiehm, 1999). However, ZDV should not be substituted for another antiretroviral agent when this is likely to reduce the efficacy of this regimen in treatment of maternal disease, i.e., with previous clinical failure of ZDV or history of documented ZDV resistance. The decision to add ZDV to an effective regimen must take into account the possible effect on adherence.
Table 7-9: Zidovudine Perinatal Transmission Prophylaxis Regimen

| Antepartum | Initiation at 14–34 wk gestation and continued throughout pregnancy  
A. PACTG 076 Regimen: ZDV 100 mg 5 times daily  
B. Acceptable Alternative Regimen:  
• ZDV 200 mg 3 times daily or  
• ZDV 300 mg 2 times daily |
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<tr>
<td>Intrapartum</td>
<td>During labor, ZDV 2 mg/kg intravenously over 1 hr, followed by a continuous infusion of 1 mg/kg/hr intravenously until delivery.</td>
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<tr>
<td>Postpartum</td>
<td>Oral administration of ZDV to the newborn (ZDV syrup, 2 mg/kg every 6 hr) for the first 6 wk of life, beginning at 8–12 hr after birth.</td>
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</table>

In some circumstances ZDV cannot be used during the antepartum period (e.g., intolerance to ZDV). Stavudine (d4T) and ZDV are pharmacologically antagonistic and should not be used together; therefore, women on d4T-containing regimens with prior ZDV failure should be continued on the most effective regimen for their disease and ZDV should be excluded if d4T is maintained.

ZDV administration is recommended during the intrapartum period and for the newborn regardless of the antepartum antiretroviral regimen.

- **Effective combination antiretroviral therapy is recommended** (including ZDV if feasible) for women with clinical, immunologic, or virologic indications for treatment and for maximum prevention of perinatal transmission (regardless of clinical or immunologic status).

Women who present in labor with no prior antepartum antiretroviral therapy should be treated with one of several effective regimens, described below (Intrapartum) and in Table 7-10.

- **Women with high CD4 counts and low or undetectable HIV-RNA levels**, for whom initiation of antiretroviral therapy for the treatment of maternal infection would be considered optional, should be counseled about the potential benefits and risks of combination therapy and offered this therapy, along with the three-part ZDV perinatal prophylaxis regimen. Combination therapy should be selected based on efficacy data (in studies generally conducted among non-pregnant individuals); safety data for both mother and fetus/infant; and general experience with use in pregnancy. When several potential effective regimens are available and no specific safety concerns have been identified, in general drugs with wider experience in pregnancy should be selected.

Using ZDV alone is an option in this situation (with current USPHS guidelines when viral load <1000 copies/mL). This has the advantage of limiting exposure to other drugs during pregnancy but there are concerns about potential selection of ZDV-resistant viral variants and limitation of future maternal therapeutic options, as well
Table 7-10: 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 Intrapartum</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>
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<td>Nevirapine</td>
<td>Clinical trial, Africa; compared to oral ZDV given intrapartum and for one week to the infant</td>
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<td>Transmission at six weeks 12% with nevirapine compared to 21% with ZDV, a 47% reduction (95% CI*, 20–64%)</td>
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<td>Inexpensive Oral regimen Simple, easy to administer Can give directly observed treatment</td>
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<td>Unknown efficacy if mother has nevirapine-resistant virus Transient nevirapine resistance mutations detected at 6 weeks postpartum in 19% of women receiving single-dose intrapartum nevirapine, and 46% of infants who became infected despite receiving nevirapine</td>
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**ZDV-Nevirapine**  
Theoretical

| 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 |
| ZDV 2 mg/kg orally every six hours for six weeks AND Nevirapine single 2 mg/kg oral dose at age 48–72 hours** |
| No data |
| Potential benefit if maternal virus is resistant to either nevirapine or ZDV Synergistic inhibition of HIV replication with combination in vitro |
| Requires intravenous administration and availability of ZDV intravenous formulation Adherence to six week infant ZDV regimen Unknown if additive efficacy with combination Transient nevirapine resistance mutations detected at 6 weeks postpartum in 15% of women receiving single-dose intrapartum nevirapine with ZDV or other antiretroviral drugs |

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* 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 [121].

** 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.
as possibly increasing the risk for transmission. The development of resistance should be minimized by the relatively short duration of therapy and the more limited viral replication present in individuals with low HIV RNA level and high CD4 count. Follow-up of women enrolled in the PACTG 076 study has shown no significant differences in immunologic status or progression of disease (median follow-up 4.2 yr) in women who received ZDV compared with placebo recipients. (Bardeguez, 1998). However, recent data from PACTG 367 suggests that there is increased efficacy for prevention of perinatal transmission with combination ARV therapy, even when HIV-RNA is <1000 copies/mL (Shapiro, 2004).

- In antiretroviral-naive patients clinicians may consider delaying initiation of ARV therapy until after 10–12 wk of gestation, based on considerations of the woman’s health status, the potential (but generally low) risk of delaying therapy for several weeks, and the potential benefits of avoiding first trimester drug exposure for the fetus and the primary time period of nausea and vomiting in pregnancy.

- In antiretroviral-experienced patients, who become pregnant or are referred into prenatal care while receiving ARV therapy, therapy should be continued or modified, subject to the considerations outlined above. If pregnancy is recognized in the first trimester, some women and their clinicians may consider temporary discontinuation of therapy until after completion of the first trimester because of concerns about potential teratogenicity, or because of significant nausea and vomiting in early pregnancy leading to concerns about inadequate absorption of medications. Current data are insufficient to either support or refute fetal risk with early exposure to antiretroviral agents with the exception of efavirenz. Discontinuation of therapy may lead to viral rebound, which could theoretically increase risk of intrauterine HIV transmission or have an adverse effect on maternal disease. The woman’s clinical, immunologic, and virologic status should also be considered in decisions regarding continuation of therapy in the first trimester.

If the decision is made to stop therapy temporarily, all agents should be stopped simultaneously and restarted simultaneously in the second trimester to avoid development of drug resistance.

- Decisions regarding use of ARV therapy during pregnancy should be made by the woman after detailed discussion of benefits and potential risks of therapy. This includes discussion of:
  - treatment recommendations for health of the HIV-infected woman,
  - current information regarding effectiveness of antiretroviral therapy in reducing perinatal transmission,
  - known or potential effects of antiretroviral drug exposure on the pregnant woman,
  - known or potential effects of antiretroviral drug exposure on the fetus/newborn, and
  - the importance of adherence to any prescribed antiretroviral regimen.
There continue to be missed opportunities in prevention of transmission of HIV from mother to child. HIV has to first be identified in the woman; situations where counseling and testing have not been available or not utilized because of lack of perception of risk on the part of the woman or her health care provider have been associated with perinatal transmission in some cases. Women who become infected or seroconvert during pregnancy may be missed unless HIV testing is repeated later in pregnancy. Lack of prenatal care and active substance abuse, which frequently coexist, have also been linked to potentially avoidable increased risk for transmission (Bardeguez, 2000).

ANTIRETROVIRAL PREGNANCY REGISTRY

The Antiretroviral Pregnancy Registry is a collaborative effort between pharmaceutical companies, the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and obstetric and pediatric practitioners to collect observational information on antiretroviral exposure during pregnancy in order to assess potential fetal/infant anomalies after exposure to these agents. Patient names are not used and information is confidential. Health care providers who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs to the Registry: 1011 Ashes Drive, Wilmington, NC 28405; telephone (800) 258-4263; fax (800) 800-1052, Internet access www.APRegistry.com.

OPPORTUNISTIC INFECTIONS

Prophylaxis indications and recommendations for primary prophylaxis of opportunistic infections in pregnancy are noted in Table 7-11. Once an individual has had the following infections, prophylaxis to prevent recurrence is recommended as standard of care. (See Chapter IV on Primary Medical Care.) First-choice regimens are outlined.

- **Pneumocystis carinii pneumonia:** same regimen as for primary prophylaxis. Criteria for discontinuation: CD4 > 200/mm$^3$ for ≥ 3 mo.

- **Toxoplastic encephalitis:** sulfadiazine 500–1000 mg po qid plus pyrimethamine 25–50 mg po qd plus leucovorin 10–25 mg po qd; counsel regarding concerns about potential teratogenicity of pyrimethamine. Criteria for discontinuation: CD4 >200/mm$^3$ for ≥ 6 mo and completed initial therapy and asymptomatic for toxoplasmosis.

- **Disseminated Mycobacterium avium complex:** azithromycin 500 mg po qd plus ethambutol 15 mg/kg po qd. Criteria for discontinuation: CD4 >100/mm$^3$ for ≥ 6 mo and completed 12 mo of MAC therapy and asymptomatic for MAC.

- **CMV:** choice of agents should be individualized in pregnancy after consultation with experts. Criteria for discontinuation: CD4 >100–150/mm$^3$ for ≥ 6 mo and no evidence of active disease and regular ophthalmic examinations.
### Table 7-11: Opportunistic Infections and Primary Prophylaxis in Pregnant Women

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication</th>
<th>Regimen</th>
<th>Alternatives</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumocystis carinii</strong></td>
<td>CD4 &lt; 200/mm³ or oral thrush</td>
<td>TMP-SMZ DS 1 po qd</td>
<td>Dapsone 50 mg po bid</td>
<td>Some providers may prefer to use AP in first trimester because of lack of systemic absorption and fetal exposure, secondary to theoretical concerns about possible teratogenicity with systemic medications. Criteria for stopping primary prophylaxis: CD4 &gt; 200/mm³ for ≥ 3 mo.</td>
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<tr>
<td></td>
<td></td>
<td>TMP-SMZ SS 1 po qd</td>
<td>Dapsone 100 mg po qd</td>
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<td></td>
<td></td>
<td></td>
<td>Aerosolized pentamidine (AP) 300 mg q mo (via Respigrad IL nebulizer)</td>
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<td></td>
<td></td>
<td></td>
<td>TMP-SMZ DS 1 po tiw</td>
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<td>Dapsone 50 mg po bid</td>
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<td></td>
<td></td>
<td></td>
<td>TMP-SMZ DS 1 po tiw</td>
<td></td>
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<tr>
<td><strong>Mycobacterium tuberculosis</strong></td>
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<td></td>
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<tr>
<td>INH-sensitive</td>
<td>TST reaction ≥ 5 mm or prior positive TST without treatment or contact with active TB</td>
<td>INH 300 mg po qd plus pyridoxine 50 mg po qd x 9 mo</td>
<td>Rifampin 600 mg po qd x 4 mo</td>
<td>Some providers may choose to initiate prophylaxis after the first trimester, because of concerns about possible teratogenicity. Anecdotal experience with rifampin has not been associated with adverse pregnancy outcomes. Pyrazinamide should generally be avoided, particularly in the first trimester, because of lack of information concerning fetal effects. INH use during pregnancy has been associated with elevated risk for hepatotoxicity and LFTs should be monitored. Choice of drugs requires consultation with obstetric experts and public health authorities. Consult with obstetric experts and public health authorities if alternative regimen required</td>
</tr>
<tr>
<td>INH-resistant</td>
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<tr>
<td>multigug (INH and rifampin) resistant</td>
<td>Same; high probability of exposure to INH-resistant M. tuberculosis</td>
<td>INH 900 mg po biw plus pyridoxine 100 mg po biw x 9 mo</td>
<td>Rifampin 600mg po qd x 4 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Same; high probability of exposure to multidrug M. tuberculosis</td>
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<tr>
<td><strong>Toxoplasma gondii</strong></td>
<td>IgG antibody to toxoplasma and CD4 &lt; 100/mm³</td>
<td>TMP-SMZ DS 1 po qd</td>
<td>TMP-SMZ SS 1 po qd</td>
<td>If patient cannot tolerate TMP-SMZ, the recommended alternative is dapsone-pyrimethamine-leucovorin; however, because of the low incidence of TE during pregnancy and possible fetal risk with pyrimethamine, chemoprophylaxis may reasonably be deferred until after pregnancy Criteria for stopping primary prophylaxis: CD4 &gt; 200/mm³ for ≥ 3 mo.</td>
</tr>
<tr>
<td><strong>Mycobacterium avium complex</strong></td>
<td>CD4 &lt; 50 mm³</td>
<td>Azithromycin 1200 mg po qw</td>
<td>Rifabutin 300 mg po qd</td>
<td>Some providers may prefer to defer prophylaxis until after the first trimester, because of general concerns about administering drugs in early pregnancy. Experience with rifabutin in pregnancy is limited. Criteria for stopping primary prophylaxis: CD4 &gt; 100/mm³ for ≥ 3 mo.</td>
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*TMP-SMZ, trimethoprim-sulfamethoxazole; INH, isoniazid; TST, tuberculin skin test; TE, toxoplasmic encephalitis; LFT, liver function tests.

Source: Adapted from USPHS/IDSA, 2001.
• **Histoplasmosis**: amphotericin B 1.0 mg/kg iv qw; may be preferred, particularly during the first trimester, because of embryotoxicity and teratogenicity in animals exposed to itraconazole.

• **Cryptococcosis**: amphotericin B 0.6–1.0 mg/kg iv qw-tiw; may be preferred, particularly during the first trimester, because of craniofacial and skeletal abnormalities in infants after prolonged in utero exposure to fluconazole. Criteria for discontinuation: CD4 >100–200/mm$^3$ for ≥ 6 mo and completed initial therapy and asymptomatic for cryptococcosis.

• **Coccidiomycosis**: amphotericin B 1.0 mg/kg iv qw; may be preferred, particularly during the first trimester, because of craniofacial and skeletal abnormalities in infants after prolonged in utero exposure to fluconazole.

**IMMUNIZATIONS** (ACOG, 1991; CDC, 1993; USPHS/IDSA, 2001)

Immunization should be considered in pregnancy when the risk for exposure is high, risk of infection for mother or fetus is high, and the vaccine is thought unlikely to cause harm. HIV-infected individuals with immune suppression should avoid live virus or live bacteria vaccines. HIV-positive persons who are symptomatic or have low CD4 cell counts may have suboptimal responses to vaccination. Some, but not all, studies have shown a transient (<4 wk) increase in viral load after immunization. This is of some theoretical concern, given the association between viral load and perinatal transmission. This increase in viremia may be prevented with appropriate antiretroviral therapy (Bartlett, 2003). For this reason, clinicians may consider deferring routine vaccination until after the patient is on an effective antiretroviral regimen and avoiding administration late in pregnancy, close to delivery, when most transmission is thought to occur.

Current immunization recommendations for HIV-positive pregnant women are:

• **pneumococcal vaccine** — “generally recommended” if not received during previous 5 years; consider revaccination if initially immunized with CD4 < 200/mm$^3$ with increase to CD4 > 200/mm$^3$ in response to ARV treatment.

• **influenza vaccine** — “generally recommended”; administer before flu season annually.

• **tetanus-diphtheria (Td) vaccine** — booster dose every 10 yr after completion of primary series.

• **hepatitis B vaccine** — “generally recommended” for all susceptible (anti-HBc-negative) patients; three doses at 0, 1, 6 mo.
**hepatitis A vaccine** — “generally recommended” for all susceptible (anti-HAV-negative) patients with chronic hepatitis C or hepatitis B; also indicated before travel to endemic areas, in injection drug users, and with community outbreaks; two doses at 0, 6 mo.

**enhanced potency inactivated polio vaccine** — use if not previously immunized and traveling to areas where risk for exposure is high; oral polio vaccine is a live virus vaccine and is contraindicated in HIV-positive persons.

**immune globulins**
- immune globulin recommended for measles exposure in symptomatic HIV-positive persons and hepatitis A with exposure to HAV in close contact/sex partner or travel to underdeveloped country (especially in patients with advanced HIV, who may have poor antibody response to vaccine)
- hyperimmune globulins recommended:
  - varicella-zoster virus (VZV) immune globulin-susceptible adult (undetectable antibodies to VZV or no history of either chickenpox or shingles) after significant exposure (household, hospital room, close indoor contact >1 hr, prolonged face-to-face contact) to chickenpox or VZV; give within 96 hr of exposure.
  - hepatitis B immune globulin (HBIG)-needlestick or sexual contact with HBsAg+ person in susceptible individual (anti-HBc-negative); HBIG should be given and HBV vaccine series should be started within 14 days of exposure.

**REDUCTION OF SECONDARY RISK FACTORS**

Treatment of STIs or other coinfections; encouragement of safer sexual practices during pregnancy; discouragement of smoking and drug use; and substance abuse treatment should be employed as measures that may decrease risk of perinatal transmission.

**FREQUENCY OF VISITS**

Determined on an individual basis, based on gestational age, health of the mother, presence of pregnancy-related complications, antiretroviral regimen and response, and psychosocial needs. In uncomplicated pregnancies visits generally are scheduled monthly in early pregnancy and every 1–2 wk from 28–30 wk of gestation until delivery. Coordinate with other health care visits when possible.

**CONSULTATIONS TO CONSIDER DURING PREGNANCY**

Certain consultations may be needed during pregnancy in the HIV-infected woman. Ideally, many of these can be handled within the same clinic or center where the patient is seen for obstetrical care or for primary medical care. When possible, referral of the pregnant woman with HIV to an obstetrician with HIV expertise and experience is advised. In this case many of the HIV-specific treatment issues may also be managed by this individual. In general, possible consultative needs include:
• **Perinatology:** to address special obstetrical concerns, including use of HIV-related or other medications in pregnancy, discussions about fetal monitoring/evaluation, other appropriate antepartum/intrapartum evaluation and management. When indicated, consultation should ideally be with a perinatologist who has HIV experience/expertise

• **Infectious disease/HIV specialist (particularly important if newly diagnosed in pregnancy):** to address HIV-related treatment issues, including choice of ARV regimen, need for OI prophylaxis or treatment

• **Pediatrics:** to address care of the infant after birth, including testing for HIV, use of zidovudine and PCP prophylaxis in exposed infants

• **Nutrition:** to address proper diet, need for nutritional or vitamin/mineral supplementation; food safety issues, when needed

• **Substance abuse management:** when indicated

• **Psychiatry/psychology:** to address signs/symptoms of depression, other psychiatric disorders and their management, if needed

• **Social services:** to address needs related to housing, transportation, domestic violence, access to medications and to medical care, etc.

**COUNSELING AND SUPPORT**

• **Support systems:** At the initial visit the health care provider should assess the patient's support system — who knows her HIV status, problems encountered with disclosure, family and/or friends to whom she turns for ongoing support, barriers to disclosure to sexual or needle-sharing partners. These issues should be readdressed at intervals throughout pregnancy as needed. The use of peer counselors may be especially helpful.

• **Contraception use postpartum:** Discussion about postpartum contraceptive plans should be initiated in early to midpregnancy to allow comprehensive education and counseling about available options and adequate time for informed decision making.

• **Condom use during pregnancy:** Sexual activity should be reviewed at each visit and condom use reinforced.

• **Drug use/treatment:** History of and/or ongoing substance abuse, including tobacco and alcohol, as well as illicit drugs, should be assessed at the initial visit and at intervals during prenatal care, if indicated. Type of substance(s), amount of use, route of administration, and prior drug or alcohol treatment should be documented. The patient should be counseled about specific risks associated with substance abuse in pregnancy (see Chapter X on Substance Abuse) and drug or alcohol treatment during pregnancy should be encouraged and facilitated for active problems.
• **Adherence:** Each patient should be educated and counseled about the importance of adherence to prescribed medications, particularly antiretroviral drugs, before they are initiated and medication adherence should be assessed and reinforced at each visit. (See Chapter V on Adherence.)

• **Clinical trials:** Pregnant HIV-positive women should be informed about the availability of and offered participation in clinical trials for which they are eligible.

• **Advance directives:** The issue of advance directives for care in the event of sudden deterioration in the woman’s health, as well as guardianship plans for children in the event of the mother’s incapacitation or death, should be discussed; legal assistance should be facilitated, if needed.

**X. INTRAPARTUM**

The goals of intrapartum management are to further reduce the risk of perinatal transmission and to minimize the risk of maternal and neonatal complications.

**A. UNIVERSAL PRECAUTIONS**

Gowns, gloves, and eye protection should be used in all deliveries and in examinations or procedures likely to generate splashing blood or amniotic fluid. (See Chapter XIII on Occupational Exposure.) When used, this should provide adequate protection for healthcare workers. Medical care should not be altered due to considerations of potential occupational exposure.

**B. FETAL/MATERNAL MONITORING**

External fetal monitoring should be employed but avoid use of fetal scalp electrodes or fetal scalp sampling unless necessary to ensure fetal well-being. Avoid artificial rupture of membranes unless obstetrically indicated.

**C. MODE OF DELIVERY**

Cesarean section, when performed before the onset of labor and/or membrane rupture (scheduled or elective), has been associated with decreases in mother-to-child transmission ranging from 55–80% in the absence of ARV prophylaxis and with ZDV alone (International Perinatal HIV Group, 1999; European Mode of Delivery Collaboration, 1999). Studies included a meta-analysis of 15 prospective cohort studies including over 7800 mother-infant pairs and an international randomized mode of delivery clinical trial. Both studies were done before viral load testing and use of optimal combination ARV regimens became standard of care in the US. Neither study found a benefit with cesarean section performed after onset of labor or membrane rupture. Recent data from PACTG 367...
(Shapiro, 2004) in almost 2900 pregnancies found that in all subgroups of viral load, combination ARV therapy was associated with the lowest rates of transmission and with viral load <1000 c/mL, MTCT rates were significantly lower with multiagent vs single-agent ARV therapy (0.6% vs 2.2%, adjusted OR 0.2, 95% CI 0.04, 0.8) but did not differ by mode of delivery. Recent observational data from over 4500 women in the European Collaborative Study found that among women with undetectable viral load and after adjusting for ARV therapy during pregnancy, scheduled cesarean section was not associated with additional benefit in reduction of transmission (Thorne, 2004).

When making decisions about mode of delivery, potential maternal risks with cesarean section should be considered. Maternal morbidity and mortality are increased with cesarean section over vaginal delivery (Hebert, 1999). Although this risk is most marked with urgent or emergency cesarean section or after labor or membrane rupture, complications after scheduled cesarean section still exceed those seen with vaginal delivery (Roman, 1998; Gregory, 1998; Van Ham, 1997; McMahon, 1996). Most complications relate to postpartum infections (e.g., endometritis, wound infection, urinary tract infection, pneumonia) but also include complications related to hemorrhage, since blood loss is generally greater with cesarean section. Factors which increase the risk of complications include low socioeconomic status, genital infections, malnutrition, and smoking, and prolonged labor or membrane rupture, some of which may be more common in the setting of HIV infection.

Current data suggest that cesarean section is associated with a slightly increased risk of complications among HIV-infected women than among uninfected women, with the greatest differences seen among women with more advanced disease (European Mode of Delivery Collaboration, 1999; Watts, 2000; Read, 2001; Marcollet, 2002; Semprini, 1995; Grubert, 1999; Maiques-Montesinos, 1999; Vimercati, 2000; Grubert, 2002; Rodriguez, 2001; Urbani, 2001; European HIV in Obstetrics Group, 2004). However, complication rates in most studies of HIV-infected women were generally within the range reported among HIV-uninfected women and were not of sufficient frequency or severity to outweigh the potential benefit in selected cases where scheduled cesarean section may further decrease risk of MTCT (Perinatal HIV Guidelines Working Group, 2004). HIV-infected women, particularly when more immunosuppressed, may be at increased risk of postpartum endometritis, even with vaginal delivery (Temmerman, 1994).

Current recommendations (Perinatal HIV Guidelines Working Group, 2004; ACOG, 2000):

- Counsel all HIV-infected pregnant women about the possible benefit vs risk of scheduled cesarean section, as well as the limitations of current data. The woman's autonomy to make an informed decision regarding route of delivery should be respected and honored.
Scheduled cesarean section should be recommended in the following situations:
- HIV-RNA >1000 c/mL (regardless of ARV therapy).
- Women with unknown HIV-RNA level, not on ARV therapy or receiving ZDV alone.

Cesarean section is unlikely to add additional benefit in reduction of MTCT with HIV-RNA < 1000 c/mL in ARV-treated mothers.

The most recently determined HIV-RNA level should be used when counseling about mode of delivery.

Scheduled cesarean section should be performed at 38 weeks gestation, based on clinical and ultrasonographic estimates of gestational age, to minimize risk of labor or membrane rupture prior to procedure. This is associated with a small increased risk of iatrogenic preterm delivery and infant respiratory distress syndrome, as compared to standard recommendations for scheduled cesarean section at 39 weeks when indicated in HIV-uninfected women.

When scheduled cesarean section is performed, ZDV infusion should begin three hours before surgery to achieve adequate blood levels.

Other ARV medications taken during pregnancy should be given on schedule.

Prophylactic antibiotics are generally recommended at the time of scheduled cesarean section, although no controlled studies have evaluated their efficacy in this situation.

Women who have planned scheduled cesarean section but present in early labor or shortly after membrane rupture should be counseled and managed on an individual basis, based on most recent HIV-RNA level, ARV therapy, and projected length of labor (based on cervical dilatation at admission, rate of cervical change, and status of membranes/length of rupture). Cesarean section after 4 or more hours of membrane rupture is less likely to reduce MTCT and risks of perioperative infection after cesarean section are increased with increasing duration of membrane rupture.

**D. INTRAPARTUM ARV MANAGEMENT**

ARV medications taken during pregnancy should be continued on schedule during the intrapartum period, regardless of route of delivery. If one or more ARV agents are not tolerated during labor because of nausea or vomiting, the entire regimen should be stopped simultaneously and restarted simultaneously after delivery. Women who are taking combination ARV regimens for the purpose of reducing risk of MTCT and who do not yet meet criteria for starting ARV therapy for treatment of maternal disease may discontinue treatment after delivery. Recent pharmacokinetics data has shown prolonged levels of nevirapine postnatally with levels persisting for over 3 weeks in a
significant proportion of women who received a single-dose of NVP in labor (Muro, 2004; Jourdain, 2004); this has raised concerns that stopping all drugs in an NVP-containing regimen at the same time will result in a variable period of time during which the woman is exposed to functional monotherapy and may be at increased risk for developing resistance. The role of staggered stopping of components of an ARV regimen in this situation is unclear and the duration of continued therapy needed with a “tail” is unknown. A recent report of women receiving NVP/ZDV/3TC during pregnancy found that stopping the NVP at delivery and continuing ZDV/3TC for 5–7 additional days made no difference in development of resistance (Lyons, 2005).

Regardless of ARV regimen used during pregnancy, women with HIV infection should receive ZDV in labor: 2 mg/kg ZDV in a 1 hr IV loading dose, followed by 1 mg/kg/hr by IV infusion. In women on a d4T-containing regimen during pregnancy, intrapartum ARV management should involve IV ZDV OR continuation of the oral combination ARV regimen, but not both, because of the pharmacologic antagonism between ZDV and d4T. As noted above, if scheduled cesarean section is planned, ZDV infusion should begin 3 hr preoperatively.

For women who present in labor with no prior antiretroviral therapy, several effective regimens are available. (Guay, 1999; Perinatal HIV Guidelines Working Group, 2004; Wade, 1998) These are outlined in Table 7-10.

There has been increasing concern with use of single-dose NVP either alone or in addition to other antiretrovirals because of data showing rates of NVP resistance after delivery ranging from 15%–40% (Eshleman, 2001; Cunningham, 2002; Jourdain, 2004; Martinson, 2004) in women with detectable viremia. Variables associated with development of maternal NVP resistance include longer half-life of nevirapine in individual women (Jackson, 2000), high baseline HIV-RNA level or low baseline CD4 count (Eschleman, 2001), viral subtype (subtype D.A) (Eshleman, 2004), body compartment (breast milk vs plasma) (Lee, 2003), and timing of sampling post NVP administration (Martinson, 2004; Eshleman, 2001). In the SAINT trial in South Africa, in which women received both an intrapartum and a postpartum NVP dose, NVP resistance was detected in 67% of women and 53% of infected infants, with no further benefit in terms of reducing transmission (Sullivan, 2002). The potential implications for future maternal treatment options from resistance to one dose of nevirapine are unclear. However, in a recent report of women who were started on NVP-containing HAART regimens after delivery, exposure to single-dose NVP in labor was associated with inferior virologic response (HIV-RNA <50 c/mL) after 6 months of treatment; those with documented NVP-resistance were least likely to have optimal viral suppression (Jourdain, 2004).

NVP-resistance has also been detected in 17%–46% of infected infants after exposure to single-dose NVP (Eshleman, 2001) or single-dose NVP in addition to short-course ZDV (Chaix, 2004). Specific resistance mutations differed between mother and infant (Eshleman, 2001) and there was no evidence that the development of NVP-resistance increased risk of MTCT (Eshleman, 2001; Chaix, 2004).
Women of unknown HIV status who present in labor with no prenatal care may be offered rapid HIV testing, after careful counseling and with informed consent. Positive results should be confirmed by standard serologic testing but enable the initiation of an appropriate antiretroviral regimen to reduce the risk of perinatal transmission.

**E. VAGINAL CLEANSING**

A promising potential intervention to reduce transmission at the time of vaginal delivery is vaginal cleansing to decrease neonatal exposure to maternal blood and genital secretions. A clinical trial of 0.25% chlorhexidine manual vaginal cleansing on admission and every 4 hr until delivery in over 3300 women compared to some 3600 controls found no significant impact on HIV transmission, except when membranes had been ruptured for more than 4 hr before delivery (Biggar, 1996). However, this intervention reduced early neonatal and maternal postpartum infectious morbidity and neonatal mortality (Taha, 1997). A prospective trial of vaginal lavage using 0.2% or 0.4% chlorhexidine or no intervention also found no overall reduction in transmission with lavage, although data suggested that lavage before membrane rupture with chlorhexidine 0.4% may reduce MTCT (Gaillard, 2001). A more recent small (n = 107) vaginal cleansing study using benzalkonium chloride found no effect on perinatal HIV transmission or perinatal/infant mortality (Mandelbrot, 2002). Currently, vaginal cleansing cannot be recommended for prevention of mother-to-child transmission.

**XI. POSTPARTUM**

**A. INFANT FEEDING**

When replacement feeding is acceptable, feasible, affordable, sustainable, and safe, breastfeeding should be discouraged in women known to be HIV-infected, because of the well-documented increased risk for MTCT of HIV with breastfeeding. In low-resource settings, where there may be no good alternatives to breastfeeding, HIV-infected women should be counseled and assisted to exclusively breastfeed (breastmilk only without any additional solids or liquids) for up to 6 months, followed by rapid weaning (WHO, 2001). Breastfeeding mothers should be taught proper breastfeeding technique, including prevention, recognition, and prompt management of breast problems (e.g., mastitis, abscess, cracked nipples) or oral thrush or other oral lesions in the infant.
B. ASSESS HEALING
Assess healing of wound sites, uterine involution, and appropriate cessation of postpartum bleeding. Because of the potential for an increase in post-cesarean section wound infection, assessment of wound healing should be done between the time of hospital discharge and the routine postpartum visit.

C. CARE FOR MOTHER AND INFANT
HIV-infected mothers may neglect their own care while trying to provide appropriate care for their infant and other children or family members. It is essential that she be linked with comprehensive medical and supportive care services, including HIV specialty care; primary medical and gynecologic care; family planning; mental health or substance abuse treatment services; and assistance with food, housing, transportation, and legal/advocacy services, if needed. Although there are few data available, HIV-infected women may be at increased risk for postpartum depression.

Women who have received ZDV monotherapy during pregnancy should be reevaluated in the postpartum period with clinical assessment, CD4 count, and HIV RNA level to determine need for ongoing antiretroviral therapy. It is essential that access to and continuity of antiretroviral treatment as needed for maternal health be ensured.

Because of the physical recovery from giving birth, the stresses and demands of caring for a new baby, and possible postpartum depression, the new mother may be particularly vulnerable to problems with adherence to ARV treatment. Additional support and attention to this issue is warranted.

Similarly, the HIV-exposed infant should be linked into ongoing pediatric care, with HIV diagnostic tests as described below and appropriate HIV specialty care if HIV-infected.

D. CONTRACEPTION/CONDOM USE
Discussions about contraception and condom use should be continuous throughout pregnancy and reviewed and reinforced at the time of the postpartum visit.

E. LONG-TERM FOLLOW-UP OF MOTHER AND INFANT
All HIV-positive mothers and infants exposed to ZDV and/or other antiretroviral drugs or combinations during pregnancy should have long-term follow-up to assess possible late effects of these therapies on HIV progression in the mother or neoplasia or organ-system toxicity in exposed children.

A. DIAGNOSIS OF HIV

The standard for diagnosis of HIV infection in exposed infants is the use of viral assays (HIV DNA PCR (preferred), HIV RNA PCR, or viral culture) obtained within 48 hr of birth, at 1–2 mo, and 3–6 mo. HIV can be excluded in non-breastfed infants with two or more negative tests performed at age ≥ 1 mo, with one of these performed at age ≥ 4 mo. HIV IgG antibody tests will generally be positive in exposed infants for up to 18 mo of age because of transplacental passage; two negative tests performed at > 6 mo and at least 1 mo apart will also exclude infection in infants without clinical evidence of infection. P24 antigen testing is less sensitive than other virologic tests and has a high frequency of false-positive results in infants < 1 mo of age.

HIV DNA PCR is the preferred virologic assay for diagnosis with 93% (90% CI=76–97%) sensitivity by age 14 days (Dunn, 1995). Data on use of HIV RNA PCR are more limited but sensitivity appears to be comparable to HIV-DNA PCR for early diagnosis of HIV infants. HIV culture is sensitive for early diagnosis but is more complex and expensive, and has a longer turnaround time for results. Using these tests approximately 40% of infected infants can be identified by age 48 hr and are considered to have early or intrauterine infection; infants with initial negative testing during the first week after birth and subsequent positive tests are considered to have intrapartum infection. Almost all infected infants can now be diagnosed by the age of 4–6 mo. ZDV monotherapy for perinatal prophylaxis has not been shown to delay detection of HIV or decrease sensitivity or predictive value of virologic assays (Connor, 1994; Kovacs, 1995), although performance of these tests when the mother has received more intensive combination antiretroviral therapies has not been studied.

B. ARV TREATMENT

All HIV-exposed infants should receive ZDV prophylaxis (2 mg/kg every 6 hr) for the first 6 wk of life as part of the three-part zidovudine regimen to prevent perinatal HIV transmission. If the mother has received no antepartum or intrapartum ZDV, the newborn regimen should be started as soon as possible after delivery, preferably with 6–12 hr of birth. For preterm infants (<35 wks), ZDV 1.5 mg/kg IV or 2.0 mg/kg po q 12 hr, then increased to q 8 hr at 2 wk (if >30 wks at birth) or 4 wk (if <30 wks at birth) is recommended (Capparelli, 2003). Initiation of ZDV prophylaxis for the neonate within 48 hr (most infants initiated
ZDV within 24 hr) of birth resulted in an approximately 50% decrease in infection compared with no therapy (Wade, 1998). A recent clinical trial of infant post-exposure prophylaxis (no maternal antepartum or intrapartum ARV exposure) in breastfeeding infants in Malawi found that single-dose infant nevirapine plus one week of ZDV had 36.4% efficacy as compared to single-dose infant nevirapine alone when evaluation was limited to infants uninfected at birth (Taha, 2003). This study does not address whether this regimen is superior to 6 wks of ZDV alone, which remains the standard recommendation from the USPHS. The use of single-dose nevirapine in mothers and newborns has been associated with the development of nevirapine resistance in a certain proportion of infants infected despite prophylaxis, as noted above. The implications of this resistance for progression of infection or response to future NNRTI-containing ARV regimens is unknown. The efficacy of other ARV agents or combinations in HIV-exposed infants, particularly in cases where the mother is known or suspected to have ZDV or NVP resistance, is unknown and appropriate dosing regimens in neonates are not well-defined for many drugs.

Once infection is documented, more intensive combination antiretroviral therapy is recommended with clinical symptoms of HIV infection or evidence of immunosuppression (immune categories 2 or 3 — Table 7-12) regardless of age or viral load. Some experts recommend initiating potent ART as soon as the diagnosis is confirmed, regardless of clinical or immunologic status or viral load, because HIV-infected infants under the age of 12 mo are considered to be at high risk for disease progression and the prognostic value of standard virologic or immunologic parameters is less than that for older children. Once HIV infection is confirmed, decisions about antiretroviral therapy should be made in consultation with a specialist in the treatment of pediatric HIV infection.
### Table 7-12: 1994 Revised Human Immunodeficiency Virus Pediatric Classification System

<table>
<thead>
<tr>
<th>Immune Category</th>
<th>&lt;12 Mo</th>
<th>5 Yr</th>
<th>6–12 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1: no suppression</td>
<td>≥1500</td>
<td>≥25%</td>
<td>≥1000</td>
</tr>
<tr>
<td>Category 2: moderate suppression</td>
<td>750–1499</td>
<td>15%–24%</td>
<td>500–999</td>
</tr>
<tr>
<td>Category 3: severe suppression</td>
<td>&lt;750</td>
<td>&lt;15%</td>
<td>&lt;500</td>
</tr>
</tbody>
</table>

#### Clinical Category

**Children < 13 Yr**

- **Category N: not symptomatic**
  - Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

- **Category A: mildly symptomatic**
  - Children with 2 or more of the following conditions but none of the conditions listed in categories B and C:
    - Lymphadenopathy (>0.5 cm at more than two sites; bilateral = one site)
    - Hepatomegaly
    - Splenomegaly
    - Dermatitis
    - Parotitis
    - Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

- **Category B: moderately symptomatic**
  - Children who have symptomatic conditions, other than those listed for category A or category C, that are attributed to HIV infection. Examples of conditions in clinical category B include, but are not limited to, the following:
    - Anemia (<8 gm/dL), neutropenia (<1,000/mm³), or thrombocytopenia (<100,000/mm³) persisting for ≥30 days
    - Bacterial meningitis, pneumonia, or sepsis (single episode)
    - Candidiasis, oropharyngeal (ie, thrush) persisting for >2 months in children aged >6 months
    - Cardiomyopathy
    - Cytomegalovirus infection with onset before age 1 month
    - Diarrhea, recurrent or chronic
    - Hepatitis
    - Herpes simplex virus (HSV) stomatitis, recurrent (ie, more than two episodes within 1 year)
    - HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month

- **Category C: severely symptomatic**
  - Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome, with the exception of LIP (which is a category B condition)

**Source:** Adapted from CDC, 1994.
C. **Pneumocystis carinii** Pneumonia Prophylaxis

All HIV-exposed infants should receive *P. carinii* pneumonia prophylaxis with trimethoprim-sulfamethoxazole (150/750 mg/m²/day in two divided doses po tiw on consecutive days) beginning at 4–6 wk and extending for the first year of life or until HIV infection is excluded. Dapsone or atovaquone are alternatives.

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