Preconception Care and Contraception for HIV Infected Women

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Chapter 7:

Preconception Care and Contraception

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Chapter 7 at a Glance

Preconception Care and Contraception

Studies of pregnancy in the HAART era indicate that pregnancy is common after a diagnosis of HIV and live birth rates are significantly increased when compared with the pre-HAART period; abortion is less common; and HIV infected women often desire more children, influenced by advances in HIV care (*Am J Public Health* 2000;90:1074; *AIDS* 2000;14:2171; *AIDS* 2004;18:281; *Am J Obstet Gynecol* 2007;196:541.e1; *AIDS Care* 2011;23:1093). Many HIV infected women, 80% of whom are of childbearing age, now feel that they can have more normal lives that include bearing children with the realistic hope of raising them to adulthood. Viewed through this lens, pregnancies among women with HIV can be seen as part of the success story of HIV—a chapter in the evolution of HIV infection from a progressive and uniformly fatal condition to a chronic disease that is serious but survivable.

The U.S. Centers for Disease Control and Prevention (CDC), the American Congress of Obstetrics and Gynecology (ACOG), and other national organizations recommend offering all women of childbearing age comprehensive family planning, including effective contraceptive counseling, and the opportunity to receive preconception counseling and care as an integral component of routine primary medical care (*Obstet Gynecol* 2007;110:1473; *Obstet Gynecol* 2009;452:1444; *MMWR Recomm Rep* 2006;*55*(RR-6):1).

This chapter reviews issues related to reproductive decision-making, including preconception care and counseling and use of contraception to reduce unintended pregnancy.

Preconception Care

The CDC defines preconception care as a series of "interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management" (*MMWR Recomm Rep* 2006;*55*(RR-6):1).

Goals of preconception care include

- prevent unintended pregnancy,
- optimize maternal health prior to pregnancy,
- improve maternal and fetal outcomes in pregnancy,
- prevent mother-to-child transmission of HIV, and
- prevent transmission of HIV to an uninfected sexual partner while trying to conceive.

When to Discuss Pregnancy

Several studies have documented predictors of the desire to conceive (*AIDS Behav* 2010;14:1106; *PLoS One* 2009;4:e7925; *AIDS Behav* 2009;13:949; *Fam Plann Perspect* 2001;33:144). Commonly, the women who most want to conceive are younger, have no children, and have a husband/partner/other family member who wants them to get pregnant. Nonetheless, the desire to have a child and decisions regarding whether and when to do so are complex, multifaceted, changeable over time, and not necessarily related to health status. Therefore, all women of childbearing capacity should be assessed for childbearing desires or intentions at their initial evaluation with an HIV care provider and at regular intervals throughout the course of care. This is particularly important if a woman

- has expressed an interest in conceiving,
- is not using effective contraception or is not using it regularly or appropriately,
- has changed sexual partners or experienced a change in personal circumstances (e.g., is postpartum),
- is taking medications with potential reproductive toxicity or interactions with hormonal contraception,
- is at risk for unintended pregnancy,
- may benefit from or be otherwise affected by new developments in the field of pregnancy and HIV, and/or
- plans to enroll in clinical trials.

Primary HIV care providers should be proactive in addressing reproductive needs and desires, as many women may not feel comfortable in raising these issues for fear of being judged harshly or discouraged (*AIDS Patient Care STDS* 2010;24:317). Patient-provider tools such as those shown in Figure 7-1 may facilitate this discussion by helping to identify patient needs.

Figure 7-1

HIV and Pregnancy: Decision Aids for the Patient and Provider

1. Patient Decision Aid

With effective HIV treatment, women and men with HIV infection can now enjoy a long and healthy life and can look forward to a future that may include planning a family. When taken during pregnancy, HIV medications can decrease the risk of transmitting HIV to the baby to 1%–2% or less. It is also important to prevent pregnancy when you are not yet ready to become a mother. As a woman with HIV, it is important to plan carefully so that you can get the treatment you need to have a safer pregnancy, prevent transmission of HIV to your baby, and prevent pregnancy until you are ready. This survey is designed to help you and your healthcare provider take the first steps in that planning.

Name: _____ Date: _____

1. Your current age is _____

2. Have you ever been pregnant? ☐ **YES** ☐ **NO**

3. If **YES**, how many times? _____ How many children do you have? _____

4. Are you interested in getting pregnant? ☐ **YES** ☐ **NO**

5. If **YES**, when do you wish to conceive?
   ☐ Trying to conceive now ☐ 6 months – 1 year from now
   ☐ 1 – 2 years from now ☐ More than 2 years from now

6. Have you had sex with a man in the last 6 months? ☐ **YES** ☐ **NO**

7. Are you currently using condoms? ☐ **YES** ☐ **NO**

8. Are you currently using birth control other than condoms?

   A. What type?
   ☐ None ☐ Birth control pill ☐ IUD ☐ Injection (Depo-Provera)
   ☐ Patch/vaginal ring ☐ Implant under the skin (Implanon)
   ☐ Sterilization (tubes tied) ☐ Unsure
   ☐ Other: _____

   B. Are you trying to get pregnant? ☐ **YES** ☐ **NO**

9. Would you or your partner like to talk to someone about planning a safer pregnancy that may reduce the risk of HIV transmission to your baby? ☐ **YES** ☐ **NO**

Figure 7-1 continued

HIV and Pregnancy: Decision Aids for the Patient and Provider

2. Provider Decision Aid

This tool is designed to help you, the health care provider, better address fertility issues (desire to conceive and desire to prevent pregnancy) with your patients.

1. Patient is postmenopausal or post-hysterectomy.
   - A. Yes – End of tool
   - B. No – Go to question 2
2. Does patient wish to have more children?
   - A. Yes – Go to question 3
   - B. No – Go to question 5
3. Does patient wish to conceive within the next year?
   - A. Yes – Go to question 4
   - B. No – Go to question 5
4. Patient would like to conceive within the next year.
   - A. Review medication list with patient for drugs that are contraindicated in women trying to conceive (e.g., efavirenz, statins, ribavarin, tetracycline/doxycycline). Other drugs should be used unless no alternate agents are available that are both effective and safer in women who are trying to conceive.
   - AND
   - B. Offer and encourage referral for preconception counseling and evaluation.
5. Patient wishes to prevent pregnancy.
   - A. Patient has completed childbearing: Refer to a gynecologist to discuss long-term or permanent options for contraception.
   - OR
   - B. Patient wants more children, but not within the next year: Review nonpermanent options for contraception and strongly recommend referral for preconception counseling.

Key Considerations:

1. Patient has a problem with irregular menses or amenorrhea: If yes, perform a pregnancy test and refer for a gynecologic evaluation.
2. Menopause: Can be difficult to diagnose
   - – If the woman is >50 y with no vaginal bleeding for >1 y, she is postmenopausal.
   - – If uncertain, refer for a gynecologic evaluation.
3. Formal preconception counseling and evaluation is strongly recommended if the patient
   - A. Is in a serodiscordant relationship
   - B. Has significant medical co-morbidities
   - C. Has problems with substance abuse
   - D. Is taking a medication that is contraindicated in women trying to conceive
   - E. Reports a desire to conceive and a history of infertility or difficulty getting pregnant

While primary HIV care providers may feel comfortable discussing contraception and prevention of mother-to-child-transmission (MTCT) of HIV, they may not feel fully able to address preconception counseling and care needs, in which case consultation and referral are appropriate.

Evaluation

Table 7-1 outlines the comprehensive preconception evaluation designed to identify factors that may affect a woman's ability to get pregnant or may increase the risk of adverse pregnancy outcomes for the mother or her fetus.

Table 7-1

Comprehensive Preconception Evaluation

History	Comments
HIV	• Date of diagnosis • History of OIs or other HIV-related illnesses • ART history, including use in prior pregnancies and/or reasons for change(s) in ART regimens (e.g., adverse effects, resistance, tolerability) • Adherence history and challenges • Results of resistance tests • Nadir and current CD4+ cell count • Current HIV VL
Pregnancy	• Number of previous pregnancies and their outcomes (e.g., miscarriages, abortions, ectopic pregnancy, preterm births) • Number of living children and ages • Number of HIV infected children • Pregnancy complications (e.g., preterm labor, preeclampsia, birth defects) • Modes of delivery
Gynecologic	• Prior and current contraception use • Satisfaction with current contraception method and/or adverse effects • Current condom use and consistency of use (100% vs <100%) • Prior STIs or genital tract infections • Past difficulties in conceiving • Abnormal Pap smears and treatment • Other gynecologic problems and treatment (e.g., fibroids, endometriosis)
General Medical and Surgical	• Other medical conditions (e.g., DM, HTN, renal or cardiac disease, depression or other psychiatric illness) • All prior surgery • Blood type and history of transfusions • Allergies
Immunizations	• HBV, HAV, influenza, pneumococcus, HPV, tetanus
Medications	• All prescribed medications • All OTC medications • All complementary medications
Nutrition	• History of anemia or nutritional deficiencies • Special diet (e.g., vegetarian, vegan, gluten-free) • Use of nutritional supplements and vitamins

Table 7-1 *continued*

Comprehensive Preconception Evaluation

History	Comments
Social History	• Relationship status • Use of illicit drugs, tobacco, alcohol • Employment status • Social support and disclosure to partner and others • Economic support • History and nature of domestic violence (i.e., physical, sexual, psychological)
Family History of Heritable Diseases	• Birth defects • Chromosomal abnormalities • Muscular dystrophy • Sickle cell disease • Mental retardation • Others
Male Partner	• HIV status and knowledge of partner's status • If HIV infected: - Disclosure status - History of OIs and other HIV-related conditions - ART history and history of adverse effects, resistance, adherence problems - Nadir and current CD4+ cell count - Current HIV VL • Medical and reproductive history • Medications • Use of illicit drugs, tobacco, alcohol • Employment status
Physical Exam	• Comprehensive, with focus on genital tract
Laboratory (Emphasis is on lab tests that will affect counseling and/or result in changes in care prior to pregnancy)	• Tests • STI screening: GC/chlamydia; syphilis; HSV culture or HSV-2 antibody, if indicated • CBC • Current CD4+ cell count • HIV RNA • Resistance testing, if indicated • Rubella • HBV: HBsAb, HBsAg • HCV antibody and HCV RNA, if indicated • Pap smear • Other, as indicated by medical history and medications

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Preconception Counseling

Preconception counseling of the HIV infected woman should address the following issues:

- Effect of pregnancy on HIV course (see Chapter 8, ***HIV and Pregnancy***)
- Effect of HIV on pregnancy course and outcome (see Chapter 8, ***HIV and Pregnancy***)
- MTCT and prevention, including the role of antiretroviral drugs (ARVs), cesarean section, etc.
- Use of HIV-related medications, including maternal and fetal safety and toxicity
- Long-term care plans, including advance directives, care for children should mother and/or father die or become disabled
- Non-HIV-related factors, including age, drug use, other medical conditions, and their potential effects on pregnancy course or outcome
- Safe conception if the patient is in a serodiscordant relationship
- Safe sexual practices
- Healthy living and health maintenance, including smoking cessation, elimination of alcohol and illicit drug use, etc.

Preconception Interventions

Preconception interventions for the HIV infected woman may include the following:

- Contraception to reduce unintended pregnancy (see below)
- Initiation or modification of antiretroviral therapy (ART) regimen. ART should be initiated prior to attempts to conceive if the woman meets criteria for starting ART, in which case maximal suppression of HIV viral load (VL) should be achieved prior to pregnancy and the patient's regimen should be well tolerated without significant adverse effects.
- If a woman does not meet current CD4+ cell count criteria, initiation of ART prior to conception may still be considered. Maximal suppression of HIV VL potentially reduces, though it does not eliminate, the risk of perinatal transmission (*AIDS* 2008;22:973; *Clin Infect Dis* 2010;50:585). Also to be considered, however, are the potential adverse effects of ART on certain pregnancy outcomes, the patient's readiness for lifelong therapy, and the risks versus benefits of stopping ART postpartum (see Chapter 8, ***HIV and Pregnancy***).
- If a patient's current ART regimen is not effective (i.e., suboptimal suppression of VL), not well tolerated, associated with significant adverse effects, or contains EFV, it should be modified prior to attempts to conceive.

Optimal treatment of other medical conditions: Also recommended is optimal therapeutic control of hypertension, diabetes, and other medical conditions. Care providers should review all of a woman's current medications (not just HIV-related medications) and, if indicated, substitute medications that may be safer in pregnancy. The risk-benefit profile of any medication is important to consider. A drug classified as U.S. Food and Drug Administration (FDA) category D signifies positive evidence of human fetal risk, but potential maternal benefits may make the risk acceptable. FDA category X is assigned to drugs for which the risk to a pregnant woman clearly outweighs any possible benefit. If a woman is taking an FDA category D or X drug, the feasibility of safely stopping or substituting for the medication must be determined, and expert consultation is advised (see Table 13-1, p. 448). (*Note:* At the time of publication of this guide, the FDA was preparing a revision of drug categories for pregnancy and lactation that will likely do away with the current letter categories.)

Other preconception interventions should include the following when indicated:

- Opportunistic infection (OI) treatment or prophylaxis
- Screening for and treatment of existing genital tract infections in both partners (genital tract inflammation is associated with increased HIV shedding in the genital tract, even when plasma VL is fully suppressed; if untreated, genital tract infections may increase the risk of adverse pregnancy outcomes and potential MTCT)
- Treatment of anemia and/or other nutritional interventions
- Treatment of drug and/or alcohol abuse
- Assistance with smoking cessation
- Treatment of depression and other mental illnesses
- Immunizations
- Provision of prenatal vitamins, including folic acid supplementation for prevention of neural tube defects
- Assistance with advance directives

Safe Conception

If both partners are HIV infected, condom use should be encouraged. Unprotected intercourse should be timed to coincide with the most fertile period of a woman's menstrual cycle. Fertile periods may be determined with ovulation predictors, basal body temperature measurement, or the use of an ovulation calculator (see, for example: http://www.marchofdimes.com/ovulation_calendar.html. Accessed 7/9/2012). Semen analysis should be considered because HIV is associated with a higher prevalence of semen abnormalities (see below).

Serodiscordant Couples

There are an estimated 140,000 HIV-serodiscordant heterosexual couples in the United States, about half of whom want more children (*Am J Obstet Gynecol* 2011;204:488.e1). Expert consultation is recommended to address the individual needs of serodiscordant couples attempting to conceive.

Female HIV infected and male uninfected: The uninfected partner of an HIV infected woman should be encouraged to use condoms with each act of intercourse. Intravaginal insemination for conception using the partner's semen can be performed at home or by the healthcare provider and is effective with normal fertility. Timed insemination during the most fertile period may be considered to maximize the chance of conception. She should be on ART and attain maximal viral suppression prior to attempting conception. PrEp (see below) can also be considered for an uninfected male partner who wants additional protection if the couple opt for timed unprotected intercourse when trying to conceive.

Male HIV infected and female uninfected: The risk of HIV transmission to an uninfected woman with an HIV infected partner can be minimized but not entirely eliminated, unless donor sperm is used. Observational studies and a meta-analysis have demonstrated a decreased rate of HIV transmission among heterosexual serodiscordant couples on ART, particularly when HIV VL is fully suppressed in the infected partner (*AIDS* 2009;23:1397). Recent data from HPTN 052, a randomized clinical trial designed to evaluate ART for the prevention of sexual transmission among serodiscordant couples, indicates that earlier initiation of ART (at CD4+ cell counts 350–550 cells/mm^3) reduced HIV transmission to the uninfected partner by 96% (*N Engl J Med* 2011; 365(6):493).

- **ART for the infected male:** He should be on ART and attain maximal viral suppression prior to attempting conception.
- Treatment of an infected partner does not fully protect against HIV transmission, even in the setting of maximal plasma VL suppression. Although effective ART decreases virus in genital secretions, discordance between plasma and genital VLs has been reported, and individuals may have isolated semen HIV shedding even when plasma VL is undetectable (*AIDS* 2008;22:1677; *AIDS* 2010;24(16):2489) and independent of semen drug levels and ART regimen (*AIDS* 2009;23(15):2050). Additionally, ARV penetration of the genital tract varies among agents (*Curr Opin HIV AIDS* 2010;5(4):335).

Screen for and treat genital tract infections: Genital tract infections, both sexually transmitted and nonsexually transmitted (e.g., bacterial vaginosis, yeast), may increase the HIV uninfected woman's vulnerability to HIV acquisition. In the HIV infected man, genital tract infections may increase his infectiousness.

Semen analysis: Semen abnormalities are more common in the setting of HIV. Abnormalities are correlated with lower CD4+ cell counts and may include lower sperm volume, concentration, and motility, and higher rates of abnormal forms (*Hum Reprod* 2004;19:2289; *Arch Gynecol Obstet* 2011; 284(1):229). Some data suggest that ART may have an adverse effect on semen quality. A longitudinal study of 34 men with serial semen analyses prior to ART and

up to 48 weeks post-ART found that the proportion of progressively motile spermatozoa was low at all time points, but decreased significantly over the course of follow-up (*AIDS* 2008;22:637). Therefore, when there is little or no likelihood of natural conception, an uninfected female partner may be at increased risk for infection through repetitive exposure over time.

Assisted reproductive technology: The method with the lowest risk of transmission is semen washing, with negative PCR testing after preparation, coupled with intrauterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI). The results of studies that, combined, included more than 6500 cycles of sperm washing plus IUI, IVF, or ICSI indicate no female seroconversions (*Reprod Biomed Online* 2005;10:135; *AIDS* 2007;21:1909; *Fertil Steril* 2009;91:2455). A more recent systematic analysis of safety and effectiveness of ART in serodiscordant couples found no seroconversions in 3900 IUI cycles (50% cumulative pregnancy rate) and 738 ICSI/IVF cycles (53% cumulative pregnancy rate (*Fertil Steril* 2011;95:1684).

Most insurance plans, however, (including Medicare/Medicaid) do not cover these services and the cost is usually prohibitive. The National Perinatal HIV Hotline (1-888-448-8765) can provide a list of institutions offering reproductive services for HIV serodiscordant couples.

Timed unprotected intercourse and condom use at all other times: For serodiscordant couples who cannot afford assisted reproduction and who, after comprehensive counseling, still wish to conceive, this is the best approach. The most fertile time in a woman's menstrual cycle can be determined with ovulation predictors (available over the counter at pharmacies), basal body temperature measurement, or ovulation calculators (e.g., http://www.marchofdimes.com/ovulation_calendar.html).

Pre-exposure prophylaxis (PrEP): Providing ARVs topically or orally to an uninfected female partner may offer some additional protection against HIV transmission from an infected male partner during attempts to conceive, but study results to date have been mixed. A Phase IIb randomized placebo-controlled trial (CAPRISA 004) of a 1% intravaginal TDF gel used before and after sex reduced HIV acquisition by 39% and by up to 54% with greater adherence (*Science* 2010;329(5996):1168); however, in the VOICE study, a multi-country, multi-arm Phase IIb study of vaginal and oral PrEP in women at high risk of acquiring HIV, 1% TDF gel used daily was no better than placebo. A Phase III study of daily oral TDF/FTC in uninfected male couples (iPrEX) reported a 44% overall reduction in HIV acquisition compared with placebo; effectiveness was significantly affected by adherence (*N Engl J Med* 2010;363(27):2587; *N Engl J Med* 2010;363(27):2663). In the Partners PrEP study conducted in Kenya and Uganda among more than 1400 HIV-serodiscordant couples, the use of daily TDF or daily TDF/FTC by the uninfected partner was found to have efficacy of 66% and 73%, respectively, compared with placebo, in reducing HIV transmission (reported 97% adherence by returned pill count, but only 81% of those assigned to the active-treatment arm had detectable blood levels of the study drug) (*N Engl J Med* 2012;367(5):399). Within a subgroup of those who received TDF/FTC and whose plasma drug levels were tested, measurable concentrations of TDF

were associated with a 90% reduction in risk compared with placebo. In another trial in Botswana, TDF/FTC given to 1200 HIV uninfected heterosexual men and women reduced transmission by 66% compared with placebo with 84% adherence by returned pill count (Curr *Opin Infect Dis* 2012;*25*(1):51; *N Engl J Med* 2012;*367*(*5*):423). The FEM-PrEP clinical trial and the VOICE study, however, both conducted in high-risk uninfected African women, found no efficacy with either daily oral TDF/FTC or TDF, but adherence was quite low with detectable drug levels found in less than one-third of those tested and randomized to active drug. (Curr *Opin Infect Dis* 2012 Feb;*25*(1):51; *N Engl J Med* 2012;*367*(*5*):411; 20th Conference on Retroviruses and opportunistic Infections, Atlanta, GA, Abstract 26LB, 2013). Therefore, it is likely that adherence is a key factor in the discrepant results of these studies.

In studies of PrEP to date, safety and tolerability were excellent and limited resistance was observed in seroconverters. Twice-weekly and coital dosing of TDF/FTC, as well as longer-acting formulations, intravaginal rings, and new candidate ARVs, are being evaluated for PrEP.

Use of this approach will require individual counseling that addresses a number of considerations: 1) effectiveness of periodic (e.g., use for a certain period of days, currently undefined, around ovulation) versus daily use; 2) effectiveness in the presence of resistance to agents used for prophylaxis in the infected partner; 3) risk of resistance should transmission occur despite the use of prophylaxis; 4) potential risk of adverse effects in pregnancy or to the developing fetus; and *5*) potential decrease in other risk-reduction behaviors, such as condom use. Providers should counsel patients that the efficacy of PrEP is highly dependent on adherence. In August 2012 the CDC issued the following interim guidance for clinicians considering the use of PrEP for HIV prevention in heterosexually active adults, particularly those with known HIV-infected partners (*MMWR* 2012; 61(31):586) (see Chapter 3). It is not known if the use of PrEP adds additional benefit when the infected partner has maximal viral suppression.

HIV and Fertility

HIV appears to have an adverse effect on fertility in both symptomatic and asymptomatic women (*AIDS* 1999;13:517; *J Acquir Immune Defic Syndr* 2000;*25*(4):345; *Lancet* 1998;351:98; *Am J Epidemiol* 2000;151:1020; *Int J STD AIDS* 2006;17(12):842). This includes increased risk of infertility and pregnancy loss. Recent data from low-resource settings suggest that fertility improves after treatment with ART (*AIDS Res Treat* 2011;2011:519492; *PLoS Med* 2010;*7*(2):e1000229).

Potential Causes of Infertility

In the setting of HIV infection there are several potential causes of infertility, some of which are confounding factors that may independently reduce fertility.

- HIV infected women frequently have a history of other sexually transmitted infections (STIs), such as gonorrhea, chlamydia, and syphilis, which reduce fertility. In a cross-sectional study of fertility assessment in 130 HIV infected women, 27.8% had tubal occlusion, generally indicative of past tubal damage with gonorrhea or chlamydia (*Reprod Biomed Online* 2007;14:488).
- HIV infected women may be at increased risk for amenorrhea and/or ovulatory dysfunction due to chronic drug use (especially use of opiates) and/or poor nutrition and weight loss.
- Menstrual dysfunction and/or amenorrhea are common in the setting of HIV; however, controlled studies have produced conflicting results regarding a direct effect of HIV or HIV-related immunosuppression on menstrual function.
- Sexual dysfunction is reported in 53%–71% of HIV infected men. It may be associated with the presence and/or treatment of depression or anxiety. Semen abnormalities are also more common in the setting of HIV (see above).
- Higher VLs have been associated with decreased fertility (*Int J STD AIDS* 2006;17:842).

Legal right to care: In a 1998 U.S. Supreme Court decision, *Bragdon v. Abbott*, the Court ruled that a person with HIV is considered to be "disabled" and therefore protected under the Americans with Disabilities Act. "Unless health care workers can show that they lack the skill and facilities to treat HIV infected patients safely or that the patient refused reasonable testing and treatment, they may be legally, as well as ethically, obligated to provide requested reproductive assistance" (*Fertil Steril* 2010;94:11). To date, there have been no reported cases of occupational transmission to personnel providing assisted reproductive care or contamination of gametes or embryos in the provision of this care that would support the denial of services to HIV infected individuals or couples.

Unintended Pregnancy in HIV Infected Women

Many pregnancies among HIV infected women are unintended or unplanned. In the United States, approximately 50% of all pregnancies are unintended, a rate that has not changed in 15 years. Approximately 50% of unintended pregnancies occur in women using contraception, and more than 50% are aborted (*Fam Plan Perspect* 1998;30:24; *Contraception* 2007;75(3):168; *Perspect Sex Reprod Health* 2006;38(2):90). A 2006 study from Italy indicated that the rate of unintended pregnancy among HIV infected women on ART was 57.6% (*Antivir Ther* 2006;11(7):941). A 2007 study of more than 1000 HIV infected pregnant adolescents in the United States found that 83.3% of those pregnancies were unplanned (*Am J Obstet Gynecol* 2007;197(3 Suppl):S123). The majority of pregnancies reported by HIV infected women in the WIHS from 1994 to 2005 occurred in women who were not seeking to conceive

(*AIDS* 2004;18:281). Recent studies have also suggested that ART increases or restores fertility, particularly in those with higher CD4+ cell counts and a good immunologic response to therapy (*AIDS Res Treat* 2011:2011:519492).

Because of advances in HIV treatment, many perinatally infected adolescents are now reaching sexual maturity and may be at particular risk for unplanned or unintended pregnancy. A report on 174 perinatally HIV infected and sexually active girls older than 13 years found that by age 19, 24.2% had been pregnant at least once and some more than once (*Am J Public Health* 2007;97:1047).

Reasons for unintended pregnancy: Women who are not using contraception of any type do not necessarily intend to become pregnant. Other reasons for unintended pregnancy include the following:

- Power imbalance in a sexual relationship
- Pressure from partner and/or family to have children
- Fear of abandonment that results in lack of disclosure and, often, nonuse of condoms or other contraception
- Belief that one cannot become pregnant
- Lack of awareness of contraception options
- Disorganized lifestyle that precludes consistent use of condoms and/or contraception
- Decision to take one's chances

Increased risk for unintended pregnancy: Women who are in any of the groups listed below are at increased risk for unintended pregnancy (*Fam Plann Perspect* 1998;30:24; *Perspect Sex Reprod Health* 2006;38(2):90):

- Adolescents
- Aged >40 years
- Poor and less educated
- Unmarried but cohabiting
- Mentally ill or mentally retarded
- Victims of domestic violence
- Abusers of drugs or alcohol
- Those with HIV-associated cognitive impairment

Unplanned does not mean unwanted: An unplanned pregnancy is not necessarily an unwanted pregnancy. In the WIHS cohort, abortion was significantly less likely in the era of effective ART than it was in the pre-ART era. Further, abortion rates among HIV infected women were not significantly different from abortion rates among high-risk uninfected women in the ART era (*AIDS* 2004;18(2):281-6). Unintended pregnancy is a predictor, however, for pregnancy termination among women with HIV (*AIDS Care* 2010;22(1):50).

Contraception

The goals of contraception are to prevent unintended pregnancy or to delay pregnancy until it is desired. Women with HIV infection should have access to effective contraception and can use all available methods. Decisions regarding contraceptive options in HIV infected women require thoughtful discussions with the patient and with her partner if appropriate; however, the high proportion of HIV infected women who report unintended pregnancy or who conceive while using contraception suggests that this counseling is not taking place or is not sufficient. A number of barriers to contraceptive counseling have been identified. For example, women may have more immediate and pressing needs that consume the time allocated for clinic visits or preclude an in-depth discussion of contraception. Care providers may not be trained to provide contraceptive counseling.

Additional challenges to contraception use occur when women experience side effects from contraception that they were not prepared for and don't know how to manage or when they do not have enough power to control the use of contraception in an intimate relationship.

Between 1994 and 2005, 2784 women enrolled in WIHS were asked every 6 months about their use of contraception. About one-third of women reported using barrier methods; approximately one-quarter reported using sterilization; and <10% reported using hormonal methods. Use of dual protection—barrier method plus a more effective method of contraception—was low but did increase somewhat over time. Use of no method of contraception was reported in >30% of visits, even though 40% of these women reported sexual activity during the previous 6 months.. Use of all forms of contraception decreased with age and behavior change was minimal over time despite long-term study participation and study participant exposure to a variety of health messages (*J Women's Health* 2007;16(5):657). Other studies have found that condom use among women rises substantially after a diagnosis of HIV (*J Acquir Immune Defic Syndr* 2005;39(4):446)

Considerations in the Choice of a Contraceptive Method

When choosing the most appropriate contraceptive method for themselves and their partners, women should be encouraged to consider several factors, described below. Voluntary informed choice and respectful contraceptive counseling are important to the successful choice and use of contraceptive methods. One effective approach is motivational interviewing (Table 7-2), a client-centered and goal-directed style of counseling that incorporates sensitivity to the patient's current stage of change (*Addict Behav* 1985;10(4):407; *J Consult Clin Psychol* 1988;56(4):520). When appropriate, it is desirable to include the partner in the conversation about contraceptive choice because partner involvement may increase successful and sustainable use of the method.

Table 7-2

Motivational Interviewing for Contraception Counseling

Stage of Change	Counseling and Goal Setting for Condom Use	Counseling and Goal Setting for Prevention of Unwanted Pregnancy
Pre-Contemplation: Patient sees no need to engage in the target behavior ("No way…")	Review information about condom use and consequences of not using condoms.	Review information about contraception and the consequences of not using contraception; prescribe EC.
Contemplation: Patient sees the need to engage in the target behavior, but barriers preclude readiness for action (Yes, but…")	Discuss pros and cons of condom use and ask patient to plan to use them during 3 of the next 5 sexual acts she engages in.	Discuss barriers to contraception use and ways to overcome them and plan initiation of contraception use. Review contraception choices; plan to review again at next visit; elicit patient's agreement to choose a method at next visit and reinforce use of EC.
Ready for Action: Patient is ready to engage in the target behavior and may already be trying the new behavior ("Let's do it…")	Ask patient to use condoms during 4 of next 5 sexual acts, and help patient practice negotiating use of condoms.	Discuss the importance of consistent use of contraception; prescribe the patient's method of choice and prescribe EC.
Action: Patient has been engaging in the target behavior for 3 to 6 mo ("Doing it…")	Ask patient to plan to use condoms during all 5 of next 5 sexual acts and discuss results of negotiations about condom use.	Discuss patient's experience with contraception use; plan ways to solve future problems, such as the need to obtain refills, how to use EC if doses are missed, and how to handle missed appointments.
Maintenance: Patient has been engaging in the target behavior for more than 6 mo ("Living it…")	Provide positive reinforcement for consistent condom use and discuss relapse prevention.	Provide positive reinforcement for consistent contraception use, and discuss prevention of imperfect use.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

An ideal strategy for HIV infected women is simultaneous protection against both unintended pregnancy and HIV transmission or STI acquisition or transmission, often called "dual protection." Dual protection can be accomplished through avoidance of penetrative sex, condom use alone, or use of condoms in combination with another more effective method of contraception.

In general, HIV infected women can use all available contraceptive methods. Condom use, while less effective at preventing pregnancy than other contraceptive methods, is the only method that reduces the risk of HIV/STI transmission or acquisition. Dual protection may be optimal, particularly for serodiscordant couples, although this approach does have both pros and cons that should be considered and discussed with a patient during contraceptive counseling.

Advantages of Dual Protection	Disadvantages of Dual Protection
• Condoms alone have a higher failure rate in prevention of pregnancy than most other methods of birth control. • Hormonal methods may have significant noncontraceptive benefits, such as a decrease in iron deficiency anemia, decreased risk of PID, and decreased risk of some cancers. • HIV infected women may be taking medications that have teratogenic potential (e.g., EFV, warfarin, tetracyclines, statins) and need more reliable contraception than is provided by condoms alone. • Seroconcordant couples may be less likely to use condoms consistently, while also wishing to prevent pregnancy. • Drug interactions between hormonal contraceptives and ART may decrease contraceptive effectiveness, creating a greater need for use of a back-up method.	• Possible reduction in consistent condom use • Potential negative effect on ART adherence (less of a concern with non-oral hormonal delivery systems) • Adverse effects and/or safety considerations or contraindications with hormonal methods

Factors to consider when helping a woman choose the best method of contraception for herself and her partner include the following:

- Age
- Childbearing plans (i.e., does she need contraception that is temporary or permanent, short-term or long-term?)
- Cost
- Convenience and ease of use
- Side effects and toxicity
- Efficacy
- Effect on HIV transmission
- Effect on HIV progression
- Noncontraceptive benefits
- Protection against STIs
- Other medical conditions
- Acceptability and accessibility
- Drug interactions

Contraception works best if a woman likes it and if it makes practical sense for her. When choosing the best method, a patient's patterns of adherence to ART and other medications as well as her adherence with clinic visits may serve as predictors of her success with particular contraceptive methods.

Contraceptive decision making should take into consideration current medications, including ART, as well as fetal safety should contraception fail. EFV is the only current ARV agent that is a proven teratogen. Anencephaly,

anophthalmia, microphthalmia, and cleft palate were seen in primates at exposures comparable to those in humans, and there are retrospective case reports and one prospective report of CNS defects in infants of women who received EFV at conception and during the first trimester (Sustiva drug label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020972s035,021360s023lbl.pdf. Accessed 4/9/12; Antiretroviral Pregnancy Registry. Interim Report. December 2011. http://www.apregistry.com/forms/interim_report.pdf. Accessed 4/9/12)

EFV is the only ARV agent labeled as FDA pregnancy category D ("positive evidence of human fetal risk based on adverse reaction data from investigational and marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks"). The absolute risk after early exposure to EFV may be low, however; a recent meta-analysis found no increased risk of overall birth defects among women exposed to EFV compared with other ARVs during the first trimester (*AIDS* 2011;25(18):2301). Nevertheless, EFV should be avoided in women who are trying to become pregnant or who do not or cannot use effective contraception consistently (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. September 14, 2011. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf. Accessed 4/4/2012). Long-acting contraceptive methods may be more desirable for women on EFV-containing regimens (*Curr HIV/AIDS Rep* 2007;4:135).

Medications taken for treatment of other medical conditions must be considered as well. In some cases, these medications are FDA category D or category X ("risk for pregnant women clearly outweighs any possible benefit").

In 2010, the CDC released *U.S. Medical Eligibility Criteria for Contraceptive Use* as evidence-based guidelines for the use of different contraceptive methods in the setting of different medical conditions, including HIV. The four categories identified by the CDC are used in the discussion of contraceptive choice in this chapter (*MMWR Recomm Rep* 2010;59(RR-4);1).

- Category 1: a condition for which there is no restriction on the use of the contraceptive method
- Category 2: a condition for which the advantages of using the method generally outweigh the theoretical or proven risks
- Category 3: a condition for which the theoretical or proven risks usually outweigh the advantages of using the method
- Category 4: a condition that represents an unacceptable health risk if the contraceptive method is used

Contraceptive effectiveness depends on both the inherent effectiveness of a method and the need for independent action by the user. Methods that require remembering to take a pill every day will have lower efficacy with typical use than methods with theoretically similar effectiveness that require keeping an appointment for an injection once every 3 months. The relative effectiveness of various contraceptives is outlined in Table 7-3.

Table 7-3

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
COMBINED ORAL CONTRACEPTIVE PILL Use is independent of sexual intercourse	• Typical: 8 • Perfect: 0.3	• History of DVT, stroke, ischemic heart disease • HTN • Hyperlipidemia (depending on type, severity, other risk factors) • Aged >35 y and smoker • Multiple risk factors for arterial cardiovascular disease (e.g., older age, smoking, DM, HTN) • Complicated valvular heart disease • Migraine, especially with aura or in women >35 y • Severe liver cirrhosis, acute hepatitis • Hepatocellular adenoma • DM with nephropathy, retinopathy, neuropathy, or vascular disease • Breast cancer • Major surgery with immobilization • Current gallbladder disease • Postpartum <3 wk	• Nausea • Headache • Weight gain • Dizziness • Breast tenderness • Vaginal spotting • Chloasma • Depression	• 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	• No STD protection • May increase susceptibility to some STDs • Must remember to take pill daily • Some ARV agents may decrease or increase bioavailability of ethinyl estradiol and/or progestin component

Table 7-3 *continued*

Contraceptive Methods					
Method and Convenience	**Pregnancies in Year 1 of Typical Use and Perfect Use, %**	**Contraindications (CDC Category 3 or 4)**	**Potential Side Effects**	**Benefits**	**Disadvantages**
COMBINED ESTROGEN/ PROGESTIN VAGINAL RING (Nuva Ring) Use is independent of sexual intercourse. Vaginal ring is inserted for 3 wk out of every mo. Precise placement is not required.	• Typical: 8 • Perfect: 0.3	• Same as for OCs	• Similar to OCs • Possible increased vaginal discharge	• Same as for OCs	• Confers no STD protection, and may increase susceptibility to some STDs
COMBINED ESTROGEN/ PROGESTIN PATCH (Ortho Evra) Use is independent of sexual intercourse. Patch is applied weekly for 3 of 4 wk.	• Typical: 8 • Perfect: 0.3	• Same as for OCs	• Similar to OCs • Skin irritation	• Same as for OCs • Improved user compliance	• No STD protection • May increase susceptibility to some STDs
DMPA Often causes amenorrhea. Requires only 4 injections per year. Requires no ongoing action by user. Use is independent of sexual intercourse.	• Typical: 3 • Perfect: 0.3	• Breast cancer • Unexplained vaginal bleeding • Multiple risk factors for arterial cardiovascular disease (e.g., older age, smoking, DM, HTN) • Ischemic heart disease, stroke	• Menstrual changes (spotting, irregular bleeding, amenorrhea) • Decreased bone density with long-term use • Weight gain • Breast tenderness • Headache • Adverse effect on lipids • Depression	• May have protective effects against PID, ovarian and endometrial cancer • Decreased blood loss, anemia • Amenorrhea • No interaction with ART established, but data are limited	• No STD protection

Table 7-3 *continued*

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
ETONOGESTREL IMPLANT (Implanon®) Lasts 3 y. Removal is easier than earlier implant (Norplant). Requires no ongoing action by user. Use is independent of sexual intercourse.	• Typical: 0.5 • Perfect: 0.5	• Unexplained vaginal bleeding • Breast cancer • Severe liver disease, tumors • Ischemic heart disease, stroke	• Tenderness or infection at site • Menstrual changes (spotting, irregular bleeding, amenorrhea • 1/3 of women have amenorrhea after 1 y • Weight gain • Breast tenderness • Depression	• Same as above	• No STD protection • Requires office insertion • Costs $400–$800
PROGESTIN-ONLY PILL Use is independent of sexual intercourse	• Typical: 1.1–13.8 • Perfect: 0.5	• Unexplained vaginal bleeding • Breast cancer • Severe liver disease, tumors • Ischemic heart disease, stroke	• Menstrual changes (spotting, irregular bleeding, amenorrhea) • Breast tenderness • Depression • Weight gain	• Same as above	• No STD protection • Ectopic pregnancy more likely with progestin-only pills than with other forms of hormonal contraception • Must remember to take pill daily • Potential drug interactions with certain seizure medications, rifampin/rifabutin, RTV-boosted PIs
CONDOM, MALE (LATEX, POLYURETHANE, NATURAL MEMBRANE) Inexpensive and readily available. Use does not require a prescription.	• Typical: 15 • Perfect: 2	• Allergy to latex condom material	• Allergy or sensitivity to latex material • Decreased sensitivity	• Protects against STDs, including HIV (except for natural membrane) • Delays premature ejaculation	• Requires partner cooperation • Possible loss of spontaneity during sex

Table 7-3 *continued*

Contraceptive Methods					
Method and Convenience	**Pregnancies in Year 1 of Typical Use and Perfect Use, %**	**Contraindications (CDC Category 3 or 4)**	**Potential Side Effects**	**Benefits**	**Disadvantages**
CONDOM, FEMALE Woman controlled. Less likelihood of breakage. Can be inserted up to 8 h before intercourse. Use does not require a prescription.	• Typical: 21 • Perfect: 5 • Data are limited	• Polyurethane allergy (rare)	• Allergy or sensitivity to polyurethane • Possible decreased sensitivity	• Protects against STDs, including HIV	• May be awkward to use • Aesthetically unappealing to some
CERVICAL CAP — PAROUS/ NONPAROUS Woman controlled. Can be inserted ahead of time.	• Typical: • 36 (parous)/ 18 (nonparous) • Perfect: 26/9	• Latex allergy • Abnormal cervical/ vaginal anatomy • History of TSS or recurrent UTIs • Known or suspected cervical/uterine malignancy • Abnormal Pap smear • Vaginal or cervical infection • Recent delivery or spontaneous or induced abortion	• Pelvic pressure • Vaginal irritation • Allergy or sensitivity to latex • Vaginal or urinary tract infections	• Limited STD protection	• Efficacy based on high motivation • Spermicide re-application required with each act of coitus • Should not be used during menses • Spermicide may increase HIV acquisition and transmission
DIAPHRAGM Woman controlled. Can be inserted up to 6 h before intercourse.	• Typical: 16 • Perfect: 6	• Latex allergy • Abnormal vaginal anatomy • History of TSS or recurrent UTIs	• Same as above	• Limited STD protection • Reduces risk of PID	• No protection against HIV transmission

Table 7-3 *continued*

Contraceptive Methods					
Method and Convenience	**Pregnancies in Year 1 of Typical Use and Perfect Use, %**	**Contraindications (CDC Category 3 or 4)**	**Potential Side Effects**	**Benefits**	**Disadvantages**
SPERMICIDES Woman controlled. Use does not require a prescription. Easily available and inexpensive.	• Typical: 29 • Perfect: 18	• Allergy to nonoxynol-9 • HIV/AIDS (CDC category 3)	• Vaginal irritation • Allergy • Vaginal and urinary tract infection	• Protection against some STDs, with significant protection against gonorrhea and chlamydia. • In vitro activity against HIV	• Efficacy reduced when used without a barrier method • Increased susceptibility to HIV with frequent sexual activity • No protection against HIV
IUD (copper-Paragard®) Provides contraception for 10 y. Requires no ongoing user action.	• Typical: 0.8 • Perfect: 0.6	• Unexplained vaginal bleeding • Recent (within 3 mo), recurrent, or active pelvic infection • Postpartum, postabortion endometritis • Active STD • Women at increased risk for STDs • Severely distorted uterine cavity	• Menstrual cramping • Increased bleeding • Risk of PID and uterine perforation following insertion • Anemia	• No increase in pelvic infection with HIV	• No STD protection • Increased risk of PID
LEVONORGESTREL INTRAUTERINE SYSTEM (Mirena) Provides contraception for 5 y. Requires no ongoing user action.	• Typical: 0.2 • Perfect: 0.2	• Unexplained vaginal bleeding • Breast cancer • Active pelvic infection/ STDs • Severe liver disease/ tumor • Distorted uterine cavity	• Increased incidence of irregular bleeding in first 6 mo compared with copper IUD • Risk of PID and uterine perforation following insertion	• Overall reduction in menstrual blood loss (20% amenorrhea after 1 y) and cramping • Possible decreased rates of anemia, PID • No increase in pelvic infection with HIV	• No STD protection

Table 7-3 *continued*

Contraceptive Methods					
Method and Convenience	**Pregnancies in Year 1 of Typical Use and Perfect Use, %**	**Contraindications (CDC Category 3 or 4)**	**Potential Side Effects**	**Benefits**	**Disadvantages**
FEMALE SURGICAL STERILIZATION Provides permanent contraception. Requires no ongoing user action.	• Typical: 0.5 • Perfect: 0.5	• Desire for future fertility • Active pelvic infection	• Pain at surgical site • Subsequent regret • Increased risk of ectopic pregnancy if sterilization not achieved	• Possible decreased risk of ovarian cancer • Decreased risk of salpingitis	• Permanent • No STD protection • Requires anesthesia • Surgical procedure in OR
TRANSCERVICAL FEMALE STERILIZATION (Essure®, Adiana®; data more limited for Adiana but suggest somewhat higher failure rate) Provides permanent contraception. Requires no ongoing user action. Lower cost; does not require incision or general anesthesia; may be performed in physician's office. Decreased risk of intra-abdominal injury.	• Typical: 0.2–0.4 • Perfect: 0.2–0.4	• Desire for future fertility • Active pelvic infection	• Subsequent regret • Increased risk of ectopic pregnancy if sterilization not achieved • Cramping, nausea, vomiting with placement • Expulsion or uterine perforation (<3%)	• Probably similar to surgical sterilization (experience limited)	• Permanent • No STD protection • Requires use of alternate contraception for 3 mo • For Adiana, requires confirmation of tubal occlusion by hysterosalpingography (Essure can be visualized radiographically)
MALE STERILIZATION Provides permanent sterilization for the man	• Typical: 0.15 • Perfect: 0.10	• Desire for future fertility	• Pain at surgical site • Subsequent regret	• None	• Same as above, except sterility not immediate

Table 7-3 *continued*

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
EMERGENCY CONTRACEPTION Levonorgestrel 0.75mg (Plan B); levonorgestrel 0.25mg/ethinyl estradiol 50 mcg (Preven); ulipristal acetate 30 mg single dose (marketed for EC as Ella®) Can be used after unprotected intercourse or with other contraceptive failure (e.g., condom breakage). Treatment should be initiated as soon as possible to maximize effectiveness and is generally recommended within 72 h after intercourse. Ulipristal given as single dose for EC is effective up to 120 h (5 d) after unprotected intercourse.	• Typical: 3.2 (57% of expected pregnancies prevented) • Perfect: 1.1 (85% of expected pregnancies prevented) • Effectiveness of ulipristal is similar to that of levonorgestrel in first 72 h and superior 72–120 h after unprotected sex	• Established pregnancy	N/A	N/A	• No STD protection • Nausea and vomiting common with levonorgesterl/ethinyl estradiol combination (30–60%); prophylactic antiemetics may be beneficial • Failure rate higher with intercourse during fertile phase of cycle • Ulipristal more expensive than other EC options

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-4);1; *Contraceptive Technology*, 19th ed, 2007

Condoms

The consistent use of male or female condoms protects against HIV and other STD transmission and acquisition and provides contraception. It is the only contraceptive method that provides dual protection against both HIV infection and pregnancy. Therefore, these two issues should be separately discussed when counseling patients. Condom use also should be reinforced for HIV infected women when prevention of pregnancy is not an issue (i.e., postmenopause, during pregnancy, after sterilization, when a woman is infertile, or for use with a more effective contraceptive method).

The female condom is less likely than the male condom to break or leak during sex; however, intrusion of the outer vaginal ring that covers the introitus into the vagina occurs in 2% of cases, allowing potential insertion of the penis between the condom and vaginal wall (*Sex Transm Infect* 2004;80:167). Some couples also complain about noise during sex; however, women who receive instruction about use of the female condom and are given the opportunity to practice its use in the clinical setting have an increased likelihood of using the device correctly and viewing it favorably (*Am J Public Health* 2002;92:109). Counseling during the early adoption phase and an increased sense of power in negotiating for safe sex have been linked to increased acceptability and adoption of the female condom (*AIDS Behav* 2006;10(4 Suppl):S67).

Spermicides

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 as compared with placebo recipients (*J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17:327). A randomized placebo-controlled clinical trial of an N-9 vaginal gel conducted in four countries among commercial sex workers with high rates of sexual activity did not demonstrate protection against HIV; instead, HIV transmission was increased among those who used the N-9–containing gel more frequently (*Lancet* 2002;360:971). A meta-analysis of randomized controlled trials of N-9 use found no evidence of protection against HIV acquisition (*Cochrane Database Syst Rev* 2002;(4):CD003936). N-9 also appears to offer no protection against STDs such as gonorrhea or chlamydia (*Reprod Health Matters* 2002;10(20):175). Newer spermicides that cause less inflammation are being tested for their potential to decrease the risk of HIV transmission. In the setting of HIV/AIDS, spermicides that may disrupt vaginal or cervical mucosa and potentially increase viral shedding and risk to uninfected partners are assigned to CDC category 3 (risk generally outweighs advantages).

Hormonal Contraception

Combined estrogen/progestin contraceptives: Studies of oral combined estrogen/progestin contraceptives and several ARVs have found drug interactions (primarily through the cytochrome p450 [CYP] 3A4 system) that resulted in an increase or decrease in levels of estrogen and/or progestin (Table 7-4). One study demonstrated a decrease in ARV blood level

(*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. January 10, 2011. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 4/4/12). To date, data on these interactions are primarily pharmacokinetic and the true clinical effect is not clear. The concern is that effectiveness may be decreased, breakthrough bleeding may occur (with decreased hormonal levels), or rates of adverse effects may increase (with increased hormonal levels), although these outcomes have not been confirmed. Only with FPV, which is metabolized to APV, does the drug-drug interaction also reduce the concentration of the ARV. Unboosted FPV should not be co-administered with hormonal contraceptives (HCs). There is minimal information about drug interactions with the use of alternative delivery methods for estrogen/progestin contraceptives (i.e., transdermal patch, intravaginal ring), although a recent study suggests that these delivery methods may also be vulnerable to drug interactions and that different progestins (e.g., norethindrone vs norelgestromin) may be affected differently in interaction with specific ARV agents (*J Acquir Immune Defic Syndr* 2010;*55*(4):473). Although data are lacking on the safety and efficacy of altering hormonal dosages in an effort to circumvent these interactions, a preparation containing a minimum of 30 mcg ethinyl estradiol is suggested.

Table 7-4

Drug Interactions Between Antiretroviral Therapy and Hormonal Contraception

	Effect on Antiretroviral or Hormonal Drug Concentrations	Dosing Recommendations for Hormonal Contraceptives and Clinical Comments
NRTIs	No effect on hormonal levels	No dosage adjustment is necessary
RTV-Boosted PIs		
ATV/r	Ethinyl estradiol ↓ 19% Norgestimate ↑ 85%	Use alternative or additional method
DRV/r	Ethinyl estradiol AUC ↓ 44% Norethindrone AUC ↓ 14%	Use alternative or additional method
FPV/r	Ethinyl estradiol AUC ↓ 37% Norethindrone AUC ↓ 34%	Use alternative or additional method
LPV/r	Ethinyl estradiol AUC ↓ 42% Norethindrone AUC ↓ 17% Norelgestromin (transdermal patch) AUC ↑ 83%	Use alternative or additional method
SQV/r	↓ Ethinyl estradiol	Use alternative or additional method
TPV/r	Ethinyl estradiol AUC ↓ 48% Norethindrone: no significant change	Use alternative or additional method
Unboosted PIs		
Indinavir (IDV)	Ethinyl estradiol AUC ↑ 25% Norethindrone AUC ↑ 26%	No additional contraceptive protection needed
Nelfinavir (NFV)	Ethinyl estradiol AUC ↓ 47% Norethindrone AUC ↓ 18%	Use alternative or additional method

Table 7-4 *continued*

Drug Interactions Between Antiretroviral Therapy and Hormonal Contraception

	Effect on Antiretroviral or Hormonal Drug Concentrations	Dosing Recommendations for Hormonal Contraceptives and Clinical Comments
ATV	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	No additional contraceptive protection needed Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol, or use alternative method. Oral contraceptives containing <25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone; ↓ APV 20%	Use alternative method
NNRTIs		
EFV	Ethinyl estradiol no change Levonorgestrel AUC ↓ 83% Norelgestromin AUC ↓ 64% With levonorgestrel alone (not as part of combined estrogen/progestin contraceptive, levonorgestrel AUC ↓ 58% Implant: ↓ etonogestrel	Use alternative or additional methods Norelgestromin and levonorgestrel are active metabolites of norgestimate Effectiveness of emergency postcoital contraception may be diminished
ETR	Ethinyl estradiol AUC ↑ 22% Norethindrone: no significant effect	No additional contraceptive protection needed
NVP	Ethinyl estradiol AUC ↓ 20% Norethindrone AUC ↓ 19%	May consider alternative or additional methods
	DMPA: no significant change	No additional contraceptive protection needed
RPV	Ethinyl estradiol AUC ↑ 14% Norethindrone: no significant change	No additional contraceptive protection needed
CCR5 Antagonist		
MVC	No significant effect on ethinyl estradiol or levonorgestrel	No additional contraceptive protection needed
Integrase Inhibitor		
RAL	No clinically significant effect on ethinyl estradiol or levonorgestrel	No additional contraceptive protection needed
Elvitegravir/ Cobicistat	Norgestimate AUC ↑ 2.26 Ethinyl estradiol AUC ↓ 0.75	No additional contraceptive protection needed

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* January 10, 2011; Tables 15a, 15b, and 15d

Concerns about drug interactions should not cause providers to avoid prescribing combined estrogen/progestin HC, but should prompt close follow-up and thorough counseling about additional or alternative contraceptive methods. The consistent use of condoms is recommended to prevent HIV transmission or other STI acquisition and to compensate for any possible reduction in the effectiveness of the HC.

Other medications are also known to interact with combined estrogen/progestin HCs (and in some cases with progestin-only contraceptives) and may require consideration of alternative and/or additional contraceptive methods and/or dose adjustment for the interacting agent, when appropriate (*Contraceptive Technology*,19th ed, 2007).

Drugs that alter estrogen and/or progestin levels and may reduce the effectiveness of HC:

- Anticonvulsant agents (i.e., phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine) used with combined estrogen/progestin methods or progestin-only pills
- Lamotrigine (if used as single agent) used with combined estrogen/progestin methods
- Rifampin or rifabutin used with combined estrogen/progestin methods, progestin-only pills, or progestin implants
- St. Johns wort used with combined estrogen/progestin methods or progestin-only pills

Recommendation: Use an alternative or additional method. If a combined oral estrogen/progestin method is used, use a formulation containing a minimum of 30 mcg ethinyl estradiol.

Drugs that may require dose adjustment and/or monitoring of drug effect when used with combined estrogen/progestin HC:

- Fluoroquinolones, some anticonvulsants (reduced drug levels)
- Theophylline, diazepam, chlordiazepoxide, tricyclic antidepressants (increased drug levels)

Recommendation: Monitor drug levels when available; dose may need to be increased.

Among HIV infected women, the use of combined estrogen/progestin contraceptives may be contraindicated because of comorbidities such as smoking or hypertension, common in this population. Because chronic viral hepatitis is a frequent comorbidity in the setting of HIV, the concomitant use of combined HCs is of special interest. Data suggest that in women with chronic hepatitis, combined hormone use does not increase the rate or severity of cirrhotic fibrosis, nor does it increase risk for hepatocellular carcinoma. In general, though, these methods should not be used in women with severe liver cirrhosis, acute hepatitis, or liver tumors.

Progestin-only contraceptives: Although data are limited, there is no evidence of significant drug interactions between depot medroxyprogesterone acetate (DMPA) and ARVs. The clinical profile associated with DMPA administration was examined in women on regimens containing NFV, EFV, or NVP and appeared similar to that observed in HIV uninfected women. DMPA prevented ovulation and did not affect CD4+ cell counts or HIV RNA levels in HIV infected women when compared with women on NRTIs only or no ARVs (*Contraception* 2008;77:84). Another study found no DMPA pharmacokinetic differences between 15 women on ZDV, 3TC, and EFV and 15 women on no ART (*Fertil Steril* 2008;90(4):965). The *U.S. Medical Eligibility Criteria* classify DMPA with HIV/AIDS as Category 1 (*MMWR Recomm Rep* 2010;59(RR-4);1). There are few data on drug interactions of progestin implants or progestin-only pills with ARVs and recommendations by experts are generally the same as for combined hormonal contraceptives.

Long-term use of DMPA has been associated with diminished bone mineral density (BMD), although recent studies indicate that the rate of bone loss is greatest in the first 24 months of use and decreases thereafter; furthermore, current evidence suggests that partial or full recovery of bone mass occurs after discontinuation of DMPA (*Fertil Steril* 2006;86:1466; *Contraception* 2006;74:90). There have been no randomized controlled trials of DMPA and fracture risk. Decreased BMD is more common among people with HIV infection and has been associated with the use of a variety of ARVs, in particular d4T and TDF. Although no studies have examined BMD and DMPA use in the setting of HIV infection, the efficacy of DMPA—particularly in adolescents or others who may have difficulty adhering to a contraceptive method—must be balanced against possible adverse effects on bone density. ACOG has stated that "concerns regarding the effect of DMPA on BMD should neither prevent practitioners from prescribing DMPA nor limit its use to 2 consecutive years." (ACOG Committee Opinion #415. September 2008. Available at http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Adolescent_Health_Care/Depot_Medroxyprogesterone_Acetate_and_Bone_Effects. Accessed 7/9/12). Daily exercise and appropriate calcium and vitamin D intake should be encouraged.

Hormonal contraception and HIV progression: Data from prospective and cohort studies conflict on the effect of HC (combined estrogen/progestin or DMPA) on HIV progression, defined as progression to AIDS or death (*Clin Infect Dis* 2008;47:945; *J Acquir Immune Defic Syndr* 2011;56(2):125; *AIDS* 2010;24(12):1937; *AIDS* 2009; 23 Suppl 1:S69; *AIDS* 2007;21:749). Members of a cohort of Kenyan women who were taking DMPA at the time of HIV acquisition were found to have higher viral set points and a greater likelihood of multiple viral variants being detected shortly after infection (*Clin Infect Dis* 2006;42(9):1333); however, the use of hormonal contraception prior to seroconversion was not associated with higher viral set points in a Ugandan cohort (*J Acquir Immune Defic Syndr* 2011;56(2):125). Most of these studies did not have VL measurements for comparison. In both a longitudinal U.S. cohort and a prospective cohort in Kenya, however, HC was not associated with a change in VL over time as compared with women who were not using contraception (*AIDS* 2003;17(11):1702; *AIDS* 2007;21(6):749). In general, these studies did not include women on ART, but there is no reason to believe

that women on ART with suppressed HIV RNA levels would be at increased risk for HIV progression related to the use of HC. Given the availability of ARVs and the fact that most studies show no effect of HC on HIV progression, which would be expected to supersede a potential effect on untreated women, the full range of HC methods should continue to be available to women with HIV.

Hormonal contraception and HIV transmission and/or acquisition: Data on the role of HC in HIV susceptibility or infectiousness also conflict. Two large prospective studies have demonstrated a modestly increased risk of HIV acquisition associated with the use of combined oral estrogen/progestin and/or DMPA (*AIDS* 2004;18(16):2179; *AIDS* 2007;21(13):1771; *AIDS* 2010;24(11):1777). A recent secondary analysis of data from a large prevention trial among more than 3700 serodiscordant African couples demonstrated an increased risk of HIV seroconversion (both transmission and acquisition) associated with HC (primarily DMPA). Moreover, HIV infected women who transmitted to their uninfected male sex partners also had higher genital HIV VL, which has the potential to increase transmission (*Lancet Infect Dis* 2012;12(1):19). Other mechanisms with the potential for altering risk of transmission or acquisition include increased cervical ectopy with HC use, possible thinning of vaginal mucosa, alterations in vaginal flora or heightened susceptibility to other STIs, or other changes in local or systemic immunity (*Am J Reprod Immunol* 2011;65(3):302).

There are, however, also significant methodologic issues with most studies, including potential selection bias and confounding factors such as changes in HC use over time, presence of STIs (including HSV-2 serostatus), and dependence on self-report regarding actual use of HC, sexual behavior, and/or condom use (*Am J Reprod Immunol* 2011;65(3):302).

Although some data suggest that HC may increase HIV susceptibility or infectiousness, there is a critical need for safe and effective contraceptive methods for women who are at risk for or infected with HIV. Rather than discouraging the use of effective HC methods, these studies highlight the importance of dual protection with condoms to prevent both acquisition and transmission of HIV in women. Moreover, now that ART has been confirmed to effectively reduce sexual transmission among serodiscordant couples by 96% (*N Engl J Med* 2011;365(6):493), this intervention will be increasingly important to circumvent transmission of HIV, regardless of HC use. A recent update to the CDC's U.S. Medical Eligibility Criteria for Contraceptive Use 2010 reaffirmed the safety of hormonal contraceptives for women at high risk for HIV, but added a clarification for women using progestin-only injectables highlighting the inconclusive nature of the evidence around hormonal contraceptive use and risk for HIV acquisition among women, and strongly encouraging condom use and other measures to prevent HIV (*MMWR* 2012:61(24):449).

Intrauterine Devices

No association between the copper IUD (Cu-IUD) and risk of HIV acquisition or progression has been demonstrated (*Am J Obstet Gynecol* 2007;197(2):144; *Best Pract Res Clin Obstet Gynaecol* 2009; 23(2):263). Although data are

limited, there is also no evidence of higher risk from Cu-IUDs for overall complications or for pelvic infections in HIV infected women in general or when stratified by CD4+ cell count (*BJOG* 2001;108(8):784; *Lancet* 1998;351:1238; *Am J Obstet Gynecol* 2007;197(2):144). Cu-IUD use also was not associated with an increased rate of cervical HIV shedding (*AIDS* 1999;13(15):2091).

In U.S. practice today, the Cu-IUD has largely been eclipsed by the levonorgestrel-releasing intrauterine system (LNG-IUD). The LNG-IUD is both highly effective as a contraceptive method and associated with reduced menstrual blood loss. It is an increasingly popular treatment for menorrhagia, dysmenorrhea, uterine fibroids, endometriosis, and adenomyosis, and also provides endometrial protection in women with or at risk for endometrial hyperplasia. Fewer data are available regarding the use of the LNG-IUD in women with HIV infection; however, a recent study comparing 15 women using the LNG-IUD with 25 age- and CD4+ cell count–matched controls followed for 5 years found no unplanned pregnancies or pelvic infections among the IUD users and no difference in CD4+ cell counts over the follow-up period compared with controls. LNG-IUD use was associated with an increase in hemoglobin levels, which remained higher over time than those of controls (*Am J Obstet Gynecol* 2011;204(2):126.e1). In another study, genital shedding of HIV RNA was not affected by LNG-IUD use and estradiol levels remained in the follicular range in all women (*Hum Reprod* 2006;21(11):2857). Although no data address the issue of drug interactions with ARV agents in the setting of LNG-IUD use, interactions would be expected to be minimal, given the low levels of systemic absorption of LNG.

Emergency Contraception

Emergency contraception (EC) is the use of a drug or device to prevent pregnancy after unprotected intercourse or contraceptive failure (e.g., condom breakage). EC works by inhibiting or delaying ovulation. It also may interfere with sperm transport, impair corpus luteum function, or inhibit implantation. Since EC does not act after implantation and establishment of pregnancy, it is not considered an abortion method (*NEJM* 1997;337(15):1058). While EC should be initiated as soon as possible after unprotected intercourse to maximize efficacy, it should be made available for up to 5 days after unprotected intercourse to patients who request it. No clinician examination or pregnancy testing is necessary before provision of EC (ACOG Practice Bulletin No. 112; *Obstet Gynecol* 2010;115(5):1100). No data specifically on EC in the context of HIV or ARV treatment are available, but EC does not protect against STI acquisition or HIV transmission.

There are currently four EC options:

- **Progestin only:** Levonorgestrel (marketed for EC as Plan B, Plan B One-Step). The levonorgestrel-only regimens are more effective, with prevention of up to 85% vs 57% of expected pregnancies when compared with combined estrogen/progestin regimens (*Lancet* 1998;352:428). They also are associated with significantly less nausea and vomiting than the combined estrogen/progestin regimens. In the United States, both progestin-only regimens are available over the

counter (OTC) to women aged ≥17 years. Available pharmacokinetic data indicate that, compared with combined estrogen/progestin regimens, progestin-only regimens should cause fewer drug interactions with ARVs.

- Two-dose regimen: levonorgestrel 0.75 mg po, to be repeated 12–24 hours after the first dose
- One-dose regimen: 1.5 mg levonorgestrel

- **Combined estrogen–progestin regimens:** Nineteen combined estrogen/progestin oral contraceptives have been declared safe and effective for use as EC by the FDA (The Emergency Contraception Website. http://ec.princeton.edu/questions/dose.html. Accessed 4/9/12). All of the combined hormonal regimens require two doses taken 12 hours apart. Each dose contains two to six active hormonal (not placebo) pills, depending on the pill formulation, and includes ethinyl estradiol (total of 100–120 mcg) and levonorgestrel (total of 0.50–0.60 mg). As noted above, these regimens are less effective and more likely to cause nausea and vomiting than progestin-only regimens. If given, prophylactic antiemetics may be useful. The EC dose should be repeated if vomiting occurs within 2 hours of ingestion. If severe vomiting occurs, pills may be administered vaginally with effective absorption (*Contraception* 1987;36(4):471).
- **Progesterone agonist/antagonist:** Ulipristal acetate 30 mg single dose (marketed for EC as Ella®) was approved by the FDA in August 2010 for EC up to 120 hours (5 days) after unprotected intercourse (*Obstet Gynecol* 2010;115(2 Pt 1):257).
- **Copper IUD:** Although not currently FDA-approved specifically for EC, the Cu-IUD can be used for EC in women who meet the standard criteria for IUD insertion. It is most effective if inserted within 5 days after unprotected intercourse. The pregnancy rate with this method is 0% to 0.09% (*Hum Reprod* 2012;27:1994). This method has the advantage of providing long-term contraception in addition to EC. The LNG-IUD is not effective as EC (*J Fam Plann Reprod Health Care* 2004;30:99).

EC use should not be encouraged as a regular contraceptive method. Randomized controlled trials have not demonstrated a reduction in unintended pregnancy or abortion associated with access to EC (*Contraception* 2008;78(5):351). Condom use should be encouraged immediately after EC use; other short- or long-term hormonal methods may be initiated following the woman's next menstrual period, when it is clear that she is not pregnant. If menses are delayed by a week or more after the expected time or if lower abdominal pain or persistent irregular bleeding develops, clinical evaluation is indicated to evaluate for intrauterine or ectopic pregnancy.

Conclusions

HIV clinics are experienced in providing systems of care that address the multiplicity of concerns relevant to people with HIV infection. Integration of family planning services within primary HIV care is an additional strategy that can improve the lives of women with HIV. Establishing relationships with local family planning agencies can help to improve linkages to those services and improve access to safe and effective contraception. Integration of HIV services into family planning clinics should be considered as well. "Every woman [at] every visit" should be engaged in discussions concerning her intentions regarding pregnancy and her use of contraception. Integration of preconception counseling and contraceptive options must be an integral part of HIV primary care.

Chapter 8:
HIV and Pregnancy

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Chapter 8 at a Glance

HIV and Pregnancy

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. The number of HIV infected women who become pregnant may grow with therapeutic advances in care and the prevention of vertical transmission and because new diagnoses of HIV are still often made in pregnancy. This chapter reviews issues related to pregnancy and discusses guidelines for care during pregnancy to optimize the health of both the mother and her baby.

Pregnancy Testing

Indications: For currently or recently sexually active women, pregnancy testing is indicated in the following circumstances:

- Missed menses, unless on etonogestrel (ETG)-releasing contraceptive implant, levonorgestrel (LNG) intrauterine device (IUD), or depot medroxyprogesterone acetate (DMPA)
- Irregular bleeding (unless on ETG-releasing implant, LNG-IUD or DMPA)
- New onset of irregular bleeding after prolonged amenorrhea on ETG-releasing implant, LNG-IUD, or DMPA
- New onset of pelvic pain
- Enlarged uterus or adnexal mass on exam
- Before instituting new therapies (consider)

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 8-1 lists types of available pregnancy tests and their sensitivity.

Table 8-1

Pregnancy Tests

Type	Source	Sensitivity	Comments
Radioimmunoassay	Blood	Positive within 7 d of fertilization	Quantitative or qualitative; used to follow women with possible ectopic pregnancy
Enzyme immunoassay	Blood, urine	Positive approximately 10 d after fertilization	Available for home urine testing; positive results require confirmation
Antibody agglutination inhibition	Urine	Positive approximately 18–21 d after fertilization	False positives may occur with hypothyroidism, renal failure, immunologic disorders, increased luteinizing hormone

Effects of Pregnancy on HIV Infection

CD4+ cell count and HIV RNA levels: The CD4+ cell count response to pregnancy is variable in all women, whether HIV infected or not (*Obstet Gynecol 1997*;89:967). Many studies have suggested that a decline in absolute CD4+ cell count occurs in pregnancy; the count returns to baseline at the end of pregnancy or during the postpartum period. The decline is thought to be secondary to hemodilution because the percentage of CD4+ cells remains relatively stable. Therefore, percentage, rather than absolute number of CD4+ cells, may be a more accurate measure of immune function for HIV infected pregnant women (*AIDS Res Hum Retroviruses* 2007;23:1469; *AIDS* 1997;11:1859; *AIDS* 1995;9:1177).

HIV RNA levels (viral load [VL]) remain relatively stable throughout pregnancy in the absence of treatment (*Am J Obstet Gynecol* 1998;178:355). Recent data suggest, however, that HIV RNA levels increase during the postpartum period regardless of antiretroviral (ARV) treatment (although use of antiretroviral therapy [ART] appears to blunt the effect), possibly as a result of immune activation associated with hormonal changes or labor-induced cytokines (*Clin Vaccine Immunol* 2010;17:2024). The implications of increased VL on the risk of transmission and on treatment recommendations in the early postpartum period are unclear (*Clin Vaccine Immunol* 2010;17:2024). The increase in postpartum VL does not appear to reflect a long-lasting effect of pregnancy on VL (*Am J Obstet Gynecol* 2003;189:552).

Clinical Course of HIV: To date, most studies of the effects of pregnancy on HIV disease have not demonstrated significant differences in HIV progression or survival in HIV infected pregnant women. A meta-analysis of 7 prospective cohort studies found no significant differences between cases and controls in death, HIV disease progression, progression to an AIDS-defining illness, or decline in CD4+ cell count to $<200/mm^3$ (*Br J Obstet Gynaecol* 1998;105:827). In a subsequently reported prospective study, 331 women with known dates of seroconversion were followed for a median of 5.5 years, during which time, 69 of the women were pregnant. No differences

in progression were found between those who were and were not pregnant during follow-up (*Arch Intern Med* 1997;157:2585). In addition, a long-term observational study showed no difference in VL, CD4+ cell count, or clinical disease progression in women with repeat pregnancies compared with women with one pregnancy (*Am J Obstet Gynecol* 2003;189:552).

Effect of HIV on Pregnancy Course and Outcome

Adverse outcomes: Adverse pregnancy outcomes may occur secondary to underlying disease processes or their treatment or for reasons that cannot be determined. In the United States, approximately 10% of pregnancies end prematurely and preterm birth is the leading cause of perinatal morbidity and mortality. No evidence supports a significant direct effect of HIV on pregnancy outcome; however, the effects of advanced disease, including anemia, malnutrition, and other HIV-related infections, may increase the risk of some adverse outcomes (*Br J Obstet Gynaecol* 1998;105:836; *AIDS* 1998;12:1087; *J Acquir Immune Defic Syndr* 2003;33:393; *Am J Clin Nutr* 2003;77:1337; *BJOG* 2001;108:1125; *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;18:293; *J Coll Physicians Surg Pak* 2011;21:356; *BJOG* 2008;115:616; *Am J Obstet Gynecol* 2002;186:903; *Lancet* 1998;351:98; *Eur J Obstet Gynecol Reprod Biol* 2010;150:34). Moreover, HIV infected women may be at risk of adverse pregnancy outcomes as a result of an increased likelihood of other risks, such as use of tobacco, alcohol, and illicit drugs; presence of sexually transmitted infections (STIs); and poor perinatal care. If these other risk factors are controlled for, however, HIV infection has no independent effect on adverse outcomes (*AIDS* 2000;14:1389).

A study of 497 HIV infected pregnant women enrolled in a perinatal clinical trial found that risk factors for adverse pregnancy outcomes (preterm birth, low birthweight, and intrauterine growth retardation) in ARV-treated women were similar to those reported for uninfected women (*AIDS* 2000;14:1389). Although concerns have been raised that ARV use may increase some adverse outcomes in pregnancy (see **Adverse Pregnancy Outcomes**, p. 300), the benefits of this therapy in reducing the risk of perinatal transmission far outweigh the risks. Results of a study comparing hospitalization among HIV infected pregnant women in the United States prior to and during the era of HAART indicate that rates of conditions responsible for increased hospitalization among HIV infected women decreased or remained stable after the introduction of ART (*J Acquir Immune Defic Syndr* 2006;43:186). Those conditions included major puerperal sepsis, genitourinary infections, influenza, bacterial infections, preterm labor/delivery, and liver disorders. Table 8-2 summarizes the relationship between common pregnancy-related complications and untreated HIV.

Table 8-2

Relationship of Adverse Pregnancy Outcomes to Untreated HIV Infection

Adverse Outcome	Relationship to Untreated HIV Infection
• Perinatal/infant mortality • Stillbirth	Evidence of increased risk in developing countries
• Chorioamnionitis	Most studies do not suggest an increased risk in clinical or histologic chorioamnionitis; however, evidence of possible increased risk in developing countries
• Group B strep infection • Intrauterine growth restriction • Spontaneous abortion	Evidence of possible increased risk
• Low birthweight (<2500 g) • Preterm delivery	Evidence of possible increased risk, especially with more advanced disease
• Fetal malformation • Gestational diabetes • Placental abruption • Placenta previa • Preeclampsia • Oligohydramnios	No evidence of increased risk

Effect of HIV and Pregnancy on Other Infections

Both HIV infection and pregnancy may affect the natural history, presentation, treatment, or significance of a number of infections, thereby causing complications in pregnancy or perinatal infection.

Vulvovaginal Candidiasis

Pregnancy is associated with both increased rates of colonization and increased symptomatic infections with species of *Candida*. HIV infection is also associated with increased rates of colonization and may be associated with increased infection rates, especially with declining immune function (*J Infect Dis* 2003;188:118; *Clin Infect Dis* 1997;24:201; *Obstet Gynecol* 1997;90:252; *Clin Infect Dis* 1998;27:1161). Therefore, HIV infected pregnant women may be particularly susceptible to yeast infections.

Treatment: Only topical azole agents should be used during pregnancy, and they should be given for at least 7 days. Prophylactic topical therapy should be considered during courses of systemic antibiotics.

Bacterial Vaginosis

Bacterial vaginosis (BV) has been associated with several adverse pregnancy outcomes, including preterm labor and birth, premature rupture of membranes, low-birthweight 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, the prevalence, persistence, and severity of which increase as CD4+ cell counts decline (*Obstet Gynecol* 2001;98:656).

Screening: Because BV is more common in the setting of HIV, and because both BV and HIV have been linked to an increased risk of preterm birth, pregnant women with HIV should be asked regularly about signs or symptoms of vaginal infection. If such signs or symptoms are present, evaluation for possible BV should follow. Infection should be treated if identified. Currently, data are insufficient to suggest that routine screening for and treatment of BV during pregnancy reduces the rate of preterm birth in the general population (*Am J Prev Med* 2001;20 suppl 3:59); no data are available in the setting of HIV infection. Multiple studies and meta-analyses have found no relationship between birth defects and metronidazole exposure during the first trimester of pregnancy (*Am J Obstet Gynecol* 1995;172:525; *Obstet Gynecol* 1993;82:348; *Br J Clin Pharmacol* 1997;44:179).

Treatment: If BV is diagnosed during pregnancy, preferred therapies are oral metronidazole 500 mg twice daily or 250 mg 3 times daily for 7 days, or oral clindamycin 300 mg twice daily for 7 days.

Genital Herpes Simplex

Primary herpes simplex virus (HSV) infection during early pregnancy has been associated with prematurity, neonatal chorioretinitis, microcephaly, and, in rare cases, skin lesions (*J Pediatr* 1987;110:97). Although congenital or intrauterine infection is uncommon, maternal HSV shedding at delivery is associated with neonatal HSV infection, which is almost always symptomatic (including skin, eye, and central nervous system [CNS] involvement or disseminated infection involving multiple organ systems). Although the mortality associated with neonatal herpes has declined significantly over the past 2 decades, it remains at 30% for disseminated disease and 4% for CNS disease. Approximately 20% of survivors of neonatal herpes have long-term neurologic sequelae (*Antiviral Res* 2009;83:207)

The risk of neonatal herpes is greatest with primary HSV, especially when acquired close to delivery (30%–60%), whereas only 3% of neonates become infected with recurrent maternal disease at delivery when the mother has recurrent HSV. Because recurrent HSV is more common than primary disease, however, most neonatal infections are associated with recurrent HSV. Two-thirds or more of mothers with HSV infected infants are asymptomatic during pregnancy; in only one-third of cases does either the mother or her sexual partner have a history of HSV infection. 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 (CS)

should be performed. CS is not indicated for recurrent HSV distant from the genital tract, such as on the thighs or buttocks (*ACOG Practice Bulletin* No. 82; *Obstet Gynecol* 2007;109:1489; reaffirmed 2009). HIV infection, particularly with evolving immune compromise and higher plasma HIV VL (*Clin Infect Dis* 2003;36:207), is associated with increased HSV shedding and more frequent, severe, and prolonged episodes of genital or perianal herpes (*Ann Intern Med* 1995;123:845). Approximately 70% of HIV infected individuals are co-infected with HSV-2 (*JAMA* 2006;296:964); co-infection with HSV-2 is common among pregnant HIV infected women, and reactivation of HSV in labor occurs more frequently in the setting of HIV infection (*Am J Obstet Gynecol* 1997;177:450).

Screening: Prevention of neonatal herpes should also emphasize prevention of herpes acquisition in susceptible pregnant women. If a pregnant woman's sexual partner has a history of oral or genital HSV infection or serologic evidence of HSV infection, or if the partner's infection status is unknown, the 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, so that judicious decisions can be made about the use of CS.

Treatment: Treatment of symptomatic HSV infections and suppressive therapy for frequent recurrences should be offered to HIV infected women during pregnancy (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 *[in press]*;. http://www.aidsinfo.nih.gov) Visceral HSV disease is more likely to occur during pregnancy and can be fatal in rare cases. Either acyclovir or valacyclovir can be used for treatment or suppression (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 [in press]; http://www.aidsinfo.nih.gov); *JAMA* 2010;304:859). During pregnancy, documented HSV infections that do not respond to these agents should be managed with expert consultation.

For pregnant women with recurrences of genital herpes, suppressive therapy with either acyclovir or valacyclovir is recommended starting at 36 weeks' gestation to reduce the need for CS delivery (*ACOG Practice Bulletin* No. 82; *Obstet Gynecol* 2007;109:1489; reaffirmed 2009). No known benefit of suppressive therapy exists for women who are only seropositive for HSV-2 without a history of genital lesions. Maternal genital herpes was a risk factor for perinatal HIV transmission in the pre-HAART era (*Obstet Gynecol* 2005;106:1341); it is not known whether HSV suppression reduces the risk of mother-to-child transmission (MTCT) among women on HAART.

Human Papillomavirus

Correlated with level of immunosuppression, both human papillomavirus (HPV) infection in general and genital warts in particular are more common in HIV infected individuals. Genital warts may be seen more frequently in

pregnancy, when they often enlarge and become friable; in some cases, they cause mechanical obstruction of the vaginal canal during labor. In rare cases perinatal exposure can result in laryngeal papillomatosis in infants and children (*Am J Obstet Gynecol* 1998;178:365).

Screening: Pregnant women with abnormal Pap smears should undergo colposcopy and cervical biopsy if lesions suspicious for high-grade HPV disease or cervical cancer are present. Increased bleeding may occur with biopsy during pregnancy. Endocervical curettage should not be performed during pregnancy. Colposcopy can be deferred until 6 weeks postpartum if Pap results indicate atypical squamous cells of unknown significance (ASCUS). Treatment of cervical intraepithelial neoplasia (CIN) is not recommended during pregnancy unless invasive disease is suspected, in which case diagnostic excision is indicated. Reevaluation with cytology and colposcopy is recommended 6 weeks postpartum. Women with preinvasive cervical lesions can deliver vaginally, if otherwise appropriate. Women with suspected invasive cervical cancer should be referred to a gynecologic oncologist.

Treatment: Podophyllin and podofilox should not be used in pregnancy because of increased risk for fetal death in several animal models and case reports in humans. At present, evidence is insufficient to recommend imiquimod use during pregnancy (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 [in press]; http://www.aidsinfo.nih.gov). Other topical treatments (e.g., bichloroacetic and trichloroacetic acid) and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy, although treatment is likely to be less effective in pregnant women than in women who are not pregnant.

CS is not currently recommended to prevent neonatal exposure to HPV, although, in rare instances, CS may be indicated when extensive HPV lesions obstruct the vagina.

Syphilis

HIV may affect clinical manifestations, serologic response, or response to treatment for syphilis. Although pregnancy does not alter the clinical manifestations of syphilis, untreated primary or secondary syphilis during pregnancy affects essentially all fetuses, with a 50% rate of prematurity, stillbirth, or neonatal death (*Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 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.

Screening: 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; testing should be repeated at 28 weeks' gestation and at delivery, particularly in women who remain at risk for infection or who live in areas with high syphilis

prevalence. Any woman with stillbirth after 20 weeks' gestation should be tested for syphilis. Development of neurologic symptoms mandates evaluation for possible neurosyphilis. Concurrent syphilis infection in the mother has been associated with increased risk for perinatal transmission of HIV (*AIDS* 2006;20:1869; *BJOG* 2004;111:579).

Treatment: Syphilis during pregnancy should be treated with the penicillin regimen appropriate for the stage of disease. Because of concerns about the effectiveness of standard therapy in pregnant women and in the setting of HIV infection, however, a second injection 1 week after the first should be considered in cases of primary, secondary, or early latent syphilis (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 *[in press]*; http://www.aidsinfo.nih.gov). Ultrasound evidence of hydrops fetalis or hepatosplenomegaly suggesting fetal syphilis increases risk for treatment failure and should be managed with expert consultation.

Treatment of syphilis during 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 (*Obstet Gynecol* 1998;92:859). Fetal and contraction monitoring for 24 hours should be considered, especially in the setting of abnormal ultrasound findings; alternatively, patients should be advised to seek immediate medical attention after treatment if contractions or a decrease in fetal movements occur after syphilis treatment (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 (in press); http://www.aidsinfo.nih.gov).

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 the treatment and prevention of congenital syphilis (*MMWR Recomm Rep* 2010;59 RR-12:1).

Even with appropriate treatment of the pregnant woman with syphilis, fetal infection may still occur; therefore, neonates should be carefully evaluated for evidence of congenital infection. Clinical and serologic follow-up should be performed in the third trimester, at delivery, and at 3, 6, 9, 12, and 24 months following treatment. Treatment failure should be managed with cerebrospinal fluid examination and retreatment. Serologic titers can be checked monthly in women at high risk for reinfection or in geographic areas in which the prevalence of syphilis is high.

Cytomegalovirus

Cytomegalovirus (CMV) is the most common cause of congenital viral infection in the United States: 0.2% to 2.2% of liveborn infants acquire this infection perinatally and it is the leading cause of congenital hearing loss (*Int J Gynaecol Obstet* 2002;76(1):95 [reaffirmed 2011]). Most maternal CMV infections are asymptomatic but may cause a mononucleosis-like illness. Because CMV has been recovered from virtually all body fluids, transmission can occur sexually or with injection drug use. Transmission can also occur with oral contact with infected secretions (e.g., from children). Primary infection, reactivation, and reinfection with different CMV strains during pregnancy all

can lead to in utero transmission and congenital CMV (*Am J Obstet Gynecol* 2010;202:297). Although about one-third of newborns acquire congenital CMV infection after primary infection, only 1%–2% of newborns acquire CMV after a recurrent infection in women who are not HIV infected. Because in most studies >90% of HIV infected pregnant women are CMV antibody positive, the risk for symptomatic infection in the fetus is expected to be low (*JAMA* 1986;256:1904; *JAMA* 1987;257:2617; *J Pediatr* 1998;132:285; *N Engl J Med* 1999;341:77); however, recent studies of HIV-exposed infants suggest that rates of congenital CMV may be increased, ranging from 2%–7%, with higher rates in babies born to mothers with CD4+ cell counts <200/mm^3 and in HIV infected infants (*Pediatr Infect Dis J* 2010;29:915; *Clin Infect Dis* 2009;48:1516).

Ninety percent of CMV infected infants are asymptomatic at birth. Symptomatic infection is more likely with maternal infection acquired early in pregnancy. Severe clinical manifestations of congenital CMV include symmetric growth restriction, hepatosplenomegaly, chorioretinitis, microphthalmia, hydrocephaly, microcephaly, and cerebral calcifications. Up to 90% of infected infants who are symptomatic at birth will have serious long-term problems, including hearing loss, visual impairment, mental retardation, and/or cognitive impairment. Among asymptomatic newborns, however, only 5%–15% are at risk for serious long-term impairment, notably late-onset hearing loss in non-HIV infected children (*J Clin Virol* 2006;35:226).

Treatment: Indications for treatment of CMV infection during pregnancy are the same as for treatment of nonpregnant HIV infected adults. Treatment of asymptomatic maternal CMV infection to prevent infant infection is not indicated. For retinal disease, use of intraocular implants or intravitreous injections for local therapy should be considered in the first trimester, if possible, to limit fetal exposure to systemically administered antiviral drugs. Systemic antiviral therapy should then be started after the first trimester. Valganciclovir is recognized as the treatment of choice for CMV during pregnancy (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 (in press); http://www.aidsinfo.nih.gov).

Fetal monitoring: The fetus should be monitored in the third trimester by fetal-movement counting and after 20 weeks' gestation by periodic ultrasound monitoring to look for evidence of hydrops fetalis indicating substantial anemia. Any ultrasound findings suspicious for congenital CMV infection (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, echogenic fetal bowel) should prompt consideration of amniocentesis for definitive diagnosis.

Although invasive fetal testing was associated with increased rates of perinatal HIV transmission in early studies (*Am J Obstet Gynecol* 1996;175:661), more recent data suggest that the risk may be minimal in women who are on effective ART and have undetectable HIV RNA levels (*Am J Obstet Gynecol* 2009;200:160.e1; *Eur J Obstet Gynecol Reprod Biol* 2008;140:212; *Eur J Obstet Gynecol Reprod Biol* 2003;108:137).

Referral to a maternal-fetal medicine specialist for evaluation, counseling, and potential further testing is recommended. Because infants who are co-infected with HIV and CMV have more rapid progression of HIV infection and develop AIDS more frequently (*J Pediatr* 1998; 132:285; *N Engl J Med* 1999;341:77), they should be a priority to receive ART. Methods to reduce the risk of exposure to CMV include safe sexual practices, careful handwashing, and transfusion of only CMV antibody–negative blood products.

Toxoplasmosis

Approximately one-third of women in the United States 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 (>60% in the third trimester vs. 10%–15% in the 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; 5% are stillborn or die in the perinatal period (*ACOG Technical Bulletin* No. 177, February 1993).

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 seems to be uncommon (0%–3.7% in two studies); there are case reports of transmission with reactivation of chronic infection in HIV infected women with severe immunosuppression (*Eur J Obstet Gynecol Reprod Biol* 1996;68:93; *Am J Obstet Gynecol* 1997;176:555).

Testing for IgG antibodies to toxoplasma is recommended for all HIV infected patients soon after the diagnosis of HIV is made and should be considered as part of prenatal testing in HIV infected pregnant women. Pregnant women with symptoms that may include fever, chills, malaise, lymphadenopathy, myalgias, and headache should be evaluated serologically for possible primary toxoplasmic infection. Primary *Toxoplasma gondii* infection can typically be distinguished from chronic infection with the use of multiple serologic assays, including IgG, IgM, IgA, and IgE antibodies; IgG avidity; and the differential agglutination (AC/HS) tests (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 [in press]; http://www.aidsinfo.nih.gov).

Screening: Detailed ultrasound examination of the fetus to evaluate specifically for hydrocephalus, cerebral calcifications, and growth restriction should be performed in cases of suspected primary or symptomatic reactivation of *T. gondii* during pregnancy (*Clin Infect Dis* 2008;47:554). Polymerase chain reaction (PCR) testing of amniotic fluid may be considered for pregnant women on ART who have serologic evidence of acquired infection during the immediate preconception period or during pregnancy and among those women with ultrasound findings suggestive of fetal *T. gondii* infection

(*Clin Infect Dis* 2008;47:554). Infants born to HIV infected women who are seropositive for toxoplasma also should be evaluated for evidence of congenital toxoplasmosis if suspected by the infant's clinical presentation.

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

Treatment: Treatment of the pregnant woman with toxoplasmic encephalitis should be the same as treatment for nonpregnant adults: pyrimethamine plus sulfadiazine plus leucovorin. This regimen is thought to also prevent transmission of *T. gondii* to the fetus and may treat affected fetuses (*Clin Infect Dis* 2008;47:554). Pregnant HIV infected women with suspected or confirmed primary *T. gondii* infection during pregnancy should be managed with expert consultation. (Primary prophylaxis and prophylaxis against recurrent disease in pregnancy are discussed below; see **Opportunistic Infections**, p. 320.)

Hepatitis B

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide (*N Engl J Med* 1997;337:1733). Most patients who become infected with HBV have complete resolution of infection and develop protective levels of antibody (anti-HBs). Of those infected as adults, 6%–10% develop chronic infection (i.e., they are chronically HBsAg+), which puts them at risk for chronic liver disease, including cirrhosis and hepatocellular carcinoma (CDC. *The ABCs of Hepatitis Fact Sheet*. http://www.cdc.gov/hepatitis/HAV/ProfResourcesA.htm. Accessed 6/27/12).

The presence of HBeAg indicates active viral replication and increased infectivity. HBV is transmitted parenterally, sexually, perinatally, and through household or institutional contact. Approximately 25% of regular sexual contacts of infected individuals will become seropositive, and sexual transmission accounts for 30%–60% of new infections. Without preventive measures, perinatal transmission, usually through intrapartum contact with maternal blood and genital secretions, occurs in 10%–20% of women who are HBsAg+. If the mother is also HBeAg+, the perinatal transmission rate increases to approximately 90%. Chronic HBV infection develops in about 90% of infected newborns, putting them at high risk for chronic liver disease (*ACOG Practice Bulletin* No. 86; *Obstet Gynecol* 2007;110:941). Rates of perinatal transmission of HBV are reduced to under 5% when hepatitis B immune globulin (HBIG) and hepatitis B vaccine are provided at birth to infants born to mothers who are HBsAg+.

Approximately 10% of HIV infected individuals have evidence of chronic hepatitis B (*J Acquir Immune Defic Syndr* 1991;4:416; *J Infect Dis* 1991;163:1138). Impaired cellular immunity is associated with higher levels of hepatitis B viremia and lower viral clearance rates following acute HBV infection. HIV patients with chronic HBV infection may be more likely to have

detectable HBeAg (*Hepatology* 1999;29:1306; *AIDS* 1997;11:597), lower rates of seroconversion, and an increased risk for liver-related mortality and morbidity (*Lancet* 2002;360:1921).

Hepatitis C

Hepatitis C virus (HCV) infection is the most common chronic bloodborne infection in the United States (*Ann Intern Med* 2006;144:705). HCV infection is transmitted primarily through injection drug use, but may also be transmitted sexually. Chronic HCV infection develops in 70%–85% of HCV infected people; 60%–70% of people with chronic HCV infection develop evidence of active liver disease and are at risk for hepatocellular carcinoma (CDC. *The ABCs of Hepatitis Fact Sheet*. www.cdc.gov/hepatitis/HAV/ProfResourcesA.htm. Accessed 6/27/12). Most people remain unaware of their infection because they are not clinically ill.

Among HIV infected pregnant women, the HCV seroprevalence rate ranges from 17%–54% (*Int J Epidemiol* 1998;27(1):108). Co-infection with HIV increases risk for and accelerates the rate of development of progressive liver disease (*Clin Infect Dis* 2001;33:562; *J Hepatol* 1997;26:1). Cofactors influencing disease progression include age, low CD4+ cell count, and history of alcoholism. Evidence suggests that HCV infection may also hasten progression of HIV infection (*J Viral Hepat* 2000;7:302). In most studies, the incidence of HCV transmission from mother to infant increases if the mother is co-infected with HIV, with transmission rates between 10% and 20% (*Clin Infect Dis* 1997;25:1121; *Lancet* 2000;356(9233):904; *J Infect Dis* 2005;192(11):1880; *J Hepatol* 2006;44 suppl 1:S6; *BJOG* 2001;108:371). This is likely related to an increase in HCV viremia and/or other HIV-related effects on HCV disease activity (*Clin Infect Dis* 2007;44(8):1123). Furthermore, maternal co-infection with HIV and HCV may also increase risk for perinatal HIV transmission (*J Infect Dis* 1997;176(2):414). Pregnancy does not appear to influence the course of HCV infection; women with chronic viral hepatitis generally do well during pregnancy unless they have progressed to decompensated cirrhosis (*Ann Hepatol* 2006;5(3):190).

Perinatal Transmission

Rate

The baseline rate of perinatal HIV transmission without prophylactic therapy is approximately 25%; however, with the use of combination ART and suppression of HIV RNA (VL) to undetectable levels, along with avoidance of breast feeding and the use of CS delivery when appropriate, the rate of perinatal transmission may be reduced to 1%–2% or less (*J Acquir Immune Defic Syndr* 2002;29:484; *AIDS* 2008;22:973; *J Public Health Manag Pract*

2010;16:481). Nevertheless, approximately 100–200 infants are infected annually in the United States (*Am J Obstet Gynecol* 2007;197(3 Suppl):S10), most commonly because the mother did not receive HIV testing or other recommended prevention interventions during pregnancy; these infections therefore represent missed opportunities (*Women Health* 2010;50(5):414). Lack of prenatal care and active substance abuse, which frequently coexist, have also been linked to a potentially avoidable increased risk for perinatal transmission (*N J Med* 2001;98:23). Acute HIV infection in pregnancy or during breastfeeding is associated with an increased risk of perinatal HIV transmission and may represent a significant proportion of residual mother-to-child HIV transmission (MTCT) in the United States (*Obstet Gynecol* 2010;115(6):1247).

Timing

The timing of transmission is a critical factor in prevention. Although transmission can occur throughout the course of pregnancy, around the time of labor and delivery, or postpartum through breastfeeding, most transmissions appear to occur during or close to the intrapartum period, particularly in non-breastfeeding populations (*JAMA* 2000;283:1175). Table 8-3 outlines the estimated timing and risk of MTCT; Table 8-4 identifies key clinical and potentially modifiable factors associated with the risk of perinatal transmission.

Risk Factors

Table 8-3

Estimated Timing and Risk of Mother-to-Child HIV Transmission (Absolute Rate) in the Absence of Antiretroviral Use

	No Breastfeeding	Breastfeeding through 6 mo	Breastfeeding through 18–24 mo
Intrauterine	5–10%	5–10%	5–10%
Intrapartum	10–20%	10–20%	10–20%
Postpartum			
Early (2 mo)		5–10%	5–10%
Late (>2 mo)		1–5%	5–10%
Overall	15–30%	25– 35%	30–45%

Source: *JAMA* 2000;283(9):1175

Table 8-4

Clinical Factors Associated with Risk of Perinatal Transmission

HIV Related Clinical Factors	
Maternal plasma HIV-1 RNA level	• Risk increases with higher maternal serum HIV-1 RNA levels (*N Engl J Med* 1999;341:394; *J Acquir Immune Defic Syndr* 2002;29:484; *N Engl J Med* 1999;341:385) • No absolute threshold exists below which transmission does not occur or above which transmission always occurs
CD4+ cell count	• Risk of transmission is higher with lower CD4+ counts
Genital tract VL	• Independently associated with perinatal transmission (*J Infect Dis* 2000;181:99), genital tract VL usually correlates with plasma VL, but discordance may occur, especially with genital tract infections
Clinical HIV stage	• Both acute infection and late-stage disease are associated with increased risk of perinatal transmission (*AIDS* 2010;24(4):573; *Obstet Gynecol* 2010; 115(6): 1247)
Maternal Related Clinical Factors	
Co-infection	• Genitally transmitted infections have been shown to increase both genital tract HIV shedding and plasma viremia (*AIDS Res Hum Retroviruses* 1998;14 suppl 1:S5), both of which may increase risk for perinatal transmission • Syphilis, HSV, and vaginal infections (BV, yeast, trichomoniasis) (*AIDS* 2008;22:1169; *Int J Gynaecol Obstet* 1998;63:247; *J Perinatol* 2010;30(11):717) have been associated with increased risk of perinatal transmission • HCV infection, TB, and placental malaria have also been associated with increased risk for vertical transmission (*J Hepatol* 2006; 44 suppl 1:S6; *Int J Epidemiol* 1998;27:296; *J Infect Dis* 2011;203:358)
Substance abuse	• Illicit drug use has been associated with increased risk for perinatal transmission (*AIDS* 1996;10:273)
Cigarette smoking	• Smoking is associated with increased risk for perinatal transmission (*J Acquir Immune Defic Syndr Hum Retrovirol* 1997;14:327)
Sexual behavior	• Unprotected intercourse during pregnancy associated with increased risk for perinatal transmission (*J Acquir Immune Defic Syndr Hum Retrovirol* 1997;15:76)
ARV use	• ARV use is consistently associated with decreased risk for perinatal transmission; the greatest reductions are associated with longer and more complex regimens (*J Acquir Immune Defic Syndr* 2002;29:484; *AIDS* 2008;22:973)

Table 8-4 *continued*

Clinical Factors Associated with Risk of Perinatal Transmission	
Obstetrical Related Clinical Factors	
Preterm delivery	• Delivery at preterm gestational age has been associated with increased risk for perinatal transmission (*J Infect Dis* 1999;179:52)
Mode of delivery	• CS delivery prior to onset of labor or membrane rupture is associated with decreased risk of perinatal transmission with HIV-1 RNA level >1000 copies/mL near time of delivery or with AZT only (studies done before routine use of VL testing/use of HAART) (*Lancet* 1999;353:1035; *N Engl J Med* 1999;340:977) • Data are insufficient to evaluate the potential benefit of CS delivery for prevention of perinatal transmission in pregnant women receiving combination ARV drugs with plasma HIV RNA levels <1000 copies/mL near the time of delivery
Invasive intrapartum monitoring	• Fetal scalp sampling and use of fetal scalp electrodes are associated with increased risk for perinatal transmission in some studies (*Eur J Obstet Gynecol Reprod Biol* 1999;87:63; *JAMA* 1994;271:1925)
Chorioamnionitis/ Placental abruption	• Placental barrier disruption and/or inflammation are associated with increased risk for perinatal transmission (*J Acquir Immune Defic Syndr* 2002;29:262)
Duration of rupture of membranes	• Longer duration of membrane rupture is associated with increased risk for perinatal transmission (*AIDS* 2001;15:357)
Forceps/vacuum/ episiotomy	• A potentially increased risk of transmission exists due to increased exposure to maternal blood/genital secretions with trauma to maternal or neonatal tissue (*Obstet Gynecol* 1999;94:897)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Breastfeeding: Globally, breastfeeding is estimated to have accounted for up to 40%–50% of newly infected children (*JAMA* 1999;282:781). Factors associated with an increased risk of breast-milk transmission are summarized in Table 8-5.

Table 8-5

Factors Associated with Increased Risk of Transmission of HIV via Breast Milk

Maternal	• Acute HIV infection (*Lancet* 1992;340:585) • Advanced HIV infection with low CD4+ cell counts • High VL in plasma or breast milk • Breast conditions (e.g., clinical or subclinical mastitis, breast abscess, cracked nipples)
Newborn	• Preterm birth or low birthweight • Loss of mucosal integrity resulting from trauma, nutritional deficiency, or infection (e.g., oral thrush) • Maternal-infant HLA incompatibility; possible protective effect (*J Infect Dis* 2008;197(8):1156)
Breastfeeding	• Timing and duration; although transmission rates are possibly higher in early breastfeeding, duration is a major determinant of transmission (*PLoS One* 2009;4(10):e7397) • Pattern of breastfeeding; mixed feeding (addition of other solids or liquids to breast milk) is associated with increased risk compared with exclusive breastfeeding (*AIDS* 2005;19:699)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Antiretroviral Drug Use In Pregnancy

The administration of ARV drugs to the mother during pregnancy and labor and to the neonate are the interventions associated with the greatest decreases in perinatal transmission. ARV drugs reduce perinatal transmission by several mechanisms, among them, by lowering maternal VL and by providing pre- and post-exposure prophylaxis for the infant through placental transfer. Therefore, at least 1 nucleoside/nucleotide agent with high placental transfer should be included in ARV regimens in pregnancy (*J Infect Dis* 2004;190(12):2167; *J Clin Pharmacol* 2001;41(7):732; *Clin Pharmacol Ther* 2009;85(2):182; *Antimicrob Agents Chemother* 2009;53(3):1067).

General Principles for Treatment

ARV prophylaxis is recommended for all HIV infected pregnant women, regardless of CD4+ cell count and/or VL. Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels, no threshold exists below which lack of transmission can be assured.

Decisions regarding use of ART or prophylaxis during pregnancy should be made by the woman after detailed and noncoercive discussion of the benefits and potential risks of therapy.

Regimen: Combination ARV regimens containing at least 3 drugs for prevention of perinatal HIV transmission are associated with the lowest risk of transmission and should be discussed and offered to all pregnant women with HIV infection. Although the initial study (PACTG 076) documenting the

effectiveness of ARVs in reducing perinatal transmission rates involved the use of AZT alone, subsequent studies and clinical experience have shown that the lowest rates of transmission are associated with more complex regimens that lower maternal VL to undetectable levels (*AIDS* 2008;22(8):973).

Choice of ARV regimens in pregnancy should follow the same principles applied when choosing ARV regimens for patients who are not pregnant: 1) optimize efficacy and durability of response; 2) maximize safety and tolerability; 3) simplify regimens to improve the likelihood of adherence and reduce the chance of resistance; and 4) for pregnant women, address special considerations such as maternal and fetal safety. To preserve future maternal options, the durability, tolerability, and simplicity of the ARV regimen is of particular importance. Table 8-6 summarizes maternal and fetal/neonatal factors to be considered when formulating an ARV regimen for a pregnant woman.

Table 8-6

Considerations in Choosing and Individualizing an Antiretroviral Regimen in Pregnancy

Mother:	**Fetus/Neonate:**
• Efficacy and durability of response • Safety and tolerability • Comorbidities • Potential for adherence • Convenience • Potential adverse drug effects • Potential interactions with other medications • Results of genotypic resistance testing • Pharmacokinetic changes in pregnancy	• Potential teratogenic effects • Potential carcinogenicity or mutagenicity • Side effects or toxicity from transplacentally transferred drugs

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 genetic make-up of the mother and fetus. Potential ARV toxicity with perinatal exposure applies both to the infected and uninfected fetus/infant.

Duration: Longer duration and/or earlier initiation of ARVs are associated with lower rates of transmission. In a French study evaluating risk factors for perinatal transmission in women with VL <500 copies/mL at the time of delivery, the overall transmission rate was 0.5%; the highest transmission rates occurred among women who were not taking ARVs at the time of conception and who did not have VL <500 copies/mL at 14, 28, and 32 weeks' gestation (*Clin Infect Dis* 2010;50(4):585). When ARVs were started during pregnancy, gestational age at initiation of therapy did not differ between groups (30 weeks), but VL decreased earlier in the nontransmitters. The ability to reach maximal viral suppression is affected by the VL at the beginning of pregnancy; in a study from the United Kingdom, with initial VL >10,000 copies/mL (c/mL), deferring ARV initiation past 20 weeks' gestation reduced the likelihood of

VL <50 c/mL at delivery, whereas only 37% of those with initial VL >100,000 c/mL reached maximal VL suppression by the end of pregnancy and this was dependent on the duration of the ARV regimen (*AIDS* 2012;26(9):1095)

Resistance: The development of ARV resistance is a major factor in treatment failure. The most common causes of resistance are the prescription of ineffective regimens and lack of adherence. ARV regimens are ineffective when they include drugs to which there is existing resistance or when they are composed of just one or two drugs or drugs from just one ARV class. Viral replication of HIV is inherently mutation-prone and resistant viral variants emerge under selective pressure, especially with incompletely suppressive regimens. Resistant viral variants are believed to be archived permanently in latent HIV reservoirs, and resistance to one drug may be associated with resistance to other drugs within the same class; therefore, if ineffective regimens are used or if ARV regimens are taken incorrectly, patients' future treatment options may be significantly limited.

When developed during pregnancy, drug resistance may compromise the prevention of perinatal transmission or may result in transmission of a resistant virus to the fetus, which would limit the infant's future treatment options. It could also limit the mother's future treatment options or decrease the effectiveness of prophylactic regimens in future pregnancies. Although perinatal transmission of resistant virus has been reported, it appears to be unusual, and little evidence exists that the presence of resistance mutations increases the risk of transmission when current recommendations for ARV management in pregnancy are followed.

Several factors unique to pregnancy may increase risk for the development of resistance:

- If prophylactic regimens include drugs with significant half-life differences, such as NVP or EFV combined with two nucleoside analogue drugs, then postpartum discontinuation of all regimen components simultaneously may result in persistent subtherapeutic drug levels and increase risk for the development of NNRTI resistance.
- Problems such as nausea and vomiting in early pregnancy may compromise adherence or absorption.
- Pharmacokinetic changes during pregnancy, such as increased plasma volume and renal clearance, may lead to subtherapeutic drug levels that increase risk for resistance.

Current recommendations for HIV drug-resistance testing in pregnant women are as follows (resistance testing requires VL >500–1000 copies/mL for accurate detection of resistance mutations):

- Before starting treatment or prophylaxis, test for resistance in all pregnant women not currently taking ARVs (unless previously tested and patient ARV-naïve).
- Test for resistance in all pregnant women entering pregnancy on ART with detectable VL.

- Test for resistance in all pregnant women who have suboptimal viral suppression after initiation of ARV drugs in pregnancy (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. 2013. http://www.aidsinfo.nih.gov).

For optimal prevention of perinatal transmission, empiric initiation of ARV drugs before obtaining the results of resistance testing is warranted for women who present late in pregnancy, with adjustment as needed after the test results are available.

Women who have documented ZDV resistance should still receive intravenous ZDV during labor **if VL >400 c/mL near delivery**, along with their established ARV regimens, and their infants should receive oral ZDV.

Recommendations for preventing ARV resistance include the following:

- Use of an effective combination ARV regimen
- Emphasis on and reinforcement of the importance of good adherence at each patient visit
- **Not recommended:** Addition of single-dose NVP (sdNVP) to a combination ARV regimen; sdNVP does not increase efficacy of MTCT prevention and may lead to maternal or infant NVP resistance (*J Infect Dis* 2002;186:181)
- For pregnant women receiving an NNRTI-based combination regimen that is discontinued after delivery:
  - Continue the NRTI components after stopping the NNRTI (*J Infect Dis* 2006;193(4):482; *PLoS Med* 2009;6(10):e1000172)
  - An alternative strategy is to substitute a PI for the NNRTI prior to the interruption and continue the PI with dual NRTIs (*AIDS* 2008;22(17):2279)

The optimal interval between stopping an NNRTI and discontinuing the other ARVs is not known, but current recommendations suggest an interval of 7–30 days. Because NNRTI concentrations may remain detectable for more than 3 weeks in patients receiving EFV-based therapy, some experts recommend continuing other ARV agents or substituting a PI plus two other agents for up to 30 days (*J Acquir Immune Defic Syndr* 2005;38(3):283; *AIDS* 2005;19(15):1716). A recent study of 412 women who received single-dose nevirapine and were randomized to receive zidovudine/lamivudine, tenofovir/emtricitabine, or lopinavir/ritonavir for either 7 or 21 days found an overall new nevirapine resistance mutation rate of 1.2% when assessed by population genotype at 2 and 6 weeks following completion of treatment, with no difference by length of treatment. However, low-frequency nevirapine-resistant mutations at codons 103, 181, and 184 detected using allele-specific PCR emerged significantly more often in the 7-day arms (13/74 [18%]) than in the 21-day arms (3/66 [5%], P = .019). (*Clin Infect Dis* 2013;56(7):1044).

All cases of ARV drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see details at http://www.APRegistry.com. Accessed 6/26/12). The registry is a collaborative project of pharmaceutical manufacturers, with an advisory committee of obstetric and pediatric practitioners, that collects observational data regarding ARV exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. The registry does not use patient names; registry staff members obtain birth outcome follow-up information from the reporting provider.

Limited data are available on both the long-term maternal consequences of ARV drug use during pregnancy solely for transmission prophylaxis and on the long-term consequences for the infant of in utero ARV exposure.

Expert consultations: Expert consultation on care of the HIV infected pregnant woman is recommended and/or should be considered in the following situations:

- When use of ZDV alone is being considered
- If maximal virologic suppression is not achieved with the prescribed ARV regimen
- When choosing an ARV regimen for a woman with extensive ART experience and/or multiple resistance mutations
- Prior to discontinuation of ARVs when they were being taken only for prophylaxis
- If a patient has significant toxicity that is related to, or potentially related to, use of ARVs
- If a patient has significant medical comorbidities that may affect drug choice (e.g., HBV)
- If premature membrane rupture occurs
- When maternal ARV resistance is known or suspected, with high maternal VL at or near delivery, or when the mother has received no ARVs prior to and/or during labor (to determine potential for use of additional drugs in the infant; consult with a pediatric HIV specialist)

Recommendations for Use of Specific ARV Agents In Pregnancy

Table 8-7 provides information about all currently Food and Drug Administration (FDA)-approved ARV agents, with information and recommendations specific to pregnancy. These recommendations specifically relate to agents used to construct initial ARV regimens in antiretroviral naïve pregnant women and are predicated on ARV sensitivity by resistance testing. If a woman enters pregnancy on a stable ARV regimen with viral suppression, the regimen should be continued. Antiretroviral drugs or drug combinations are divided into several categories for use in pregnancy, based on efficacy and durability; safety for mother, fetus and newborn; ease of use; available pregnancy-specific pharmacokinetic data; medical comorbidities limiting drug choice; and experience in pregnancy.

Table 8-7

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
NRTIs/NtRTIs: *Nucleoside/nucleotide reverse transcriptase inhibitors are recommended for use as part of combination regimens that usually include 2 NRTIs and/or NtRTIs plus either an NNRTI or 1 or more PIs. Use of single or dual NRTIs/NtRTIs alone is not recommended for treatment of HIV infection. Long-term use is associated with potential maternal and infant mitochondrial toxicity.*				
PREFERRED				
LAMIVUDINE (Epivir®, 3TC)	**Dose:** 150 mg po bid or 300 mg po qd **Food requirements:** Take without regard to meals. **Available as:** • Tabs: 150 mg; 300 mg • Oral sol: 10 mg/mL • Combivir: ZDV 300 mg/3TC 150 mg (1 tab po bid) • Trizivir: ZDV 300 mg/3TC 150 mg/ABC 300 mg (1 tab po bid) • Epzicom: 3TC 300 mg/ABC 600 mg (1 tab po qd)	Generally very well tolerated Occasional headache, nausea, diarrhea, abdominal pain, and insomnia Lactic acidosis/hepatic steatosis not generally associated with 3TC Severe acute exacerbation of hepatitis may occur in HBV-co-infected patients who d/c 3TC	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard doses	Because of extensive experience with 3TC in pregnancy in combination with ZDV, 3TC + ZDV is a recommended dual NRTI/NtRTI backbone for pregnant women Active against HBV Resistance profile is identical to FTC No evidence of human teratogenicity
ZIDOVUDINE (Retrovir®, AZT, ZDV)	**Dose:** 300 mg po bid or 200 mg po tid **Food requirements:** Take without regard to meals. **Intrapartum:** 2 mg/kg IV for first hour then 1 mg/kg IV until birth **Available as:** • Caps: 100 mg • Tabs: 300 mg • IV sol: 10 mg/mL • Oral sol: 10 mg/mL • Combivir: ZDV 300 mg/3TC 150 mg (1 tab po bid) • Trizivir: ZDV 300 mg/3TC 150 mg/ABC 300 mg (1 tab po bid)	GI intolerance, malaise; headache (in 5%–10%); bone marrow suppression (anemia and neutropenia), myopathy/myalgia; transaminase elevation; fingernail discoloration Rare cases of lactic acidosis and severe hepatomegaly with steatosis have been reported	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard doses	Because of extensive experience with ZDV in pregnancy in combination with 3TC, ZDV + 3TC is a recommended dual NRTI/NtRTI backbone for pregnant women ZDV should not be included in prenatal regimen if there is severe toxicity, d4T use, documented resistance, or if already on effective and well-tolerated regimen that does not include ZDV No evidence of human teratogenicity Short-term safety for mother and infant has been demonstrated

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
PREFERRED				
ABACAVIR (Ziagen®, ABC)	**Dose:** 300 mg po bid or 600 mg po qd **Food requirements:** Take without regard to meals **Available as:** • Tabs: 300 mg • Oral sol: 20 mg/mL • Trizivir: ZDV 300 mg/3TC 150 mg/ ABC 300 mg (1 tab po bid) • Epzicom: 3TC 300 mg/ABC 600 mg (1 tab po qd)	Hypersensitivity reaction: fever, rash, fatigue, malaise, GI symptoms, and arthralgias~4% before HLA B5701 testing in nonpregnant patients (rate in pregnancy unknown) Deaths reported upon rechallenge	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard dose	Must screen for HLA-B5701 before starting ABC and results documented as negative before initiating ABC. Mandatory and permanent d/c with hypersensitivity reaction Patients should be educated regarding symptoms of hypersensitivity reaction No evidence of human teratogenicity
EMTRICITABINE (Emtriva®, FTC)	**Dose:** 200 mg po qd or 240 mg (24 mL) oral solution once daily **Food requirements:** Take without regard to meals **Available as:** • Caps: 200 mg hard gel • Oral sol: 10mg/mL • Truvada: FTC 200 mg/ TDF 300 mg (1 tab po qd) • Atripla: FTC 200 mg/EFV 600 mg/TDF 300 mg (1 tab po hs; take on empty stomach to reduce side effects)	Generally well tolerated Occasional headache, diarrhea, nausea, rash; hyperpigmentation/skin discoloration Lactic acidosis/hepatic steatosis not generally associated with FTC Severe acute exacerbation of hepatitis may occur in HBV-co-infected patients who d/c FTC	**Placental transfer:** High **PK:** Slightly lower concentrations in 3rd trimester compared with postpartum; no clear need to increase dose	Active against HBV Resistance profile is identical to 3TC No evidence of human teratogenicity

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
TENOFOVIR DF (Viread®, TDF)	**Dose:** 300 mg po qd **Food requirements:** Take without regard to meals **Available as:** • Tabs: 300 mg • Truvada: TDF 300 mg/FTC 200 mg (1 tab po qd) • Atripla: FTC 200 mg/EFV 600 mg/TDF 300 mg (1 tab po hs; take on empty stomach to reduce side effects)	Generally well tolerated Headache, diarrhea, nausea and vomiting reported; renal insufficiency, Fanconi's syndrome; potential decrease in bone mineral density Lactic acidosis with hepatic steatosis not generally associated with TDF Severe acute exacerbation of hepatitis may occur in HBV–co-infected patients who d/c TDF	**Placental transfer:** High **PK:** Lower AUC in the 3rd trimester compared with postpartum, but adequate trough levels	Considered a preferred NtRTI in combination with 3TC or FTC in women with chronic HBV infection; monitor renal function. Possible HBV flare if drug is d/c'ed postpartum. No evidence of human teratogenicity Clinical studies in humans (particularly children) show bone demineralization with chronic use. Recent study found no difference in growth patterns, bone health or markers of bone metabolism in infants with and without in utero TDF exposure (*Antivir Ther* 2011;16:1259).
NOT RECOMMENDED				
DIDANOSINE (Videx® EC, generic didanosine enteric coated (EC), ddI)	**Dose:** Wt ≥ 60 kg: 400 mg po qd; with TDF, 250 mg po qd Wt <60 kg: 250 mg po qd; with TDF, 200 mg po qd Preferred dosing with oral solution is bid (i.e., total daily dose divided into 2 doses) **Food requirements:** Take 1/2 h before or 2 h after meals **Available as:** • Caps (enteric coated): 125 mg, 200 mg, 250 mg, or 400 mg • Oral sol: 10 mg/mL	GI intolerance (diarrhea, mouth sores); peripheral neuropathy (in 5%–12% of patients); pancreatitis (in 1%–9% of patients with 6% of cases fatal); transaminase elevation; rare cases of lactic acidosis and severe hepatomegaly with steatosis; noncirrhotic portal hypertension resulting in esophageal variceal bleed, liver failure, and death have been reported; optic neuritis	**Placental transfer:** Moderate **PK:** Not significantly altered in pregnancy; use standard dose	Not recommended due to toxicity Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving ddI and d4T together. In the Antiretroviral Pregnancy Registry, an increased rate of birth defects with ddI compared with general population was noted after both 1st trimester (4.6%) and later exposure (4.3%). No specific pattern of defects was noted and clinical relevance is uncertain.

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
STAVUDINE (Zerit®, d4T)	**Dose:** Wt ≥ 60 kg: 40 mg po bid Wt <60 kg: 30 mg po bid WHO recommends 30 mg po bid for all patients **Food requirements:** Take without regard to meals **Available as:** • Caps: 15 mg, 20 mg, 30 mg, 40 mg • Oral sol: 1mg/mL	Peripheral neuropathy (in 5%–15% of patients); transaminase elevation (in 8% of patients); rare cases of lactic acidosis and severe hepatomegaly with steatosis; lipoatrophy; pancreatitis; rare cases of rapidly progressive ascending neuromuscular weakness	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard doses	Not recommended due to toxicity Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving combination of d4T and ddI as component of ARV therapy. Due to antagonism, ZDV and d4T should never be used together as a part of a combination ARV regimen No evidence of human teratogenicity
NNRTIs: *Non-nucleoside reverse transcriptase inhibitors are recommended for use in combination regimens that include 2 NRTI/NtRTI drugs. Hypersensitivity reactions, including hepatic toxicity and rash, are more common in women; unclear if risk is increased in pregnancy.*				
PREFERRED				
EFAVIRENZ (Sustiva®, EFV) May be initiated after first 8 wks of pregnancy.	**Dose:** 600 mg po qhs **Food requirements:** Take on empty stomach to decrease side effects **Available as:** • Caps: 50 mg, 200 mg • Tabs: 600 mg • Atripla: EFV 600 mg/FTC 200 mg/TDF 300 mg (1 tab po hs; take on empty stomach to reduce side effects)	Morbilliform rash in 15%–27% of patients, with 1%–2% requiring d/c; 1 case of Stevens-Johnson syndrome reported; CNS effects (confusion, depersonalization, abnormal dreams) seen in up to 52% of patients (generally resolves in 2–4 wk); transaminase elevation in 2%–3% of patients, hyperlipidemia	**Placental transfer:** Moderate **PK:** AUC decreased during the 3rd trimester compared with postpartum, but generally exceeded target exposure; no change in dose needed	Significant malformations (anencephaly, anophthalmia, cleft palate) observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving EFV during 1st trimester at a dose that produced plasma levels comparable to systemic human therapeutic exposure. Human retrospective reports and 1 prospective case report of NTDs with 1st-trimester exposure and 1 prospective case of anophthalmia with facial clefts. However, meta-analysis of >1300 1st-trimester EFV exposures found no increased risk of birth defects and only 1 NTD (incidence 0.07%) (*AIDS* 2011;25:2301). More data are needed to conclusively determine association (or lack of) between EFV and NTDs. EFV should be avoided during 1st trimester whenever possible. However, EFV should be continued in women presenting in 1st-trimester on EFV-containing regimen and with maximal VL suppression. After 1st-trimester, EFV may be considered if best choice compared with alternatives Women of childbearing age trying to conceive or not using effective contraception should not use EFV unless other effective and acceptable regimens are not available Recommend effective contraception if EFV is to be continued or initiated postpartum. Because EFV may decrease hormonal contraceptive efficacy, a reliable method of contraception (e.g., barrier) should be used in addition to hormonal contraceptives.

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
ALTERNATIVE				
NEVIRAPINE (Viramune®, NVP)	**Dose:** 200 mg po qd for 14 d, then 200 mg po bid **Note:** If mild to moderate rash develops without constitutional symptoms, continue lead-in dosing until rash resolves, but no longer than 28 d total **Food requirements:** Take without regard to meals **Available as:** • Tabs: 200 mg • Oral suspension: 50 mg/5mL	Rash in 17% of patients (7% d/c'ed due to rash; many patients require hospitalization) Stevens-Johnson syndrome reported; transaminase elevation; severe hepatitis; fever; nausea; headache Women may be at increased risk of rash and liver toxicity, especially with CD4+ cell count >250/mm^3 (*AIDS* 2002;16(11):1566; *Clin Infect Dis* 2001;32(1):124; *J Acquir Immune Defic Syndr* 2003;34 suppl 1:S21) or with baseline elevated liver enzymes (*HIV Med* 2010;11(10):650); unclear if pregnancy increases risk. This toxicity not reported in women receiving single-dose NVP for prophylaxis of perinatal transmission.	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard doses.	Initiate NVP in pregnant women with CD4+ cell counts >250/mm^3 only if benefit clearly outweighs risk, because of increased risk of potentially life-threatening hepatotoxicity in women with high CD4+ cell counts. Elevated transaminase levels at baseline also may increase the risk of NVP toxicity. Women who enter pregnancy on NVP regimens and are tolerating them well may continue therapy, regardless of CD4+ cell count Monitor LFTs q 2 wk x 1 mo, then q 1 mo x 4 mo, then q 1–3 mo Repeat lead-in dosing period if therapy d/c'ed for >7 d No evidence of human teratogenicity

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
INSUFFICIENT DATA TO RECOMMEND USE				
RILPIVIRINE (Endurant, RPV)	**Dose:** 25 mg po qd **Food requirements:** Take with a meal **Available as:** • Tabs: 25 mg • Complera (RPV 25 mg/TDF 300 mg/FTC 200 mg) 1 tab po qd with meal	Rash; depression, insomnia, headache	**Placental transfer:** Unknown **PK:** No pharmacokinetic studies in human pregnancy	Limited experience in human pregnancy. Safety and pharmacokinetic data in pregnancy are insufficient to recommend use during pregnancy. RPV not recommended with pretreatment HIV RNA >100,000 c/ml or CD4+ cell count <200 cells/microliter. Do not use with proton pump inhibitor.
NOT RECOMMENDED				
ETRAVIRINE (Intelence, ETR)	**Dose:** 200 mg po bid **Food requirements:** Take with food **Available as:** • Tabs: 100 mg, 200 mg	Rash in up to 17%, severe in 1.3% of patients; generally occurs in first 2 wk and resolves within 1–2 wk on continued therapy, but 2% required ETR d/c Stevens-Johnson syndrome reported Hypersensitivity reactions have been reported (rash; constitutional symptoms; and organ dysfunction, including liver failure)	**Placental transfer:** Unknown **PK:** Limited data in pregnancy suggests no change in dose needed (*HIV Med* 2011;12(4):257)	Not recommended in naïve adults as limited data. Limited experience in pregnancy

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
PIs: *Protease inhibitors are recommended for use in combination regimens with 2 NRTI/NtRTI drugs. Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis have been reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs.*				
PREFERRED				
ATAZANAVIR (Reyataz®, ATV)	**Dose:** (ATV 300 mg po + RTV 100 mg po) qd **2nd and 3rd trimesters:** Some experts recommend increased dose (ATV 400 mg + RTV 100 mg po qd) in all pregnant women in the 2nd and 3rd trimesters **Note:** Increased dose (ATV 400 mg po + RTV 100 mg po) qd is recommended in the following situations: • With TDF or H2-receptor antagonist in ARV-experienced pregnant patients • With EFV in ARV-naïve patients Concurrent use of ATV with EFV in ARV-experienced patients is not recommended due to decreased ATV levels **Food requirements:** Take with food **Available as:** • Caps: 100 mg, 150 mg, 200 mg, 300 mg	Reversible benign hyperbilirubinemia (grade 3–4 occurring in 35%–47% of patients), jaundice, scleral icterus PR interval prolongation, 1st-degree AV block reported Nausea, vomiting, abdominal pain (generally better tolerated compared with LPV/r); skin rash (20%); headache; serum transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution and hyperglycemia ATV alone has less impact on serum lipids, but elevated lipids can be a problem with RTV boosting	**Placental transfer:** Low **PK:** With standard ATV/r dosing, lower ATV concentrations during pregnancy as compared to nonpregnant adults (*J Acquir Immune Defic Syndr* 2011;56(5):412; *AIDS* 2007;21(18):2409). Use of an increased dose during 2nd and 3rd trimesters resulted in plasma concentrations equivalent to those in nonpregnant adults on standard dosing. ATV concentrations further reduced ~25% with concomitant TDF use (*J Acquir Immune Defic Syndr* 2011;56(5):412; *AIDS* 2007;21(18):2409)	Must be combined with low-dose RTV boosting Theoretical concern of increased indirect bilirubin exacerbating physiologic hyperbilirubinemia in neonates not observed in clinical trials to date (*J Acquir Immune Defic Syndr* 2011;56(5):412; *AIDS* 2007;21(18):2409) No evidence of human teratogenicity

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
LOPINAVIR/ RITONAVIR (Kaletra®, LPV/r)	**Dose:** LPV 400 mg /r 100 mg (2 tabs or 5 mL) po bid **2nd and 3rd trimesters:** PK studies suggest dose should be increased to LPV 600 mg/ r 150 mg po bid, especially in PI-experienced patients If standard dosing is used, monitor virologic response and LPV drug levels, if available **Note:** Once-daily dosing (LPV 800 mg/r 200 mg) is not recommended during pregnancy because no data address whether drug levels are adequate with such administration Dose adjustment required if co-administered with NVP or EFV: LPV500 mg/r 125 mg po bid **Food requirements:** Tabs: Take without regard to food Oral sol: Take with food **Available as:** • Tabs: (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg) • Oral solution: Each 5 mL contains (LPV 400 mg + RTV 100 mg) Oral solution contains 42% alcohol and therefore may not be optimal for use in pregnancy	Generally well tolerated, good short-term safety profile Diarrhea in 13.8%–23.8% of patients; nausea, vomiting, abdominal pain, asthenia, headache, and rash reported Serum transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Low **PK:** AUC decreased in 2nd and 3rd trimesters with standard dosing (*AIDS* 2010;24(14):2193; *AIDS* 2006;20(15):1931; *HIV Med* 2011;12(3):166). AUC with dose of LPV/r 600 mg/150 mg bid in 3rd trimester resulted in AUC similar to nonpregnant adults taking LPV/r 400 mg/100 mg bid (*J Acquir Immune Defic Syndr* 2010;54(4):381).	No evidence of human teratogenicity. Short-term safety demonstrated in Phase I/II studies.

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
ALTERNATIVE				
DARUNAVIR (Prezista®, DRV)	**Dose:** Must be combined with low-dose RTV boosting: • ARV naïve: DRV 800 mg po + RTV 100 mg po qd • ARV experienced with no DRV resistance mutations: (DRV 800 mg po + RTV 100 mg po) qd • ARV experienced and any DRV resistance mutations: (DRV 600 mg po + RTV 100 mg po) bid Some experts recommend use of only bid dosing (DRV 600 mg po + RTV 100 mg po) during pregnancy **Food requirements:** Take with food **Available as:** • Tabs: 75 mg, 150 mg, 400 mg, 600 mg	GI intolerance (20%); diarrhea, but less common than with LPV/r; headache (15%); rash (7%); contains a sulfa moiety Stevens-Johnson syndrome and erythema multiforme have been reported; serum transaminase elevation and hepatitis Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal to low **PK:** In the 3rd trimester and postpartum, decreased DRV levels, especially with qd dosing	Must be combined with low-dose RTV boosting Use with caution or avoid in patients with sulfa allergy Limited experience in human pregnancy
SAQUINAVIR (Invirase®, SQV)	**Dose:** (SQV 1000 mg po + RTV 100 mg po) bid Unboosted SQV is not recommended in pregnancy **Food requirements:** Take with meals or within 2 h after a meal **Available as:** • Caps (hard gel): 200 mg • Tabs: 500 mg	GI intolerance: nausea, diarrhea, abdominal pain; transaminase elevation; PR interval prolongation; QT interval prolongation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal **PK:** Limited data on SQV-HGC and 500 mg tablet suggest that (SQV 1000 mg + RTV 100 mg) bid achieves adequate drug levels in pregnancy	Must be combined with low-dose RTV boosting Well tolerated; short-term safety demonstrated for mother and infant for SQV in combination with low-dose RTV Baseline EKG recommended before starting because of potential PR and/or QT interval prolongations. Drug is contraindicated in patients with pre-existing conduction-system disease. Insufficient data to assess for teratogenicity in humans

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
NOT RECOMMENDED				
INDINAVIR (Crixivan®, IDV)	**Dose:** (IDV 800 mg po + RTV 100 mg-200 mg po) bid Unboosted IDV is not recommended in pregnancy **Meals:** Take without regard to meals **Available as:** • Caps: 100 mg, 200 mg, 400 mg	Nephrolithiasis +/- hematuria in 5%–15% of patients; indirect hyperbilirubinemia (≥2.5 mg/dL in 10–15% of patients); transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal **PK:** Significantly lower levels with standard dosing of IDV alone during pregnancy compared with postpartum. (*Antimicrob Agents Chemother* 2007;51(2):783; *AIDS* 2000;14(8):1061) With (IDV 400 mg + RTV 100 mg po) bid, 82% of women met target trough level (*Antimicrob Agents Chemother* 2008;52(4):1542)	Because of 2x daily dosing, pill burden, and potential for renal stones and hyperbilirubinemia, IDV is not recommended in pregnancy. No evidence of human teratogenicity
NELFINAVIR (Viracept®, NFV)	**Dose:** 1250 mg po bid (750 mg po tid not recommended in pregnancy) **Food requirements:** Take with fatty meal **Available as:** • Tabs: 250 mg, 625 mg • Oral powder: 50 mg/g	Generally well tolerated Diarrhea; serum transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal to low **PK:** Adequate drug levels with 1250 mg po bid during 1st and 2nd trimester, but higher variability and lower concentrations observed during 3rd trimester compared with postpartum. NFV 1250 mg po bid was associated with lower blood levels in the 3rd trimester than in the 2nd trimester (*Br J Clin Pharmacol* 2006;62(3):309; *HIV Med* 2008;9(10):875).	Not recommended due to lower rate of viral suppression with NFV. In Antiretroviral Pregnancy Registry, a small increase in overall birth defect rates was noted. No specific pattern of defects was noted and clinical relevance is uncertain. Good short-term safety profile for mothers and infants.

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
NOT RECOMMENDED				
RITONAVIR (Norvir®, RTV) When used as low-dose booster with other PIs	**Dose:** RTV is used at low doses (i.e., 100–200 mg qd or bid) with other PIs as a pharmacologic enhancer or booster (refer to other PIs for specific dosing recommendations) **Food requirements:** Tabs: Take with food Caps: Take with food if possible (may improve tolerability) **Available as:** • Caps: 100 mg • Tabs: 100 mg • Oral sol: 80 mg/mL (contains 43% alcohol and therefore may not be optimal for use in pregnancy)	GI intolerance: nausea, vomiting, diarrhea; abdominal pain Dose-dependent taste perversion; asthenia; circumoral and peripheral paresthesias; pancreatitis; transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal **PK:** Lower drug concentrations during pregnancy compared with postpartum	Should be used only in combination with second PI as low-dose RTV "boost" because of low drug levels in pregnant women when used as a sole PI and poor tolerance when given at full dose RTV as a single PI is not recommended because of inferior efficacy and increased toxicity Limited experience at full dose in human pregnancy No evidence of human teratogenicity
TIPRANAVIR (Aptivus®, TPV)	**Dose:** Must be combined with low-dose RTV boosting: (TPV 500 mg po + RTV 200 mg po) bid **Food requirements:** When taken with RTV tablets, take with meals; with RTV caps or sol, take without regard to meals **Available as:** • Caps: 250 mg • Oral sol: 100 mg/mL	GI intolerance LFTs elevation (17.5%) more common with TPV; severe hepatitis Rash (8-14%); contains a sulfa moiety Rare cases of intracranial hemorrhage Class adverse events such as hyperlipidemia, fat redistribution and hyperglycemia	**Placental transfer:** Moderate, based on very limited data **PK:** Limited studies in human pregnancy	Not recommended in naïve adults and increased toxicity with higher ritonavir dose Limited experience in human pregnancy Must be combined with low-dose RTV boosting Use with caution or avoid in patients with sulfa allergy Insufficient data to assess for teratogenicity in humans

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
INSUFFICIENT DATA TO RECOMMEND USE				
FOSAMPRENAVIR (Lexiva®, FPV)	**Dose:** • ARV naïve: (FPV 1400 mg po + RTV 100–200 mg po) qd • or (FPV 700 mg po + RTV 100 mg po) bid • or FPV 1400 mg po bid ARV experienced: (once daily dosing NOT recommended): • (FPV 700 mg po + RTV 100 mg po) bid • With EFV: (FPV 700 mg po + RTV 100 mg po) bid • **or** (FPV 1400 mg po + RTV 300 mg po) qd **Food requirements:** Tabs: Take with meals when RTV-boosted Oral suspension: Take without food **Available as:** • Tabs: 700 mg • Oral suspension: 50 mg/mL	GI intolerance most common: nausea, vomiting, diarrhea; headache; rash (in 19% of patients) (contains a sulfa moiety), usually mild-moderate but Stevens-Johnson syndrome reported; serum transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Low **PK:** With RTV boosting, AUC reduced in 3rd trimester; however, exposure is greater in 3rd trimester with boosting than in nonpregnant adults without boosting, and trough concentrations in 3rd trimester are adequate for patients without PI resistance mutations	Limited experience in human pregnancy Recommended to be given with low-dose RTV boosting Use with caution or avoid in patients with sulfa allergy Insufficient data to assess for teratogenicity in humans
Integrase Inhibitor				
ALTERNATIVE				
RALTEGRAVIR (Isentress®, RAL)	**Dose:** RAL 400 mg po bid (with rifampin: 800 mg po bid) **Food requirements:** Take without regard to meals **Available as:** • Tabs: 400 mg	Generally well tolerated with adverse effect rates comparable to placebo Nausea, headache, diarrhea, pyrexia Reports of myopathy and rhabdomyolysis Reports of CNS side effects (dizziness, ataxia, depression)	**Placental transfer:** Variable but high **PK:** Extensive variability in 3rd trimester, but RAL exposure not consistently altered compared with postpartum/historical data. Standard dosing recommended.	May be used when drug interactions with PI regimens a concern Limited experience in human pregnancy Insufficient data to assess for teratogenicity in humans

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
INSUFFICIENT DATA TO RECOMMEND USE				
ELVITEGRAVIR (EVG)—currently only availabe as a co-formulation with Cobicistat (COBI/ TDF/FTC) Stribild	**Dose:** (EVG 150 mg + COBI 150 mg + TDF 300 mg + FTC 200 mg) po qd with food	GI intolerance (nausea, diarrhea) New onset or worsening renal impairment Potential decrease in bone mineral density Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC and TDF	**Placental transfer:** No information **PK:** No data in human pregnancy	No experience in human pregnancy
Entry Inhibitors				
NOT RECOMMENDED				
ENFUVIRTIDE (Fuzeon®, T-20)	**Dose:** T-20 90 mg (1 mL) subcut bid into upper arm, anterior thigh, or abdomen, with each injection given at a site different from the preceding injection **Available form:** Single-use vial containing 108 mg of T-20 (as powder) to be reconstituted with 1.1 mL of sterile water for injection, with delivery of approx. 90 mg/mL	Local site reaction (grade 3 or 4) including pain (9%), erythema (32%), pruritus (4%), induration (57%), and nodules or cysts (26%) (with 3% requiring d/c) Bacterial pneumonia (reported in 4.68 events vs. 0.61 events per 100 pt-y) Hypersensitivity reaction (<1%); symptoms may include rash, fever, nausea, vomiting, chills, hypotension, elevated transaminases; may recur on rechallenge	**Placental transfer:** None, but limited data **PK:** Limited data in human pregnancy	Not recommended due to lack of data in ART-naïve adults Minimal data in human pregnancy Insufficient data to assess for teratogenicity in humans Requires twice daily injections

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
INSUFFICIENT DATA TO RECOMMEND USE				
MARAVIROC (Selzentry®, MVC)	**Dose:** • MVC 150 mg po bid when given with strong CYP3A inhibitors, with or without CYP3A inducers, including PIs (except TPV/r) • MVC 300 mg po bid when given with NRTIs, NVP, RAL, T-20, TPV/r, and other drugs that are not strong CYP3A inhibitors or inducers • MVC 600 mg po bid when given with CYP3A inducers, including EFV, ETR (without a CYP3A inhibitor) **Food requirements:** Take without regard to meals **Available formulation:** • Tabs: 150 mg, 300 mg	Generally well tolerated Abdominal pain; cough; upper respiratory tract infections; musculoskeletal symptoms; pyrexia; rash; dizziness, orthostatic hypotension (especially with chronic renal insufficiency) Rare cases of hepatotoxicity	**Placental transfer:** Unknown **PK:** No data in human pregnancy	Limited experience in human pregnancy Insufficient data to assess for teratogenicity in humans

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Adapted from: Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.* HHS Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*

For ARV-naïve pregnant women, preferred or alternative regimens include one of the preferred or alternative PIs, NNRTIs or integrase inhibitors, as noted in Table 8-7, combined with a 2 NRTI backbone. This backbone may be ZDV/3TC, ABC/3TC or TDF/FTC. 3TC and FTC can substitute for each other. TDF/FTC and ABC/3TC may be preferred because of once daily co-formulations and less frequent toxicity than ZDV-containing regimens, but there is less experience with use of these regimens in pregnancy. ABC should NOT be used in patients who test positive for HLA-B*5701. Drugs listed in the Do Not Recommend category are placed in that category either because of toxicity or lower rate or viral suppression, or because they are not currently recommended in naïve adults and adolescents due to limited data. The latter group may eventually move to a different category as more data becomes available.

Special Considerations

Pharmacokinetics: Physiologic changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, biotransformation, and elimination, thereby also affecting requirements for drug dosing and potentially altering a pregnant woman's susceptibility to drug toxicity (*Clin Pharmacokinet* 2004;43(15):1071; *Br J Clin Pharmacol* 2008;66(2):179). In general, the pharmacokinetics of NRTI and NNRTI drugs are similar in women who are and are not pregnant; protease inhibitor (PI) pharmacokinetics are more variable, particularly in later pregnancy. The need for a dose adjustment depends on the PI, the patient's treatment experience, and the use of interacting concomitant medications (Reyataz [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011. http//www packageinserts.bms.com/pi/pi_reyataz.pdf. Accessed 7/11/2012; *AIDS* 2006;20(15):1931; *Br J Clin Pharmacol* 2006;62(3):309; *Br J Clin Pharmacol* 2006;62(3):309; *J Acquir Immune Defic Syndr* 2008;49(5):485; *J Antimicrob Chemother* 2009;63(6):1223; *J Acquir Immune Defic Syndr* 2010;54(4):381).

Gastrointestinal upset and/or hyperemesis: ARV 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 absorption. Some pregnant women also develop hyperemesis in early pregnancy, though there is no evidence this is increased in the setting of HIV. If antiemetics are not effective, consideration should be given to temporary discontinuation of all ARVs, in which case, all drugs should be stopped simultaneously and restarted simultaneously when nausea and vomiting have resolved or been effectively treated.

Teratogenicity: The potential harm to the fetus from maternal intake of a specific drug depends on a number of factors: the drug itself, dose, gestational age at exposure, duration of exposure, interaction with other agents to which the fetus is exposed, and, to an unknown extent, the genetic makeup of the mother and fetus. Of the currently FDA-approved ARV drugs available in the United States, only EFV is considered to have significant teratogenic potential. Primate studies have demonstrated an increase in significant malformations (anencephaly, anophthalmia/microophthalmia, cleft palate) at doses similar to human therapeutic exposures, and both retrospective and prospective studies have reported CNS defects in human infants exposed to

EFV in utero. The magnitude of the risk is not known, however, and may be low. A recent systematic review and meta-analysis of data from 21 studies reporting on first-trimester exposures did not indicate an increased risk of birth defects among infants born to women taking EFV during the first trimester compared with those taking other ARVs during the first trimester (*AIDS* 2011;25(18):2301); one neural tube defect occurred among 1,437 live births (incidence 0.07%). No visible anomalies were found among 147 infants in a West African cohort born after first-trimester use of EFV, whereas an analysis of the PACTG219 database found a significantly increased risk of birth defects (including one neural tube defect) among 5 of 32 infants exposed to EFV in the first trimester (*Pediatr Infect Dis J* 2010;29(8):721; *J Acquir Immune Defic Syndr* 2011;56(2):183).

EFV has been classified as an FDA Pregnancy Category D drug. Because of the potential for teratogenicity, women who are taking EFV should avoid pregnancy and use of EFV should whenever possible be avoided during the first trimester, which is the primary period of fetal organogenesis; however, EFV can be continued in women who present for care in the first trimester on EFV-containing regimens that are effective in suppressing VL. This is because the risk of neural tube defects is restricted to the first 5-6 weeks of pregnancy (and pregnancy is rarely recognized prior to this) and unnecessary ARV drug changes during pregnancy may be associated with a loss of virologic control and may thus increase the risk of transmission to the infant (*HIV Clin Trials* 2010; 11:303). Initiation after the first trimester can be considered if, after considering other alternatives, EFV is the best choice for an individual woman. If EFV is to be continued postpartum, adequate contraception should be assured.

Adverse Pregnancy Outcomes

Preterm birth: Although currently published data show conflicting results, there may be a small increased risk of preterm birth in pregnant women who are taking PI-based combination ART or prophylaxis (*AIDS* 2007;21(5):607; *AIDS* 2006;20(18):2345; *AIDS* 2004;18(17):2337; *N Engl J Med* 2002;346(24):1863; *J Acquir Immune Defic Syndr* 2005;38(4):449). A variable that may confound published observational studies is the increased rate of preterm birth if combination ART is started before conception, as compared with later in pregnancy, which itself may reflect confounding by severity or indication (*Sex Transm Infect* 2009;85(2):82). When data from the IMPAACT P1025 observational cohort were examined by multivariable analysis to correct for HIV disease stage, excluding delivery initiated at preterm gestation due to medical or obstetrical factors, PI-based combination ART was no more likely than non-PI-based combination ART to be associated with spontaneous preterm birth (odds ratio [OR] 1.22; 95% confidence interval [CI], 0.70–2.12) (*J Infect Dis* 2010;201(7):1035). A recent combined analysis of three large studies, two from Europe and one from the United States, found that injection drug use and more advanced HIV disease were associated with preterm birth in all three cohorts (*BJOG* 2010;117(11):1399). Given the clear benefits of such therapy for both a woman's health and prevention of MTCT, PIs should not be withheld for fear of altering pregnancy outcome.

Hyperglycemia and/or diabetes: Although hyperglycemia and diabetes have been reported in individuals on PIs and pregnancy is a risk factor for hyperglycemia (*Ann Intern Med* 1997;127(10):948; *AIDS Clin Care* 1998;10(6):41), the majority of studies to date have not shown an increased risk of glucose intolerance associated with PI-based regimens in pregnancy (*Infect Dis Obstet Gynecol* 2002;10(4):187; *Obstet Gynecol* 2006;107(50):1115; *Am J Obstet Gynecol* 2007;196(4):331).

Secondary analyses of two large cohorts did not find an association with type of ART and gestational diabetes, except for an association of PI initiation before pregnancy or during the first trimester with gestational diabetes in the PACTG 316 cohort (*Am J Obstet Gynecol* 2004;190(2):506; *J Acquir Immune Defic Syndr* 2005;38(4):449). Standard glucose screening at 24–28 weeks of gestation should be performed in HIV infected women who are taking ART during pregnancy. Some experts recommend earlier glucose screening in women who continue PI-based therapy that was initiated prior to pregnancy (particularly in women of minority race/ethnicity); this approach is similar to the recommendations for women with risk factors for glucose intolerance, such as maternal obesity, advanced maternal age, and family history of type II diabetes mellitus (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. 2012. http://www.aidsinfo.nih.gov).

Mitochondrial toxicity (maternal risk): NRTI drugs are known to induce mitochondrial dysfunction; risk varies by specific drug and is associated with long-term use. In one study, ddI and ddI-containing regimens were associated with the greatest degree of mitochondrial suppression (*Antimicrob Agents Chemother* 2008;52(8):2825). Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may occur more frequently in women (*Clin Infect Dis* 2007;45(2):254; *Clin Infect Dis* 2007;45(2):261). 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. Bristol-Myers Squibb has reported several maternal deaths due to lactic acidosis/hepatic steatosis, all in women who were taking a combination of d4T/ddI as part of their ARV regimen at the time of conception and for the duration of pregnancy (the d4T/ddI combination is no longer recommended for HIV infected adults, pregnant or not). Other nonfatal cases of lactic acidosis have been reported in pregnant women taking this combination (*Sex Transm Infect* 2002;78(1):58; *AIDS* 2003;17(2):272). Cases of lactic acidosis have also been described with exposure to other NRTIs (*Lancet* 1999;353(9156):901). 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 several rare but life-threatening disorders of liver metabolism (acute fatty liver of pregnancy, hemolysis, elevated liver enzymes and low platelets—the HELLP syndrome). Data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in the development of these disorders, as well as ARV-related mitochondrial toxicity (*Proc Natl Acad Sci USA* 1995;92(3):841; *N Engl J Med* 1999;340(22):1723;

Semin Perinatol 1999;23(2):100; *Mol Genet Metab* 2000;71(1-2):182). Therefore, obstetric providers should be aware of lactic acidosis/hepatic steatosis syndrome, be alert to and educate patients about suggestive signs and symptoms, and consider it in their differential diagnosis when appropriate. If the diagnosis is suspected, then serum lactate, liver enzymes, and electrolyte levels should be obtained, expert consultation engaged, and all ARV drugs should be discontinued.

Mitochondrial toxicity (infant risk): Some studies suggest that mitochondrial dysfunction might develop in infants with in utero exposure to NRTI drugs (*AIDS* 2003;17(12):1769; *Lancet* 2002;359(9306):583; *AIDS* 2003;17(14):2053), generally presenting as neurologic disease, and in some cases resulting in death; however, results from large clinical studies from the United States and Europe have been reassuring (*J Acquir Immune Defic Syndr* 2000;25(3):261; *J Acquir Immune Defic Syndr* 2003;32(4):380). Several studies, often small, have reported laboratory abnormalities without clinical symptoms (differences in mtDNA, lactate levels, echocardiographic abnormalities, and hematologic parameters) among infants with perinatal ARV exposure compared with unexposed infants (*Pediatrics* 2009;124(6):e1189; *J Infect Dis* 2008;198(6):851; *Environ Mol Mutagen* 2007;48(3-4):201; *Environ Mol Mutagen* 2007;48(3-4):173; *AIDS* 2005;19(10):1071; *J Infect Dis* 2006;194(8):1089; *J Am Coll Cardiol* 2011;57:76). The clinical significance of these laboratory findings is unclear. Even if an association is more clearly demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and the benefit of reduced perinatal transmission is thought to clearly outweigh the risk. Mitochondrial dysfunction should be considered in uninfected children with perinatal ARV exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings. Current recommendations call for long-term clinical follow-up for any child with in utero exposure to ARVs.

Hepatotoxicity and/or skin rash: Although all ARV drugs may cause liver toxicity, special concerns have been raised regarding the use of NVP. Several studies have demonstrated an increased risk of developing symptomatic, often rash-associated, NVP-related hepatotoxicity among women, particularly those with CD4+ cell counts >250/mm^3 (*J Acquir Immune Defic Syndr* 2004;35:538; *Clin Infect Dis* 2001;32:124; *J Acquir Immune Defic Syndr* 2003;34:S21). Deaths from hepatic failure have been reported in pregnant women taking ARV regimens that include NVP (*J Acquir Immune Defic Syndr* 2004;36:772; *HIV Med* 2006;7:255). In general, in controlled clinical trials, hepatic events, regardless of severity, have occurred in 4.0% (range 0%–11.0%) of patients on NVP and severe or life-threatening rash has occurred in approximately 2% of patients taking NVP (Viramune package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2011. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Viramune/Viramune.pdf. Accessed 7/11/2012).

In a recent analysis of two multi-center prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (RR 4.7; 95% CI; 3.4–6.5) but NVP use was not, regardless of pregnancy status (*AIDS* 2010;24(1):109). Nevertheless, because some of the early symptoms of hepatotoxicity are relatively nonspecific and can be confused with common symptoms during

pregnancy, care providers should be aware of potential liver toxicity with or without rash if NVP is used in pregnancy and should conduct frequent and careful monitoring of clinical symptoms and liver enzymes (i.e., ALT and AST), particularly during the first 18 weeks of therapy. NVP should be used only as a component of a combination regimen when ART is being initiated in women with CD4+ cell counts >250 cells/mm^3 if the benefit clearly outweighs the risk. In patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter (*Semin Liver Dis* 2003;23(2):173). Liver enzyme levels should be checked in all women who develop a rash while taking NVP. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe liver enzyme elevations (i.e., more than 5X the upper limit of normal) should stop NVP and should not take NVP in the future. Hepatic toxicity has not been seen in women receiving single-dose NVP during labor for prevention of perinatal transmission of HIV (*Drug Saf* 2009;32(2):147). Women who enter pregnancy on NVP-containing regimens and are tolerating them well may continue therapy, regardless of CD4+ cell count.

Anemia: Several ARVs, and ZDV in particular, 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; the addition of ARV regimens that include ZDV may exacerbate anemia. Nutritional counseling, along with iron and folate supplementation, should be provided to ensure adequate intake of other nutrients. Administration of ZDV is usually associated with macrocytosis. When evaluating anemia in a pregnant woman who is taking ZDV, the presence of macrocytosis should not exclude consideration and evaluation of causes of anemia usually resulting in microcytic or normocytic red blood cell indices; nor should the presence of macrocytosis result in an assumption of more typical causes of macrocytic anemia, such as folate or B12 deficiency. Depending on severity, anemia should be treated and a non-ZDV-containing regimen may be considered.

Guidelines for Antepartum Care

History and Physical Examination

The following is the key information that should be obtained from the initial and follow-up history and physical evaluation for the HIV infected pregnant woman. Certain symptoms of HIV disease, ARV toxicity, and normal or abnormal pregnancy may overlap, resulting in possible delays in appropriate diagnosis and management. (See also Chapter 4, ***Primary Medical Care***.)

HIV History

- Date of diagnosis
- History of HIV-related symptoms, OIs, or malignancies
- CD4+ cell count nadir and current value
- Current and highest VL

- Results of any prior drug resistance testing
- Complete ARV history, including specific drugs, side effects or toxicity, length of treatment, adherence, response to treatment, and reasons for any changes
- Partner's HIV status
- Disclosure of HIV status: to whom

Pregnancy History

- Previous pregnancies and outcomes
- Pregnancy complications
- Mode(s) of delivery
- Use of ARV prophylaxis or ART in previous pregnancy(ies)
- HIV status of other children

Family History

- Relevant family history of possible heritable diseases

Signs and Symptoms of HIV/AIDS (initial and follow-up visits)

- Generalized lymphadenopathy
- Thrush
- Constitutional symptoms, such as fever (38.5°C) or diarrhea >1 mo
- Herpes zoster involving 2 episodes or >1 dermatome
- Peripheral neuropathy
- Wasting
- Dysphagia
- Dyspnea
- Persistent mucocutaneous herpetic ulcerations
- Cognitive dysfunction

Signs and Symptoms of Pregnancy-Related Complications

- Elevated blood pressure
- Significant edema
- Severe headache
- Vaginal bleeding or fluid leakage
- Intractable nausea and vomiting
- Dysuria
- Abnormal vaginal discharge
- Persistent abdominal or back pain or cramping
- Decreased fetal movement

Signs or Symptoms of ARV Toxicity

- Nausea/vomiting
- Abdominal pain
- Jaundice
- Extreme fatigue
- Skin rash

Laboratory Examination

Recommended laboratory evaluations for HIV infected pregnant women are listed in Table 8-8.

Table 8-8

Recommended Laboratory Evaluations for the HIV Infected Pregnant Woman

Upon Entry into Prenatal Care and Ongoing

Test	Frequency and Comments
HIV serology	• Test at initial visit if HIV infection not previously confirmed • Test if there is positive rapid or screening test without confirmatory assay
CD4+ cell count and/or CD4+%	• At baseline and every 3 mo during pregnancy • Consider repeat test if significant change in clinical status or near milestones for therapeutic decisions (e.g., OI prophylaxis) • Consider extending test interval to every 6 mo for patients who are adherent to therapy, with sustained viral suppression and stable clinical status >2–3 y
HIV RNA	• At baseline • 2–4 wk after initiating or changing ART (should see decrease by minimum of 1 log 10 copies/mL by 1 mo after start of potent regimen) • Monthly until RNA levels are undetectable • At least every 3 mo during pregnancy • At 36 wk to determine mode of delivery • More frequently if adherence is a concern
ARV resistance assay	• At baseline with VL >500–1000 c/mL, whether ARV naïve or currently on therapy • Repeat with virologic failure • Genotypic testing preferred over phenotypic
CBC	• At baseline • Repeat (at least) every trimester in women on stable ARV regimen • Consider more frequent testing if marrow-toxic drugs (e.g., ZDV) are used or with anemia
Liver enzymes	• At baseline • Repeat at least every trimester in women on stable ARV regimen • More frequent monitoring with initiation of NVP or with clinical signs/symptoms of hepatotoxicity • Repeat as indicated with abnormal results or use of other hepatotoxic drugs
Electrolytes, BUN, creatinine	• At baseline • Repeat as indicated with abnormal results or use of potentially nephrotoxic drugs
Urinalysis, calculated creatinine clearance	• At baseline in newly diagnosed patients and those not previously evaluated, in Black patients and in those with advanced HIV or comorbid conditions • Consider prior to initiating regimens containing TDF or IDV
Syphilis serology	• At baseline • Repeat, as noted below, on the basis of gestational age

Table 8-8 *continued*

Recommended Laboratory Evaluations for the HIV Infected Pregnant Woman

Upon Entry into Prenatal Care and Ongoing

Test	Frequency and Comments
Hepatitis serology: • HBsAg • HBcAb • HBsAb • HCV Ab • HAV Ab	• Initiate HBV vaccine series if negative for HBsAg, HBcAb, and HBsAb • Initiate HAV vaccination if negative HAV Ab, particularly in the setting of HBV or HCV Infection • If anti-HCV+, order HCV RNA • Consider HCV RNA with negative HCV Ab with risk factors for HCV or unexplained liver enzyme abnormalities, especially with CD4+ cell count <200/mm^3
Rubella, blood type and Rh, antibody screen, urine culture, GC/chlamydia, Pap smear	• At baseline • Repeat antibody screen, as noted below, on the basis of gestational age • Repeat urine culture as needed with symptoms • Repeat GC/chlamydia, as noted below, on the basis of gestational age; as needed with signs/symptoms of infection; or on the basis of risk factors • Cytobrush can be used for Pap smear during pregnancy
PPD or interferon-gamma release assay	• Positive skin test = ≥5 mm induration • Anergy testing not indicated and prior BCG vaccination not contraindication to skin testing • Positive results: obtain CXR and other evaluation to rule out active TB • Consider repeat testing if recent TB exposure
Hemoglobin electrophoresis, red blood cell indices	• Perform in women at increased risk for hemoglobinopathies
G6PD	• Consider screening women with predisposing racial/ethnic background (e.g., Black, Middle Eastern) before receiving oxidant drugs (e.g., dapsone, sulfonamides)
CMV IgG	• Consider baseline serology in patients at low risk for CMV (non-IDU)*
Toxoplasmosis IgG	• Screen all patients with initial HIV diagnosis • Repeat with CD4+ cell count <100/mm^3 if not on TMP-SMZ, or with symptoms suggestive of toxoplasmic encephalitis
Varicella zoster virus IgG	• Consider if no history of chicken pox or shingles • Consider for post-exposure prophylaxis considerations
Urine toxicology screen	• As indicated on the basis of patient history, signs/symptoms, and local protocols
Serum screening for Tay-Sachs disease	• Consider screening both partners if at increased risk (i.e., Ashkenazi Jewish, French-Canadian, or Cajun descent)
Bacterial vaginosis screening	• Perform if signs/symptoms of vaginitis
Ultrasound	• Perform in first trimester for confirmation of gestational age

Table 8-8 *continued*

Recommended Laboratory Evaluations for the HIV Infected Pregnant Woman

Test	Frequency and Comments
Upon Entry into Prenatal Care and Ongoing	
Nuchal translucency, PAPP-A, free or total beta-hCG	• Voluntary; requires counseling • Screening for Down syndrome; abnormal result requires further evaluation
At 16–20 Weeks	
Ultrasound	• Anomaly screen • Repeat as indicated to monitor fetal growth
Maternal serum alpha-fetoprotein	• Voluntary; requires counseling • Screening test for neural tube and abdominal wall defects • Abnormal result (usually >2.5 multiple of the median) requires further evaluation
Quadruple screen (hCG, unconjugated estriol, MSAFP, Inhibin A)†	• Voluntary; requires counseling • Noninvasive test to determine risk of neural tube and abdominal wall defects, Down syndrome, and trisomy 18 • Abnormal result requires further evaluation
At 24–28 weeks	
CBC, syphilis serology, antibody screen	
Diabetes screen	• Glucose 1 h after 50 g Glucola ; 3 h oral GTT if abnormal (an alternative screen is a "one-step" 75 g oral GTT, recently endorsed for non-HIV-infected pregnant women by the American Diabetes Association and the International Association of Pregnancy Study Groups [*Am J Obstet Gynecol* 2010; 202(6):654.e1; *Diabetes Care* 2010; 33(3):676]). • Consider earlier screening in women with ongoing PI-based therapy initiated prior to pregnancy or other high-risk factors for glucose intolerance.
At 32–36 weeks	
GC/chlamydia testing	
Group B streptococcus culture – 35–37 wk; vaginal and rectal	• Recommend intrapartum chemoprophylaxis with IV PCN G (2.5 million units q 4 h) 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 <37 wk gestation, membrane rupture ≥18 h, or IP temperature ≥100.4°F/38.0°C or positive intrapartum GBS nucleic acid amplification test (*ACOG Practice Bulletin* No. 485, April 2011. Available at http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Obstetric_Practice/Prevention_of_Early-Onset_Group_B_Streptococcal_Disease_in_Newborns. Accessed 6/26/2012)
HIV RNA	• Results may influence decisions about mode of delivery
Syphilis serology	• Consider in high-risk patients or populations

Table 8-8 *continued*

Recommended Laboratory Evaluations for the HIV Infected Pregnant Woman	
Upon Entry into Prenatal Care and Ongoing	
Test	**Frequency and Comments**
Other Considerations	
HLA B*5701	• Obtain prior to starting ABC
Coreceptor tropism assay	• Obtain prior to prescribing CCR5 entry inhibitor
Serum lactate, electrolytes, liver enzymes; consider anion gap, CPK, amylase, lipase	• Signs or symptoms suggest possible lactic acidosis in setting of NRTI therapy, especially if long term
Fasting lipid profile	• May delay until postpartum, unless baseline history of hyperlipidemia +/- treatment • If obtained, subsequent measurements on the basis of history and initial results
Liver enzymes (ALT, AST)	• With initiation of NVP (does not apply to single-dose prophylactic therapy in labor); q 2 wk during mo 1; monthly through mo 4; every 1–3 mo thereafter. More frequently in patients with pre-existing liver disease.
Type-specific HSV serology	• May be useful to identify women at risk for HSV and to guide counseling, especially if sexual partner has HSV infection

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

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

† Accurate gestational age is essential for interpretation

Antepartum Fetal Surveillance and Testing

The general purpose of antepartum fetal surveillance and testing is to identify fetal abnormalities or compromise so that appropriate interventions can be undertaken to optimize fetal health and prevent fetal damage or death. In some instances, the purpose is to aid in decisions regarding continuation of the pregnancy versus early delivery (*ACOG Practice Bulletin* No. 9; *Int J Gynaecol Obstet* 2000;68(2):175; reaffirmed 2009).

Indications for antepartum fetal surveillance and testing:

- **Maternal conditions that increase risk of fetal death:** include but are not limited to the following conditions: hemoglobinopathies, chronic renal disease, systemic lupus erythematosus, hypertension, and diabetes
- **Pregnancy-related conditions that increase risk of fetal death:** include pregnancy-induced hypertension, decreased fetal movement, oligohydramnios, polyhydramnios, intrauterine growth retardation, post-term pregnancy, mild to moderate isoimmunization, previous fetal death, and multiple gestation
- **HIV considerations:** Data are lacking specifically on the need for and use of fetal surveillance techniques in HIV infected women during pregnancy. HIV infection per se is not an indication for fetal testing; however, fetal surveillance should be performed in HIV infected women with comorbidities that may increase fetal risk. 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. Fetal surveillance may be considered for pregnant women on ART, particularly when the mother's regimen contains newer agents with which there is little experience in pregnancy. Ultimately, the need for fetal surveillance should be determined case by case.

Fetal surveillance techniques include the following:

- **Fetal movement assessment:** Also known as kick counts; the perception of 10 distinct movements in a period of up to 2 hours is reassuring.
- **Nonstress test (NST):** A reactive or reassuring result is defined as two or more fetal heart rate accelerations (at least 15 beats/minute above baseline and lasting at least 15 seconds on a fetal monitor) within a 20-minute period.
- **Contraction stress test (CST):** A negative or reassuring result is the absence of late or significant variable fetal heart rate decelerations with at least three contractions (lasting at least 40 seconds) within 10 minutes.
- **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 assigned 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, which is characterized by high-velocity diastolic flow in a normally developing fetus. This technique is beneficial only in pregnancies complicated by intrauterine growth restriction.

Although data from randomized clinical trials are lacking, antepartum fetal surveillance has been consistently associated with lower rates of fetal death when compared with rates among untested pregnancies from the same institution or among historic controls with similar complicating factors. Testing should be initiated at 32–34 weeks' gestation, but may be started as early as 26–28 weeks' gestation in very high-risk pregnancies. When the condition prompting testing persists, testing should be repeated periodically (weekly or, in some cases, twice weekly) until delivery. Fetal reevaluation should also be repeated if the mother's medical condition deteriorates significantly or if there is an acute decrease in fetal movement, regardless of the amount of time elapsed since the previous test.

NST, CST, biophysical profile, and modified biophysical profile are the most commonly used forms of testing; they have a negative predictive value >99%. They are not predictive of acute events, however, 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. Management should be based on test results, gestational age, degree of oligohydramnios (if assessed), and maternal condition. Oligohydramnios should prompt evaluation for membrane rupture. Depending on the degree of oligohydramnios, gestational age, and maternal medical condition, oligohydramnios warrants either delivery or close maternal/fetal surveillance.

Ultrasound: There are many indications for obstetric ultrasound; some of the more common include the following (*Obstet Gynecol* 2009;113(2 Pt 1):451):

- 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
- Documentation of fetal viability and/or to rule out fetal death
- Biophysical profile for antepartum fetal surveillance
- Suspected polyhydramnios and/or oligohydramnios
- Placental localization
- Abnormal serum alpha-fetoprotein or quadruple 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 as early as 5 weeks after the woman's last menstrual period and fetal heart activity can be detected by 6 weeks. 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 late in the first trimester or in the second trimester; screening for anomalies is best performed at 16–20 weeks' gestation. A third-trimester (or other follow-up) ultrasound(s) should be considered, particularly in women with more advanced disease and/or other maternal pregnancy-related factors that could affect fetal growth.

Amniocentesis, chorionic villus sampling, cordocentesis: Though data are still somewhat limited, risk of MTCT does not appear to increase during amniocentesis or other invasive diagnostic procedures among women who are on effective combination ART. HIV infected women who have indications for invasive testing in pregnancy, such as abnormal ultrasound or aneuploidy screening, should be counseled about the potential risk of HIV transmission along with other risks of the procedure so they can make an informed decision about testing. Ideally, a woman should have an undetectable VL at the time of any procedure. Procedures should be performed under continuous ultrasound guidance and, if possible, the placenta should be avoided. Some experts consider chorionic villus sampling and cordocentesis too risky to offer to HIV infected women and recommend limiting procedures to amniocentesis (*Am J Obstet Gynecol* 2006;194(1):192).

Prevention for Positives

All HIV infected pregnant women should be encouraged to disclose their HIV status to their sexual partners, with assistance if needed, and HIV testing should be encouraged for partners. Condom use during pregnancy is recommended, particularly if partners are serodiscordant; recent data suggest that pregnancy may increase risk of female-to-male HIV transmission (*AIDS* 2011;*25* (15):1887). However, even when both partners are HIV infected, condom use is encouraged to prevent both acquisition of other STIs and potential reinfection with another HIV strain. Women who have active substance abuse problems should be encouraged and assisted in accessing treatment, including opioid-assisted therapy if indicated. Harm reduction practices, such as needle exchange and not sharing injection equipment, should be discussed and encouraged in IDUs who are not able or not willing to stop using altogether.

Antepartum Scenarios for Antiretroviral Drug Use

(Source: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. 2012. http://www.aidsinfo.nih.gov)

ARV naïve (no prior experience with ARVs): Current adult treatment guidelines are updated regularly and can be accessed online at http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/.

- HIV infected pregnant women should be prescribed standard potent combination ART, taking into account current information about use in pregnancy, including safety and risk of teratogenicity. (See Table 8-7.)
- **Current adult treatment guidelines recommend ART for all HIV-infected individuals. The strength of this recommendation varies on the basis of the pretreatment CD4+ cell count (see Chapter 4 *Primary Medical Care*).**
  - **CD4+ cell count ≤500 cells/mm³ (strong recommendation)**
  - CD4+ cell count >500/mm³ (moderate recommendation)
  - ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV (strong recommendation) and therefore should be recommended for women with partners who are HIV-negative or of unknown status, without regard to CD4+ cell count.
  - Patients starting ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence. The potential benefits of early therapy must be weighed against possible drug toxicity, cost, and the patient's risk of developing viral resistance with suboptimal adherence, which may be more likely during the postpartum period (*AIDS Care* 2008;20(8):958; *J Acquir Immune Defic Syndr* 2008;48(4):408; *Curr Opin Infect Dis* 2012;25(1):58; *J Womens Health* 2010;19(10):1863; *AIDS* 2012:26:2039).
- In women who require immediate initiation of therapy for their own health, ART can begin in the first trimester, but use of EFV should be avoided in the first trimester.
- Pregnant women with CD4+ cell counts >500/mm³ should be counseled about current treatment recommendations, the potential risks and benefits of stopping and continuing with an ART regimen following delivery, and the need for strict adherence if the regimen is continued postpartum.
- The use of raltegravir in late pregnancy for women who are diagnosed late in pregnancy and have high viral loads has been suggested because of its ability to rapidly suppress viral load (approximately 2-log copies/mL decrease by Week 2 of therapy). (*AIDS Patient Care STDS* 2012; 26(12):717; *J Antimicrob Chemother* 2010;65(9):2050;. *AIDS* 2010; 24(15):2416). However, this approach has only been described in anecdotal reports and efficacy and safety of this approach is unclear; it is not routinely recommended and should only be used in consultation with an expert.
- While it is considered suboptimal to use a non-HAART regimen (i.e., triple NRTIs, ZDV only) for prophylaxis alone during pregnancy, with ARV discontinuation after delivery, that approach may be considered in some limited circumstances.
- The decision to start the ARV regimen in the first trimester or delay until 12 weeks of gestation will depend on CD4+ cell count, VL, and maternal conditions such as nausea and vomiting. Earlier initiation of a combination

ARV regimen may be more effective in reducing in utero transmission, but the benefit must be weighed against the potential long-term effects of first-trimester drug exposure.

- If possible, one or more NRTIs with high levels of placental transfer to the fetus should be included to provide pre-exposure prophylaxis (ZDV, 3TC, FTC, d4T, TDF, ABC).
- If VL is above the threshold for resistance testing (e.g., >500–1000 c/mL), ARV drug resistance studies should be performed before therapy is initiated. If HIV is diagnosed late in pregnancy, the ARV regimen should be initiated promptly without waiting for the results of resistance testing.
- NVP may be used as a component of initial therapy for pregnant women with CD4+ cell counts <250/mm^3; however, due to an increased risk of hepatic toxicity, NVP should be used as a component of ART in pregnant women with CD4+ cell counts >250 cells/mm^3 only if the benefit clearly outweighs the risk.

ARV experienced (currently on ART):

- In general, a pregnant woman who is taking and tolerating an ART regimen that is effective in suppressing her VL should continue on the regimen. Discontinuation or interruption of therapy may lead to an increase in VL, with possible disease progression and a decline in immune status, and has been associated with increased risk of perinatal transmission (*Clin Infect Dis* 2009;48(9):1310).
- ARV drug resistance testing is recommended if a pregnant woman has detectable viremia (e.g., >500–1000 copies/mL) on therapy. Results of this testing can be used to select a regimen that may be more effective in suppressing VL to an undetectable level.
- If a woman is taking EFV and her pregnancy is recognized during the first trimester, EFV should be continued if there is maximal VL suppression and the regimen is well tolerated.
  - Treatment changes during pregnancy increase the risk of incomplete viral suppression at the end of pregnancy (*HIV Clin Trials* 2010;11(6):303).
  - The risk of neural tube defects is restricted to the first 5–6 weeks of pregnancy and pregnancy is rarely recognized prior to 4–6 weeks of pregnancy.
- If a pregnant woman has an undetectable VL and is taking and tolerating NVP, she should continue with that ARV regimen regardless of CD4+ cell count. Increased risk of hepatic toxicity has not been seen in pregnant women who are taking and have achieved immune reconstitution with NVP-based therapy.

Prior ART for treatment or prophylaxis:

- If a patient has taken ARVs in the past for treatment or prophylaxis, the care provider should obtain an accurate history of all prior ARV use, including tolerance; clinical, virologic, and immunologic efficacy; the indication for stopping therapy; and results of prior resistance testing.

- Perform HIV ARV resistance testing prior to initiating repeat ARV prophylaxis or therapy if VL >500-1000 c/mL. In women who present late in pregnancy, treatment or prophylaxis should be initiated promptly, based on available history, without waiting for the results of resistance testing. Limited data regarding rates of resistance after pregnancy-limited use of combination ARV regimens for prophylaxis, particularly with documented virologic suppression at the time of labor, suggest that PI-based regimens may be less likely than NNRTI-based regimens to be associated with detection of resistance mutations (*Clin Infect Dis* 2010;50(6):890; *AIDS* 2010;24(1):45; *J Acquir Immune Defic Syndr* 2009;51(5):522; *AIDS Res Hum Retroviruses* 2010;26(3):293). This may be related to the longer half-life of NNRTIs, resulting in functional monotherapy if the regimen is stopped abruptly (see **Guidelines for Postpartum Care**, p. 333, for discussion of strategies to prevent resistance with NNRTI regimens). No data exist to guide the choice of ARV regimens for women with prior experience taking ARVs as pregnancy-limited prophylaxis solely for prevention of MTCT.
- Data are limited on ART efficacy following the use of ARV solely for prevention of MTCT. Most experience is with NVP-based ART regimens initiated after peripartum single-dose NVP. Data suggest decreased virologic and clinical efficacy when regimens are started within 12–24 months after delivery (*N Engl J Med* 2010;363(16):1499; *PLoS Med* 2010;7(2):e1000233; *AIDS* 2007;21(8):957; *N Engl J Med* 2007;356(2):135). Investigators recently assessed data from the French Perinatal Cohort on virologic suppression with PI-based ART administered for prevention of MTCT to women who had received ARV prophylaxis during a previous pregnancy; no differences were seen in rates of VL suppression at delivery among ARV-naïve women compared with those who had received previous prophylaxis or according to previous prophylaxis regimens (*J Acquir Immune Defic Syndr* 2011;57(2):126).
- If a woman is ARV-experienced and requires ART for her own health, her care provider should perform a thorough clinical evaluation (including assessment of liver, renal, and cardiovascular function) prior to reinitiating ART.
- Initiate a combination ARV drug regimen, with the regimen chosen on the basis of resistance testing and prior ART history (including efficacy and toxicity), avoiding EFV in the first trimester or drugs with known risk for the pregnant woman (e.g., combination ddI/d4T). Virologic response should be monitored carefully; if virologic response is inadequate, resistance testing should be repeated.
- Expert consultation is recommended when choosing ARVs for pregnant women with prior ARV experience.

Stopping ART During Pregnancy

HIV infected women taking ART who present for care during the first trimester should generally not discontinue or interrupt treatment during pregnancy. Women who present in the first trimester and are taking an EFV-containing regimen should not interrupt therapy but can continue on treatment if VL is suppressed. A recent analysis from a prospective cohort of 937 HIV infected mother-child pairs found that interruption of ART during pregnancy, including interruption in the first and third trimesters, was independently associated

with perinatal transmission (*Clin Infect Dis* 2009;48(9):1310). Furthermore, unnecessary ARV drug changes during pregnancy may be associated with a loss of virologic control and thus may increase the risk of MTCT (*HIV Clin Trials* 2010;11(6):303).

If an ARV regimen for therapy and/or prophylaxis is stopped abruptly for severe or life-threatening toxicity, severe pregnancy-induced hyperemesis unresponsive to anti-emetics, or other acute illnesses precluding oral intake, all ARVs should be stopped at the same time and reinitiated at the same time.

If an ARV regimen is being stopped electively and the patient is receiving an NNRTI, then one of the following options should be considered: (1) stop the NNRTI first and continue other ARVs for a period of time; or (2) switch from an NNRTI to a PI prior to interruption and continue the PI with the other ARVs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and stopping other ARVs is not known, but a period of at least 7 days is recommended. Given the potential for prolonged (i.e., >3 weeks) detectable EFV concentrations, some experts recommend continuing the other ARVs or substituting a PI plus two other agents for up to 30 days. A recent study of 412 women who received single-dose nevirapine and were randomized to receive zidovudine/lamivudine, tenofovir/emtricitabine, or lopinavir/ritonavir for either 7 or 21 days found an overall new nevirapine resistance mutation rate of 1.2% when assessed by population genotype at 2 and 6 weeks following completion of treatment, with no difference by length of treatment. However, low-frequency nevirapine-resistant mutations at codons 103, 181, and 184 detected using allele-specific PCR emerged significantly more often in the 7-day arms (13/74 [18%]) than in the 21-day arms (3/66 [5%], P = .019). (*Clin Infect Dis* 2013;56(7):1044).

If NVP is stopped and more than 2 weeks have passed prior to restarting therapy, then NVP should be restarted with the 2-week dose escalation period.

Failure of Viral Suppression in Pregnancy

Women on antiretroviral (ARV) regimens who have detectable virus at any time during pregnancy using ultrasensitive assays should

- be evaluated for resistant virus (if plasma HIV RNA is >500–1,000 copies/mL);
- be assessed for adherence, tolerability, incorrect dosing, or potential problems with absorption (such as with nausea/vomiting or lack of attention to food requirements);
- be considered for ARV regimen modification.

Treatment modification during pregnancy has been independently associated with an HIV-1 RNA level >400 copies/mL in late pregnancy highlighting the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize need to modify treatment. (*HIV Clin Trials* 2010;11(6):303–311.)

Baseline HIV RNA levels have been shown to affect the time to response; most patients with an adequate viral response at 24 weeks have had at least a 1-log copies/mL HIV RNA decrease within 1–4 weeks after starting therapy. In a retrospective multicenter cohort of 378 pregnant women, 77.2% achieved HIV RNA <50 c/ml by delivery, with success of viral suppression varying by baseline HIV RNA level: with baseline <10,000 c/ml, gestational age at initiation did not affect success up to 26.3 weeks but with baseline >10,000 c/ml, delaying initiation past 20.4 weeks significantly reduced ability for maximal suppression at deliver. (*AIDS* 2012;26(9):1095)

A recent systematic review and meta-analysis of adherence to antiretroviral regimens during and after pregnancy in low-, middle- and high-income countries (27% of studies were from the US) found a pooled estimate of 73.5% adherence during pregnancy (threshold defining good adherence to ART varied across studies from >80–100%) (*AIDS* 2012;26(16):2039) Therefore, evaluation of and support for adherence during pregnancy is critical to achievement and maintenance of maximal viral suppression.

The addition of raltegravir in late pregnancy has been suggested for women who have high viral loads and/or in whom multiple drug-resistant mutations have resulted in incomplete suppression of viremia because of the ability of raltegravir to rapidly suppress viral load. In the setting of a failing regimen related to nonadherence and/or resistance, there are concerns that the addition of a single agent may further increase risk of resistance and potential loss of future effectiveness with raltegravir. A recent report found 10–23-fold increase in transaminase levels following introduction of a raltegravir-containing regimen in late pregnancy, with return to normal levels after raltegravir discontinuation. (*J Obstet Gynaecol Can* 2013;35(1):68). Therefore, at the current time, this approach cannot be recommended.

Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >400 copies/mL near the time of delivery.

Special Situations

Acute infection: Preventing HIV acquisition is a subject that should be addressed with all pregnant and breastfeeding women. Several studies suggest that pregnancy may be a time of increased risk for HIV transmission (*Lancet* 2005;366(9492):1182; *AIDS* 2009;23(10):1255; *J Clin Virol* 2010;48(3):180), even when controlling for sexual risk behaviors (*Lancet* 2005;366(9492):1182). Primary or acute HIV infection in pregnancy or while a woman is breastfeeding is associated with an increased risk of perinatal HIV transmission and may represent a significant proportion of residual MTCT in the United States. This high rate of transmission is likely related to two factors: 1) the high VL of plasma, breast milk, and the genital tract associated with acute infection; and 2) the difficulty of diagnosis. Because acute infection is easily missed, opportunities for prevention are missed as well (*AIDS* 2002;16(8):1119; *AIDS* 2010;24(4):573).

All pregnant women with acute or recent HIV infection should start combination ART as soon as possible to prevent MTCT, with the goal of suppressing plasma HIV RNA levels to below detectable levels.

Data from the United States and Europe indicate that transmitted virus may be resistant to at least one ARV in 6%–16% of patients (*J Infect Dis* 2005;192(6):958; *AIDS* 2010;24(8):1203). Genotypic resistance testing should be performed at baseline, simultaneously with initiation of ART or prophylaxis, with a subsequent adjustment in ARV regimen if needed to optimize virologic response. Because clinically significant PI resistance is less common than NNRTI resistance in ARV-naïve patients, an RTV-boosted PI-based regimen should generally be initiated.

Healthcare providers should maintain a high level of suspicion of acute HIV infection in pregnant or breastfeeding women who have a compatible clinical syndrome (e.g., fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias) even in the absence of reported high-risk behaviors.

When acute retroviral syndrome is suspected in pregnancy or during breastfeeding, a plasma HIV RNA test should be obtained in conjunction with an HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test because values in acute infection are generally very high (i.e., >100,000 copies/mL) (*Ann Intern Med* 2001;134(1):25; *AIDS* 2002;16(8):1119); however, non-B HIV-1 subtypes may not amplify as well as subtype B, which may result in a lower HIV RNA level, even with acute infection.

If seroconversion is suspected in nursing mothers, breastfeeding should be interrupted until definitive confirmation of infection is obtained; if seroconversion is confirmed, breastfeeding should not be resumed.

Hepatitis B infection: Women with chronic HBV infection (persistent hepatitis B surface antigenemia for at least 6 months) and who are hepatitis A virus (HAV) IgG negative should receive the HAV vaccine series because of the added risk of acute HAV in people with chronic viral hepatitis. This vaccine can be given safely during pregnancy (*ACOG Practice Bulletin* No. 86; *Obstet Gynecol* 2007;110(4):94; reaffirmed 2009).

An ART regimen that includes drugs active against both HIV and HBV (i.e., TDF + 3TC or FTC) is recommended for pregnant women with HIV/HBV co-infection to avoid reactivation of HBV and development of immune reconstitution inflammatory syndrome (IRIS). An IRIS-related flare of HBV activity during pregnancy can occur even among women with relatively high CD4+ cell counts. Use of ARVs that have anti-HBV activity will also reduce HBV viremia and may decrease the risk of failure of neonatal HBV immune globulin (HBIG) and HBV vaccine for prevention of perinatal transmission of HBV.

Elevation of hepatic enzymes after ART initiation may be related to HBV flare due to immune reconstitution with effective ARV regimens; HBV infection also increases hepatotoxic risk of PIs and NVP. Liver enzymes should be assessed 2–4 weeks after initiation of ARVs and then at least every 3 months. If hepatic toxicity occurs, consultation with an expert in HIV and HBV co-infection is strongly recommended. Pregnant women with HBV/HIV co-infection should be counseled about signs and symptoms of liver toxicity and advised to avoid alcohol. If ARVs are discontinued postpartum in women with HIV/HBV co-infection, frequent monitoring of liver function tests for potential HBV flare is recommended, with prompt re-initiation of treatment for both HIV and HBV if a flare is suspected.

Interferon (IFN) and peg-IFN are not recommended for use in pregnancy because of direct antigrowth and antiproliferative effects and should be used only if the potential benefit outweighs the risk (*Neurology* 2005;65(6):807).

All infants born to mothers who are HBsAg+ should receive hepatitis B immune globulin (HBIG) and should receive an initial dose of HBV vaccine within 12 hours after birth. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively. This regimen is >95% effective in preventing HBV infection in these infants.

Hepatitis C infection: Because of an increased risk for fulminant HAV or HBV in patients infected with HCV, HAV vaccination is recommended for HCV infected women who are anti-HAV-negative; HBV vaccination is recommended for women who are HBV uninfected. These vaccinations may be given safely during pregnancy (*ACOG Practice Bulletin* No. 86; *Obstet Gynecol* 2007;110(4):94; reaffirmed 2009).

Treatment of HCV aims to eradicate infection and prevent the long-term complications of progressive liver disease. It generally includes combination therapy with pegylated interferon plus ribavirin; however, treatment with these agents is not recommended during pregnancy (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. Updated Sept. 14, 2011; http://www.aidsinfo.nih.gov/Guidelines/HTML/3/perinatal-guidelines/188/initial-postnatal-management-of-the-hiv-exposed-neonate). Ribavirin is teratogenic at low doses in multiple animal species. Both women and men of childbearing potential who are receiving ribavirin should be counseled about the need to use effective contraception during therapy and for 6 months after completion. Interferons are not recommended for use in pregnancy because of direct antigrowth and antiproliferative effects. The recently FDA-approved drugs boceprevir and telaprevir should be used only in combination with interferon and ribavirin and therefore should not be used in pregnancy. Evaluation for treatment, including liver biopsy, can be delayed until 3 months or more after delivery to allow pregnancy-related changes in disease activity to resolve.

A European study of perinatal HCV transmission found that the use of effective combination ART was associated with a strong trend for reduction in HCV transmission [OR 0.26, 95% CI, 0.07–1.01] (*J Infect Dis* 2005;192(11):1872).Therefore, standard recommendations for ARV drug use during pregnancy for treatment of HIV and/or prevention of MTCT HIV transmission should be followed.

As with HBV infection, elevation in hepatic enzymes may occur after starting ARVs; this may be related to HCV flare due to immune reconstitution with effective ARV regimens or to greater vulnerability to hepatotoxicity with ARVs drugs.

Liver enzymes should be assessed 2–4 weeks following initiation of ARVs and then at least every 3 months. (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*). If hepatic toxicity

occurs, consultation with an expert in HIV and HCV co-infection is strongly recommended. Pregnant women with HCV/HIV co-infection should be counseled about signs and symptoms of liver toxicity and advised to avoid alcohol.

Internal fetal monitoring, amniocentesis, and duration of membrane rupture greater than 6 hours may increase risk of HCV transmission (*J Infect Dis* 2005;192(11):1880; *Ann Hepatol* 2010;9 suppl:92). Most studies that have included both HIV infected and uninfected pregnant women with HCV have found that elective CS delivery does not reduce the risk of perinatal HCV transmission (*AIDS* 2007;21(13):1811; *Am J Obstet Gynecol* 2008;199(3):315; *Arch Gynecol Obstet* 2011;283:255).

HIV-2 infection: HIV-2 infection is endemic in some West African countries and in parts of India (*JAMA* 1993;270(17):2083; *AIDS* 1989;3 suppl 1:S89). It also occurs in countries with large numbers of immigrants from these regions (*Bull Epidemiol Hebd* 2007;46-47:386). HIV-2 is less infectious than HIV-1, with a 5-fold lower rate of sexual transmission and a 20–30-fold lower rate of vertical transmission (*Lancet* 1990;335(8697):1103; *Lancet* 1994;343(8903):943).

HIV-2 infection should be suspected if a pregnant women or her partner is from an endemic country and presents with the following pattern of HIV testing: a positive test on HIV screening assay with a repeatedly indeterminate HIV-1 western blot and HIV-1 RNA VL at or below the limit of detection. Although most commercially available HIV screening tests can detect both HIV-1 and HIV-2, the Bio-Rad Laboratories Multispot HIV1/2 test is the only FDA-approved antibody test that can distinguish between HIV-1 and HIV-2; in some laboratories HIV-2 supplemental tests such as HIV-2 immunoblot or HIV-2-specific western blot are available, but these tests do not have FDA approval for diagnosis. One HIV-2 VL assay is now commercially available in the United States; it can be ordered through the University of Washington (1-800-713-5198 or commserv@u.washington.edu).

For HIV-2+ pregnant women who require treatment for their own health (e.g., significant clinical disease or CD4+ cell count $<500/mm^3$), two NRTIs and a boosted PI are currently recommended for treatment. On the basis of available safety data in pregnancy, ZDV/3TC + LPV/r, or, alternatively, TDF/FTC + LPV/r or TDF + 3TC + LPV/r is recommended for treatment during pregnancy.

Optimal prophylaxis regimens for HIV-2+ pregnant women (without HIV-1 co-infection) who do not require treatment for their own health (e.g., CD4+ cell count $>500/mm^3$ and no significant clinical disease) have not been defined. Some experts would use a boosted PI-based regimen for prophylaxis and stop the drugs postpartum. Other experts would use ZDV prophylaxis alone during pregnancy and intrapartum (*Clin Infect Dis* 2010;51(7):833). Some experts would not provide any drug prophylaxis because the risk of transmission from such women is very low (*HIV Med* 2008;9(7):452). The infant should receive the standard 6-week ZDV prophylactic regimen. Expert consultation is advised.

NNRTIs and ENF are not active against HIV-2 and should not be used for treatment or prophylaxis.

Infants born to HIV-2+ mothers should be tested with HIV-2-specific virologic assays at similar time points as HIV-1 testing would be conducted. Because these tests are not commercially available, testing must be referred to academic or research laboratories. Determining loss of HIV-2 antibodies by age 18 months is also recommended (*HIV Med* 2008;9(7):452). Breastfeeding is not recommended for infants of HIV-2+ mothers.

Opportunistic Infections

Prophylaxis indications and recommendations for primary prophylaxis of OIs in pregnancy are noted in Table 8-9. Once an individual has had the listed infections, prophylaxis to prevent recurrence is recommended as standard of care. Criteria for discontinuation of secondary prophylaxis vary by infection. See the USPHS *Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents* (http://aidsinfo.nih.gov/Guidelines/) for current recommendations for treatment and secondary prophylaxis of each OI In pregnancy.

Table 8-9

Primary Prophylaxis for Opportunistic Infections in Pregnant Women*

Pathogen	Indication	Regimen	Alternatives[1]	Comment
Pneumocystis pneumonia	Strong recommendation: CD4+ cell count <200 c/mm^3 or oral thrush Moderate recommendation: CD4+% <14% or history of AIDS-defining illness	TMP-SMZ DS or SS 1 po qd	Dapsone Atovaquone	Test for G6PD deficiency before administration of dapsone Criterion for stopping primary prophylaxis: CD4+ cell count >200 c/mm^3 for >3 mo in response to ART
Toxoplasma gondii	Strong recommendation: Toxoplasma IgG+ with CD4+ cell count <100 c/mm^3 or if toxoplasma seroconversion occurs	TMP-SMZ DS 1 po qd	TMP-SMZ (alternate dosing) Dapsone + pyrimethamine + leucovorin	Test for G6PD deficiency before administration of dapsone Criterion for stopping primary prophylaxis: CD4+ cell count >200 c/mm^3 for >3 mo in response to ART

Table 8-9 *continued*

Primary Prophylaxis for Opportunistic Infections in Pregnant Women*

Pathogen	Indication	Regimen	Alternatives[1]	Comment
Mycobacterium tuberculosis	Strong recommendation: Positive diagnostic test for latent TB (e.g., TST reaction ≥ 5 mm or (+) interferon gamma release assay), no prior treatment for active or latent TB and no evidence of active TB, ***or*** Negative diagnostic test for latent TB but contact with active TB and no evidence of active TB	INH 300 mg qd or 900 mg twice weekly plus pyridoxine 25 mg qd for 9 mo	Rifampin Rifabutin	Must rule out active TB prior to beginning prophylaxis; for persons exposed to drug-resistant TB, select drugs with consultation
Mycobacterium avium complex	Strong recommendation: CD4+ cell count <50 c/mm^3	Azithromycin 1200 mg po once weekly or 600 mg po twice weekly	Rifabutin (must rule out active TB)	Must rule out active MAC infection Criterion for stopping primary prophylaxis: CD4+ cell count >100 c/mm^3 for >3 mo in response to ART

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* See OI Guidelines for Dosing (http://aidsinfo.nih.gov/Guidelines) (accessed 5/20/13)

Immunizations

See the USPHS *Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents* (http://aidsinfo.nih.gov/Guidelines/) for current recommendations for immunizations in pregnancy.

Immunization should be considered in pregnancy when the risk for exposure or maternal and/or fetal infection is high and the vaccine is thought unlikely to cause harm. Immune-suppressed HIV infected patients and pregnant women should avoid live-virus or live-bacteria vaccines. HIV-infected patients 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 weeks) increase in VL after immunization. This increase in viremia may be prevented with appropriate ART (*Medical Management of HIV Infection*, 2009–2010. Johns Hopkins University School of Medicine). For this reason, clinicians may consider deferring routine vaccination until after the patient is on an effective ARV regimen and avoiding administration late in pregnancy (i.e., close to delivery), when most transmission is thought to occur. Table 8-10 presents current immunization recommendations for HIV-infected pregnant women.

Table 8-10

Immunizations Recommended for HIV Infected Pregnant Women

Vaccines	Recommendation	Comments
Pneumococcal (see Table 4-9)	Recommended if patient has not received the vaccine during the previous 5 y	
Influenza	Recommended	Administer annually before flu season begins Use of live attenuated influenza vaccine is contraindicated
Tetanus-diphtheria-pertussis (Tdap)	Recommended with each pregnancy • optimal timing is 27–36 weeks gestation • if tetanus booster indicated for wound management, administer at any time • if unknown or incomplete tetanus vaccination, administer 3 vaccinations containing tetanus and diphtheria (Td) toxoids with recommended schedule 0, 4 weeks, 6–12 mo. Tdap should replace 1 dose of Td, preferably between 27–36 wks gestation	Pregnant women who have not already received Tdap should receive a dose as soon as possible after delivery to ensure pertussis immunity and reduce the risk for transmission of Td to the newborn
HBV	Recommended for all susceptible patients	3 doses: at 0, 1 mo, 6 mo of pregnancy

Table 8-10 *continued*

Immunizations Recommended for HIV Infected Pregnant Women

Vaccines	Recommendation	Comments
HAV	Recommended for all susceptible (HAV Ab-negative) patients with chronic HCV or HBV; also indicated before travel to endemic areas, in IDUs, and with community outbreaks	2 doses: at 0, 6 mo of pregnancy
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 infected people
Immune Globulins		
	Recommended for measles exposure in persons with symptomatic HIV	
	Recommended for HAV, with exposure to HAV in close contact/sex partner, or with travel to underdeveloped country (especially in patients with advanced HIV, who may have poor antibody response to vaccine)	
	Recommended for rubella, within 72 h of exposure	
Hyperimmune Globulins		
Varicella-zoster virus (VZV) immune globulin	Recommended for susceptible adults (i.e., undetectable antibodies to VZV or no history of either chickenpox or shingles) after significant exposure to chickenpox or VZV (significant exposure = household, hospital room, close indoor contact >1 h, prolonged face-to-face contact)	Give within 96 h of exposure
Hepatitis B immune globulin	Recommended for needlestick or sexual contact with HBsAg+ person in susceptible individuals	Give HBIG; start HBV vaccine series within 14 d of exposure

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Frequency of Visits

The frequency of prenatal care visits depends on several factors specific to each patient, including the health of the mother, gestational age, presence of pregnancy-related complications, ARV regimen and response, and psychosocial needs. In uncomplicated pregnancies, visits generally are scheduled monthly in early pregnancy and every 1–2 weeks from 28–30 weeks of gestation until delivery; when possible, they should be coordinated with other healthcare visits.

Consultations to Consider During Pregnancy

HIV infected women may need certain specialty consultations during pregnancy. Ideally, many of these consultations can be handled within the same clinic or center where the patient is seen for obstetrical or primary medical care. When possible, referral of the HIV infected pregnant woman to an obstetrician with HIV expertise and experience is advised, in which case the obstetrician may manage many of the patient's HIV-specific treatment issues.

In general, consultative needs may include the following:

- **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** to address HIV-related treatment issues, including choice of ARV regimen and need for OI prophylaxis or treatment. This consultation is particularly important if the patient is newly diagnosed with HIV infection during pregnancy.
- **Pediatrics** to address care of the infant after birth, including testing for HIV, use of ZDV, and *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis in exposed infants
- **Nutrition** to address proper diet, the need for nutritional or vitamin/mineral supplementation, and food safety issues when needed
- Substance abuse management when indicated
- **Psychiatry/psychology** to address signs/symptoms of depression and other psychiatric disorders and their management, if needed
- **Social services** to address needs related to housing, transportation, domestic violence, access to medications and medical care, etc.

Counseling and Support

Support systems: At the initial visit, the healthcare provider should assess a patient's support systems (i.e., determine who knows the patient's HIV status, what problems she has encountered with disclosure, which family members and/or friends provide ongoing support, and what barriers exist to disclosing her HIV status 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 mid-pregnancy to allow time for comprehensive education and counseling about available options and adequate time for informed decision making. Women who receive family planning counseling during prenatal care are more likely to use effective contraception postpartum (*Thromb Res* 2011;127 Suppl 3:s35).

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 use of 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 9, **Psychosocial Issues**) and drug or alcohol treatment during pregnancy should be encouraged and facilitated for active problems.

Adherence: Before initiating an ARV regimen, each patient should be educated and counseled about the importance of adherence to prescribed medications, and medication adherence should be assessed and reinforced at each visit (see Chapter 5, **Adherence**).

Clinical trials: Pregnant HIV infected 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, and legal assistance should be facilitated, if needed.

Guidelines For Intrapartum Care

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

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 12, **Occupational Exposure**.) When used, this should provide adequate protection for healthcare workers. Medical care should not be altered because of considerations of potential occupational exposure.

Intrapartum ART and Prophylaxis (http://aidsinfo.nih.gov)

Intravenous (IV) ZDV is recommended during the intrapartum period for HIV infected pregnant women with VL ≥ 400 c/mL (or unknown VL), regardless of their antepartum regimen or mode of delivery, to reduce perinatal HIV transmission.

- Administer a loading dose of 2 mg/kg IV over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery.
- For a scheduled CS delivery, IV ZDV should begin 3 hours before surgery; with unscheduled CS, consideration may be given to shortening this interval, depending on the indications for CS.
- IV ZDV should be given even with documented or suspected ZDV resistance.

However, IV ZDV is not required for HIV infected women receiving combination ARV regimens who have HIV RNA <400 copies/mL near delivery. In a study from the French Perinatal Cohort, intrapartum prophylaxis was not associated with transmission in women with VL <400 c/mL at delivery (*AIDS* 2008;22(2):289).

Women who are taking an antepartum combination ARV regimen should continue it on schedule, to the degree possible, during labor and prior to scheduled CS delivery to maximize virologic efficacy and minimize the development of resistance. If oral ZDV is a part of the antepartum regimen and IV ZDV is indicated, the oral ZDV component of the regimen can be stopped while the patient receives IV ZDV. For women who are receiving a d4T-containing antepartum regimen, d4T should be discontinued during labor if IV ZDV is being administered. If maternal ART must be interrupted temporarily (e.g., for less than 24 hours) in the peripartum period, all drugs (except for intrapartum IV ZDV, when indicated) should be stopped and reinstituted simultaneously to minimize the chance of developing resistance.

When CS delivery is planned, oral medications may be continued preoperatively with sips of water. Medications requiring food ingestion for absorption can be taken with liquid dietary supplements, contingent on consultation with the attending anesthesiologist during the preoperative period.

HIV infected women in labor who have not received antepartum ARV drugs should receive IV ZDV during labor, with subsequent infant combined ARV prophylaxis for 6 weeks. Women of unknown HIV status who present in labor should have a rapid HIV test performed. If the test is positive, a confirmatory HIV test should be sent as soon as possible and maternal/infant ARVs should be initiated without waiting for results of the confirmatory test. Rapid HIV testing (see http://www.cdc.gov/hiv/topics/testing/rapid/index.htm. Accessed 4/10/12) should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit. The National HIV/AIDS Clinicians' Consultation Center website provides information on state HIV testing laws (http://www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws. Accessed 4/10/12).

Mode of Delivery

(Current recommendations: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*, http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed 4/9/12)

Planned vaginal delivery: Vaginal delivery can generally be safely planned in women who are taking combination ARV regimens and who have plasma HIV RNA levels <1000 copies/mL near the time of delivery because of the low rate of transmission among this group and the lack of data that establish the additional benefit of CS in this situation. Recent studies indicate that the use of combination ARV regimens and attainment of a very low or undetectable HIV VL are associated with very low rates of perinatal HIV transmission. These include a recent report from a comprehensive national surveillance system in the United Kingdom and Ireland, where HIV transmission occurred in three (0.1%) of 2,309 and 12 (1.2%) of 1,023 infants born to women with HIV RNA of <50 copies/mL and 50–999 copies/mL, respectively. The transmission rate among all women who received at least 14 days of ART was 40 (0.8%) of 4,864, regardless of mode of delivery (*AIDS* 2008;22(8):973). In this and another large cohort (*Clin Infect Dis* 2005;40(3):458), there were no significant differences in transmission rates by mode of delivery when VL and the use of combination ARV regimens were taken into account.

Scheduled cesarean section: Scheduled CS at 38 weeks' gestation is recommended for women with HIV RNA levels >1000 copies/mL near the time of delivery (whether on ARVs or not) and for women with unknown HIV RNA levels near the time of delivery. Early studies, performed before VL testing and the use of optimal combination ARV regimens became the standard of care, found that scheduled CS, when performed before the onset of labor and/or membrane rupture, reduced MTCT by 55% to 80% in the absence of ARV prophylaxis and with ZDV alone (*Lancet* 1999;353:1035; *N Engl J Med* 1999;340:977).

When CS is performed to prevent HIV transmission, it should be scheduled at 38 weeks' gestation to decrease the likelihood of labor onset or membrane rupture before delivery. In a study of 1,194 infants born to HIV infected mothers, no statistically significant association was observed between mode of delivery and infant respiratory distress syndrome when adjusted for gestational age and birthweight (*Obstet Gynecol* 2010;116 2 Pt 1:335).

For women who are not HIV infected, ACOG recommends that planned CS not be performed before 39 weeks' gestation due to the risk of iatrogenic prematurity (*Obstet Gynecol* 2008;112(3):717; *N Engl J Med* 2009;360(2):111). When CS is performed for standard obstetrical indications (e.g., malpresentation), it should be scheduled at 39 weeks, with timing based on menstrual dating and ultrasound.

For HIV infected women presenting in late pregnancy and not taking ARVs, scheduled CS is likely to provide additional benefit in reducing risk of perinatal transmission of HIV unless viral suppression can be documented

prior to 38 weeks. Depending on the baseline RNA level, reduction in plasma HIV RNA to undetectable levels usually takes several weeks (*Clin Infect Dis* 2007;44(12):1647).

It is not clear whether CS after membrane rupture or labor onset provides benefit in preventing perinatal transmission. Management of women originally scheduled for CS who present with ruptured membranes or in labor must be individualized on the basis of the duration of rupture, progress of labor, plasma HIV RNA level, current ARV therapy or prophylaxis, and other clinical factors.

When preterm membrane rupture occurs (<37 weeks' gestation), decisions about delivery should be made on the basis of gestational age, HIV VL level, current ARV regimen, and evidence of acute infection (e.g., chorioamnionitis). Expert consultation is recommended. The ARV regimen should be continued and initiation of IV ZDV, if indicated, considered if imminent delivery seems possible.

Maternal morbidity and mortality are increased with CS compared with vaginal delivery (*Obstet Gynecol* 1999;94:942). Most studies have demonstrated that HIV infected women have increased rates of postoperative complications, mostly infectious, compared with women who do not have HIV infection, and that the risk of complications is related to the degree of immunosuppression (*Acta Obstet Gynecol Scand* 1999;78(9):789; *Eur J Obstet Gynecol Reprod Biol* 2000;90(1):73; *Int J Gynaecol Obstet* 2001;74(1):9; *Am J Obstet Gynecol* 2001;184(6):1108).

A Cochrane review of six studies of HIV infected women concluded that urgent CS delivery was associated with the highest risk of postpartum morbidity, that scheduled CS was intermediate in risk, and that vaginal delivery had the lowest risk of morbidity (*Cochrane Database Syst Rev* 2005;(4):CD005479).

Complication rates in most studies (*Am J Obstet Gynecol* 2000;183(1):100; *J Acquir Immune Defic Syndr* 2001;26(3):236; *Am J Obstet Gynecol* 2002;186(4):784; *AIDS* 2004;18(6):933) were within the range reported in populations of women who were not HIV infected but had similar risk factors, and were not of sufficient frequency or severity to outweigh the potential benefit of reduced transmission.

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 CS. Factors that increase the risk of complications include low socioeconomic status, genital infections, malnutrition, smoking, and prolonged labor or membrane rupture, some of which may be more common in the setting of HIV infection.

Prophylactic antibiotics should be given when CS is performed for prevention of HIV transmission.

Women should be counseled about the risks and potential benefits of CS for the purpose of reducing perinatal HIV transmission; decisions should be individualized on the basis of this discussion and the specific situation. The woman's autonomy to make an informed decision regarding route of delivery should be respected and honored.

Other Intrapartum Considerations

If spontaneous membrane rupture occurs before or early in the course of labor, interventions to decrease the interval to delivery, such as administration of oxytocin, may be considered in women without indications for CS.

Absent clear obstetric indications , the following procedures should generally be avoided because of potential increased risk of transmission: artificial rupture of membranes, routine use of fetal scalp electrodes, operative delivery with forceps or vacuum extractor, or episiotomy.

Delayed cord clamping has been associated with improved iron status and additional benefits (e.g., decreased risk of intraventricular hemorrhage) in both term and preterm births to HIV uninfected mothers (*Pediatrics* 2006;117(4):1235; *Neonatology* 2007;93(2):138; *J Perinatol* 2011;31 suppl 1:S68). Although HIV-specific data are lacking, there is no reason to modify this practice when the mother is HIV infected.

Treatment for postpartum hemorrhage due to uterine atony: If a woman is receiving a CYP3A4 enzyme inhibitor (e.g., PI), methergine should not be used unless alternative treatments for postpartum hemorrhage (e.g., prostaglandin F2-alpha, misoprostol, oxytocin) are not available and if the need for pharmacologic treatment outweighs the risks. If used, methergine should be administered in the lowest effective dose for the shortest duration possible. If she is receiving a CYP3A4 enzyme inducer (e.g., NVP, EFV, etravirine), the potential exists for decreased methergine levels and inadequate treatment effect; therefore, additional uterotonic agents may be needed.

Postnatal Care for the HIV-Exposed Infant

Antiretroviral prophylaxis

The 6-week neonatal component of the ZDV prophylaxis regimen is recommended for all HIV exposed neonates. Short-term toxicity of infant ZDV prophylaxis has been minimal, consisting primarily of transient hematologic toxicity, mainly anemia, which generally resolves by age 12 weeks.

A 4-week neonatal ZDV prophylaxis regimen is recommended in the United Kingdom and several European countries when the mother has taken ARVs prenatally (*HIV Med* 2008;9(7):452; *Pediatr Infect Dis J* 2011;30(5):408). This approach may be considered if there are concerns about adherence or toxicity with the 6-week regimen. The 4-week ZDV regimen may allow earlier recovery of anemia in otherwise healthy infants compared with the 6-week ZDV course (*Pediatr Infect Dis J* 2010;29(4):376). Consult with a pediatric HIV specialist if early discontinuation of infant prophylaxis is considered.

Table 8-11 presents recommendations for neonatal ZDV dosing to prevent MTCT; Table 8-12 presents recommended neonatal combination antiretroviral regimens for use in special circumstances.

Table 8-11

Recommendations for Neonatal Zidovudine Dosing to Prevent Mother-to-Child Transmission of HIV

Age	Dosing	Duration
>35 wk gestation	• 4 mg/kg body weight per dose, po bid • Start as close to the time of birth as possible and within 12 h of delivery • If unable to tolerate oral agents: 3 mg/kg body weight per dose given IV, started within 6–12 h of delivery, then q 12 h	Birth through 6 wk
<35–>30 wk gestation	• 2 mg/kg body weight per dose po ***or*** • 1.5 mg/kg body weight per dose IV • Start within 6–12 h of delivery, then q 12 h • Advance to 3 mg/kg per dose po (or 2.3 mg/kg per dose IV) q 12 h at 15 days of age	Birth through 6 wk
<30 wk gestation	• 2 mg/kg body weight per dose po ***or*** • 1.5 mg/kg body weight per dose IV • Start within 6–12 h of delivery, then q 12 h • Advance to 3 mg/kg per dose po (or 2.3 mg/kg per dose IV) q 12 h at 4 wk of age	Birth through 6 wk

Source: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. Sept 14, 2011. http://aidsinfo.nih.gov/content files/PerinatalGL.pdf

Table 8-12

Recommended Neonatal Combination Antiretroviral Regimens for Use in Special Circumstances

Regimen	Administration	Notes
ZDV 4 mg/kg bid + NVP • 12 mg po if birth weight >2 kg • 8 mg po if birth weight 1.5–2.0 kg	• Give birth through 6 wk • Administer 3 doses in first week of life: - Dose 1: Give within 48 h of birth (birth–48 h) - Dose 2: Give 48 h after Dose 1 - Dose 3: Give 96 h after Dose 2	• ZDV dosing regimen is for infants >35 weeks' gestation. See Table 8-11 for recommended doses for premature infants. • NICHD HPTN 040/PACTG 1043 used NVP 12 mg po bid if birth weight >2 kg and 8 mg po bid if birth weight 1.5-2.0 kg

Source: NICHD HPTN 040/PACTG 1043. 18th Conference on Retroviruses and Opportunistic Infections. Boston, MA, 2011.

ZDV should be initiated as close to the time of birth as possible, preferably within 6–12 hours. The 6-week ZDV prophylaxis regimen is recommended at gestational age-appropriate doses (see Table 8-11). Use of ARVs other than ZDV and nevirapine is not recommended in premature infants because of a lack of dosing and safety data. The use of neonatal ZDV is recommended regardless of maternal ZDV resistance history.

Infants born to HIV infected women who have not received antepartum or intrapartum ARVs or who have received only intrapartum ZDV should receive prophylaxis with a combination ARV regimen started as close to the time of birth as possible. This recommendation is based on a phase III randomized trial conducted in 4 countries (see Table 8-12) (*N Engl J Med* 2012 Jun 21;366(25):2368), which enrolled 1,746 infants born to HIV infected women who did not receive any ARVs during pregnancy prior to labor. The study compared the standard 6-week ZDV regimen alone with two different combination regimens: 6 weeks of ZDV plus three doses of NVP; or 6 weeks of ZDV plus 2 weeks of 3TC and NFV. In this trial, 41% of women received ZDV during labor and transmission rates did not vary by whether intrapartum ZDV was given. The overall HIV transmission rate was significantly lower in the two- and three-drug arms compared with the ZDV-alone arm; however, the two-drug regimen (ZDV plus NVP) was less toxic than the three-drug regimen (ZDV plus 3TC plus NFV). Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the three-drug regimen compared with the two-drug regimen (27.5% vs. 15%, $p < .0001$). Furthermore, NFV powder is no longer commercially available in the United States.

No specific data address whether a more intensive combination infant prophylaxis regimen provides further protection against transmission when the mother receives antepartum/intrapartum prophylaxis but has suboptimal viral suppression near delivery, particularly in the absence of scheduled CS, or when the mother has ARV drug-resistant virus. On the basis of extrapolated findings

from the NICHD HPTN 040/PACTG 1043 study, the use of a combination infant prophylaxis regimen should be considered, depending on risk assessment (e.g., maternal VL and mode of delivery). Expert consultation is advised. The decision to use other drugs with 6 weeks of ZDV in other scenarios should be made only after expert consultation and a discussion of risks and benefits with the mother, preferably before delivery.

Appropriate drug formulations and dosing regimens for neonates are incompletely defined and minimal data are available concerning the safety of combination drugs in the neonate. Neonatal dosing information is not available for currently available boosted PIs; both RTV and LPV/r have been associated with cardiac toxicity, lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death, predominantly in preterm neonates. The FDA now recommends that LPV/r ***not*** be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained.

Infants of women with positive HIV rapid test results while the mother is in labor should begin combination ARV prophylaxis as described above. If the maternal confirmatory HIV test is positive, then ARVs should be continued in the infant for 6 weeks; if the test is negative, the infant ARVs should be stopped.

Initiation of ART is recommended for infected infants aged <12 months, regardless of clinical status, CD4+ percentage, or VL. If the infant becomes infected despite combination prophylaxis that includes NVP, the risk of NVP drug resistance is increased; expert consultation is advised when choosing ARV regimens.

Neonatal Evaluation

A baseline complete blood count (CBC) and differential should be performed on the newborn. Decisions about the timing of subsequent hematologic testing depend on baseline results, gestational age at birth, clinical condition, dose of ZDV being administered, receipt of other ARV drugs and concomitant medications, and maternal antepartum therapy. Some experts recommend more intensive monitoring of hematologic, serum chemistry and liver function assays at birth and when diagnostic HIV PCR tests are obtained for infants exposed to combination ART in utero or during the neonatal period. Because of the potential for enhanced hematologic toxicity in infants receiving a zidovudine/lamivudine-containing prophylaxis regimen, a recheck of hemoglobin and neutrophil counts is recommended 4 weeks after initiation of prophylaxis. If hematologic abnormalities are identified while the infant is receiving prophylaxis, decisions regarding continuation of prophylaxis should be individualized. Expert consultation is advised if discontinuation of prophylaxis is considered. Routine measurement of serum lactate is not recommended; but measurement of serum lactate may be considered if an infant develops severe clinical symptoms, particularly neurologic symptoms, of unknown etiology.

Follow-up of children with ARV exposure should continue into adulthood because of the unknown long-term effects of these drugs.

Diagnosis of HIV

Source: *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*; http://aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0/. Accessed 6/27/12)

HIV infection can be definitively diagnosed with virologic assays in most nonbreastfed HIV infected infants by 1 month of age and in virtually all infected infants by 4 months of age. Because of transplacental passage, HIV antibody tests will be positive up to 18 months after birth and therefore are not valid for infant diagnosis. Virologic assays (HIV DNA PCR or HIV RNA assay) are used to diagnose HIV infection in infants younger than 18 months.

HIV DNA PCR or HIV RNA assay in HIV exposed infants is recommended at age 14–21 days, 1–2 months, and 4–6 months. Virologic testing at birth should be considered for infants at high risk of HIV infection (e.g., born to HIV infected mothers who did not receive prenatal ARV drugs and/or those with high VLs at the time of labor/delivery). Data do not indicate any delay in HIV diagnosis with HIV DNA PCR assays in infants who have received the ZDV regimen (*Pediatr Infect Dis J* 1995;14(11):948); however, the effect of combination ART in the mother or newborn on the sensitivity of infant virologic diagnostic testing, particularly HIV RNA assays, is unknown. Therefore, although HIV RNA assays may be acceptable for diagnosis (particularly in older infants) HIV DNA PCR assays may be optimal for diagnosing infection in the neonatal period.

Confirmation of HIV infection should be based on two positive virologic tests from separate blood samples. Definitive exclusion of HIV infection should be based on at least two negative virologic tests (at >1 month and >4 months of age). Consider confirmation of HIV status with HIV antibody testing at 12–18 months in infants with prior negative virologic tests. In children aged ≥18 months, HIV antibody assays alone can be used for diagnosis.

Pneumocystis jirovecii Pneumonia Prophylaxis

To prevent *Pneumocystis jirovecii* pneumonia (PCP; formerly known as *Pneumocystis carinii* pneumonia), all infants born to women with HIV infection should begin PCP prophylaxis with TMP-SMZ (150/750 mg/m^2/day in two divided doses po three times weekly on consecutive days) at age 4–6 weeks, after completing 6 weeks of ZDV, unless there is adequate test information to presumptively exclude HIV infection. Dapsone and atovaquone are alternatives.

Guidelines for Postpartum Care

Infant feeding: Breastfeeding (BF) by HIV infected mothers is not recommended in the United States, even for women who are on ART and have undetectable VL, because of potential toxicity arising from drug transmission via breast milk

and the risk of drug resistance due to insufficient drug levels in breast milk if the baby is infected despite prophylaxis. Furthermore, ART may not affect the presence of cell-associated virus (intracellular HIV DNA) in breast milk, which may therefore continue to pose a transmission risk (*J Acquir Immune Defic Syndr* 2004;35(2):178).

Late HIV transmission events in infancy have recently been reported among HIV infected children suspected to have acquired HIV infection as infants as a result of consuming premasticated food; this was supported by phylogenetic comparisons of virus from cases and suspected sources and supporting clinical history. Healthcare providers should routinely inquire about this feeding practice and instruct HIV infected caregivers to avoid this practice and advise on safe feeding options (*Pediatrics* 2009;124(2):658; *J Acquir Immune Defic Syndr* 2012;59(2):207).

In most low-resource settings internationally, however, BF has significant benefits that outweigh the risks, including provision of ideal infant nutrition in the first 6 months of life, reduction of infant morbidity and mortality through protection against both diarrhea and respiratory-associated mortality in the first year of life (*Lancet* 2000;355:451), delays in the return of fertility with exclusive breastfeeding (promotes child spacing and maternal recovery from blood loss), low cost, and cultural acceptability. Therefore, current WHO recommendations regarding BF for HIV infected mothers include the following:

- When infants are HIV uninfected or of unknown status:
  - Exclusive BF for the first 6 months of life unless replacement (formula) feeding is acceptable, feasible, affordable, sustainable, and safe
  - At 6 months, introduce appropriate complementary foods and continue BF for the first 12 months of life. All BF should then stop once a nutritionally adequate and safe diet without breast milk can be provided.
- When infants are HIV infected:
  - Exclusive BF for the first 6 months of life and continue BF as per recommendations for the general population (up to 2 years or beyond)

In addition, data from several recent randomized controlled trials support the use of extended infant NVP prophylaxis or continuation of maternal triple ARV prophylaxis throughout BF to further reduce the risk of perinatal transmission (*Lancet* 2008;372(9635):300; *N Engl J Med* 2010;362:2271; *N Engl J Med* 2010;362:2282; *N Engl J Med* 2008;359:119). The WHO now recommends one of these two strategies when ongoing maternal ART is not indicated (World Health Organization. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants*. 2010 version. http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf. Accessed 3/26/12).

Care for mother and infant: HIV infected mothers may neglect their own care while trying to provide appropriate care for their infants and other children or family members. The immediate postpartum period is an important time to assess new mothers' psychological, emotional, and physical health. New

mothers should be monitored for signs of postpartum depression or worsening of underlying psychiatric disorders and referred to mental health services if necessary. In addition, this is an important time to review the completeness of preventive health interventions, including immunizations and cervical cancer screening. The care of other chronic medical conditions should be reviewed. It is essential that women 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. A team approach with multiple support services may also help to provide optimal care. Similarly, the HIV-exposed infant should be linked into ongoing pediatric care, with HIV diagnostic tests as described above and appropriate HIV specialty care if HIV infected.

Antiretroviral Treatment

Whether to continue or discontinue ARVs after delivery: Decisions regarding continuation of ARV drugs after delivery should take the following into account: current recommendations for initiation of ART (available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 5/17/13), current and nadir CD4+ cell counts and trajectory, HIV RNA levels, clinical symptoms/disease stage, presence of other indications for ART (e.g., chronic hepatitis B, HIV-associated nephropathy), adherence issues, HIV infection status of the woman's sexual partner, and patient decision after careful counseling.

Following delivery, women who meet the indications for ART should continue therapy without interruption. Doses of some PIs may be increased during late pregnancy; for women continuing therapy, available data suggest that standard doses can be used again starting immediately after delivery.

When ARV drugs have been given in pregnancy to women with CD4+ cell count >500 cells/microliter, the decision to stop or to continue ARV drugs postpartum has become increasingly controversial because of increasing evidence of benefit in starting therapy at higher CD4+ levels and recommendations for earlier initiation of ART (http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 5/17/13) and because therapy interruption when ART has been given for treatment in nonpregnant adults has been associated with increased morbidity (*J Infect Dis* 2008;197:1145).

At issue is the potential impact of postpartum ARV discontinuation on the short- and long-term health of the mother. This is especially important as women may have multiple pregnancies, resulting in episodic receipt of ARVs. To date, studies of pregnant women with relatively high CD4+ cell counts who stop therapy after delivery have not shown a risk for increased disease progression (*J Infect Dis* 2007;196(7):1044; *HIV Med* 2009;10(3):157; *Infect Dis Obstet Gynecol* 2009:456717). Unplanned changes in ARV regimens and discontinuations of treatment in the postpartum period have led to viral load rebound (*HIV Clin Trials* 2011;12(1);9).The risks versus benefits of stopping therapy postpartum in women with high CD4+ counts is being evaluated in the ongoing PROMISE study.

The potential benefits of continuing ART in women with higher CD4+ counts must be weighed against possible drug toxicity, cost, and the risk of development of viral resistance with suboptimal adherence, which may be more likely during the postpartum period (*AIDS Care* 2008;20(8):958; 6th International AIDS Society Conference on HIV Pathogenesis and Treatment and Prevention 2011; Abstract #1016).

Women who have uninfected sexual partners should continue ART postpartum to reduce risk of HIV transmission (*New Engl J Med* 2011;365:493). Safe sexual practices should continue to be recommended.

The decision to continue therapy after delivery should be discussed with the woman and decisions made prior to delivery. Until definitive evidence is available to guide this decision, continuation of therapy in women with high CD4+ cell counts should be based on individualized discussions with the woman and consideration of willingness and ability to commit and adhere to lifelong therapy.

Stopping ARV Drugs Postpartum

For women whose antepartum regimen included an NNRTI and who plan to stop ARV prophylaxis after delivery, consider one of the following two options: 1) stop the NNRTI first and continue other ARVs for a period of time; or 2) switch from an NNRTI to a PI prior to interruption and continue the PI with the other ARVs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and the other ARV drugs is not known; at least 7 days is recommended. Given the potential for prolonged detectable NNRTI concentrations for more than 3 weeks in patients taking EFV-based therapy, some experts recommend continuing the other ARVs or substituting a PI plus two other agents for up to 30 days. A recent study of 412 women who received single-dose nevirapine and were randomized to receive zidovudine/lamivudine, tenofovir/emtricitabine, or lopinavir/ritonavir for either 7 or 21 days found an overall new nevirapine resistance mutation rate of 1.2% when assessed by population genotype at 2 and 6 weeks following completion of treatment, with no difference by length of treatment. However, low-frequency nevirapine-resistant mutations at codons 103, 181, and 184 detected using allele-specific PCR emerged significantly more often in the 7-day arms (13/74 [18%]) than in the 21-day arms (3/66 [5%], P = .019). (*Clin Infect Dis* 2013; 56(7):1044).

Women whose antepartum regimen did not include an NNRTI and who plan to stop ARV prophylaxis after delivery should stop all ARVs at the same time.

Adherence support: For women continuing ARVs postpartum, adherence support should be available during the postpartum period and adherence should be assessed at each clinical visit. 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. Providers should be especially aware that depression or drug or alcohol use/abuse may negatively affect adherence and should screen postpartum women for these conditions.

It is essential that access to and continuity of ART as needed for maternal health be ensured. Simplification of an ARV regimen may be considered. If a woman is not able to adhere to her regimen, temporary interruption of ART may be needed while strategies are devised to improve adherence.

Contraception and Condom Use

Discussions about contraception and safe sexual practices should continue throughout pregnancy and should be reviewed and reinforced at the postpartum visit. Lack of breastfeeding is associated with earlier return of fertility; ovulation returns as early as 6 weeks postpartum and potentially even earlier in some women, putting them at risk for pregnancy shortly after delivery (*Obstet Gynecol* 2011;117(3):657). Interpregnancy intervals <18 months have been associated with increased risk of poor perinatal and maternal outcomes in HIV-uninfected women (*J Obstet Gynaecol* 2010;30(2):107). Because of the stresses and demands of a new baby, women may be both more receptive to the use of effective contraception and more at risk for nonadherence to contraceptive methods and unintended pregnancy. This is an important concern when the woman is on an EFV-containing regimen or other drugs that are potential teratogens. An ideal contraceptive strategy for women with HIV infection is to provide simultaneous protection against both unintended pregnancy and HIV transmission or sexually transmitted disease acquisition or transmission, often called "dual protection" (i.e., condoms plus a highly effective contraceptive) (*Sex Transm Dis* 2002;29(3):168). The use of longer-term, reversible contraceptive methods (e.g., injectable, implants, and/or IUD) should be included as options.

National Perinatal HIV Hotline

This toll-free hotline provides free clinical consultation on all aspects of perinatal HIV, including infant care: 1-888-448-8765.

Dolutegravir (Tivicay, DLG)

FDA approved 8/13. It is classified as FDA Pregnancy Category B.

Standard adult dose: ARV-naïve or ARV-experienced but integrase inhibitor naïve patients: DLG 50 mg once daily

ARV-naïve or ARV-experienced but integrase inhibitor naïve if given with EFV, fos-APV/r, TPV/r, or rifampin; or integrase inhibitor experienced: DLG 50 mg twice daily

Formulation: 50 mg tablets

Adverse effects: The most common adverse reactions of moderate to severe intensity and incidence ≥2% are insomnia and headache. Hypersensitivity reactions have been reported in 1% or fewer study subjects and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. Patients with underlying hepatitis B or C may be at increased risk for abnormal liver enzymes.

Drug Interactions: Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. Dolutegravir should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications. DLG should be given as 50 mg twice daily when coadministered with rifampin.

Use in pregnancy: Insufficient data to recommend use: No studies of dolutegravir use in human pregnancy. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits. Placental transfer and PK in pregnancy are unknown

Chapter 13:

Pharmacologic Considerations in HIV Infected Pregnant Patients

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Chapter 13: Pharmacologic Considerations in HIV Infected Pregnant Patients

Chapter 13 at a Glance

Introduction

Information included in this chapter may include off-label recommendations for specific drugs or indications.

The information presented in this chapter includes detailed information about pharmacologic agents commonly used in the treatment of HIV infected women and drugs often used in pregnancy or as complementary therapies, with particular emphasis on issues related to their use in pregnancy.

Risk versus benefit: The decision to administer drugs to a pregnant woman depends on the potential therapeutic benefit versus the potential risk to the mother and/or the developing fetus. Clinicians are often advised to avoid prescribing drugs for pregnant patients because human safety data in pregnancy are lacking for many, if not most, medications; however, effective treatment for HIV, opportunistic infections, and other serious medical conditions should not be withheld in pregnancy. There are important considerations when selecting agents to treat women with HIV to prevent mother-to-child transmission and to prevent or treat opportunistic infections or other related or coexisting conditions. In general, when more than one effective treatment is available, the regimen with the best evidence for safety in pregnancy should be chosen. When animal studies suggest teratogenic or embryotoxic risk and human studies are lacking or also of concern, expert consultation is recommended.

Caveats: The literature on drug safety in pregnancy should be interpreted with caution and with the following caveats: animal studies (including studies of mutagenicity, carcinogenicity, and teratogenicity), which are the basis for most data on safety in pregnancy, are often inconsistent across species and may not accurately reflect risk in human pregnancy. For example, animals are often administered doses 5 to 20 times higher than those given to humans and the clinical applicability of such dosing to human treatment may not be clear. In humans, drug dose, intensity of exposure, placental transfer, and gestational age at exposure may all affect the presence or magnitude of risk. Teratogenic potential does not reflect the expected frequency of malformations; adequately controlled human studies are necessary to establish the degree of risk. A drug with teratogenic potential may be appropriate for use when there are no safer alternatives and when the benefits are expected to outweigh the risk.

It is now standard practice to treat HIV infected patients with a combination of antiretroviral (ARV) agents, which makes it difficult to assess the safety of a single agent, and information about the safety of newer ARVs in pregnancy is limited; additional prospective clinical data are needed. Clinicians are encouraged to report all in utero exposures to the Antiretroviral Pregnancy Registry (800-258-4263; fax: 800-800-1052; http://www.apregistry.com/). The registry is a collaborative effort of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners; the group collects observational data on ARV exposure during pregnancy to assess the potential teratogenicity of these drugs.

Pharmacokinetics of Drugs in Pregnancy

Although many physiologic changes occur during pregnancy, few trials have been conducted to evaluate the clinical significance of these changes to the pharmacokinetics of commonly used drugs. Physiologic changes that may affect drug pharmacokinetics include delayed gastric emptying, decreased intestinal motility, increased volume of distribution (average increase, 8 L), increased renal blood flow (25%–50%), and increased glomerular filtration rate (by 50%) (*Fundamentals of Gynecology and Obstetrics*, Philadelphia: J.B. Lippincott Co; 1992; *J Obstet Gynaecol* 1974;81:588; *J Obstet Gynaecol Br Commonw* 1970;77:900).

Pharmacokinetic parameters of NVP given as a single dose of 200 mg at the onset of labor were similar to but more variable than those in nonpregnant adults, possibly because of incomplete absorption associated with altered gastrointestinal function during labor (*J Infect Dis* 1998;178:368). Data suggest that NVP levels may be detectable as long as 3 weeks after a single dose given at onset of labor (11th Conference on Retroviruses and Opportunistic Infections, February 8, 2004 [abstract 41LB]). Pregnancy does not change the pharmacokinetics of ABC, ZDV, 3TC, d4T, or ddI (*J Infect Dis* 1998;1778:1327; 6th International Conference on AIDS, June 20, 1990 [abstract FB17]; *J Infect Dis* 1999;180:1536). On the other hand, FTC serum concentrations are slightly lower in the third trimester. Similarly, third-trimester TDF concentrations are lower, but trough concentrations are adequate. The clinical significance of these findings remains to be determined (see Table 8-7, pp. 285–298).

Serum concentrations of the protease inhibitors (PIs) that have been studied in pregnancy (ATV, IDV, RTV, and SQV) appear to be lower in pregnancy when the agents are given as single, unboosted PIs (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*; http://www.aidsinfo.nih.gov. Accessed 8/6/12). When boosted with RTV, SQV levels are adequate (*HIV Clin Trials* 2001;2:460), and adequate NFV levels are achieved when it is given at a dose of 1250 mg bid; in the third trimester, however, concentrations were lower and more variable (9th Conference on Retroviruses and Opportunistic Infections, February 2002 [abstract 795w]). When the old formulation of LPV/r capsules was administered to pregnant patients, LPV serum concentrations were lower during the third trimester. A pharmacokinetic study with the new LPV/r tablets is ongoing. Some experts recommend increasing the LPV/r dose to three tablets twice per day to compensate for the decreased LPV concentrations during the third trimester; other experts, however, recommend using the standard dose with close monitoring (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*). In patients with PI mutations, a higher dose (e.g., three LPV/r tablets twice per day) should be considered in the third trimester. Use of newer ARVs (e.g., RAL, MVC, DRV, TPV, ETR) or older ARVs with limited clinical data in pregnancy (e.g., ENF, FPV) should be reserved for cases in which the benefit outweighs the risk to the pregnant woman and/or when better-studied agents are not options because of concerns for safety, tolerability, or effectiveness.

Sex-Based Differences in Response to HIV Treatment

Clinical response: There are conflicting data on sex differences in clinical response to ARV treatment. Several studies have documented sex differences in CD4+ lymphocyte counts and HIV viral loads (VLs), indicating that women have higher CD4+ cell counts and lower HIV RNA levels early in the course of infection; however, differences in VL tend to dissipate several years after initial infection and rates of progression are similar in men and women (*J Infect Dis* 1999;180:666; *N Engl J Med* 2001;344:720; *Clin Infect Dis* 2002;35:315). Early studies suggested poorer outcomes for women, but when controlled for later presentation and lower rates of care and/or treatment with effective antiretroviral therapy (ART), these sex-based differences in HIV disease course generally disappeared (*J Acquir Immune Defic Syndr* 2000;24:475; *AIDS* 2001;15:1115). Several studies have shown sex differences in ART prescription and utilization, even with free access to ART and CD4+ cell counts <200 cells/mm^3 at baseline (*J Acquir Immune Defic Syndr* 2000;24:475; *Women's Health Issues* 2006;16:104; *J Acquir Immune Defic Syndr* 2003;32:499; *J Acquir Immune Defic Syndr* 2005;38:96; *South Med J* 2007;100:775). A recent retrospective cohort study with 6,657 person-years follow-up found that women had an increased risk of death, even after adjustment for HAART use (hazard ratio, 1.62; p = .002) (*J Infect Dis* 2009;199:991); however, other large cohort studies found comparable or lower rates of clinical progression and death in women compared with men (*J Women's Health* 2007;16:1052; *AIDS* 2007;21:835; *HIV Med* 2006;7:520). Virologic and clinical responses in clinical trials are comparable between men and women, although most trials have not been powered to detect gender differences. A recent open-label Phase 3b study specifically designed to enroll a high proportion of women examined treatment responses to DRV-RTV plus an investigator-selected optimized background regimen and found no significant difference in virologic response by sex, although women were more likely to discontinue therapy for reasons other than virologic failure (*Ann Intern Med* 2010;153:349).

Adverse drug events: A number of studies have shown a higher incidence, greater severity, or altered presentation of adverse drug events in women compared with men (*Expert Rev Anti Infect Ther* 2005;3:213). Women with higher CD4+ cell counts appear to be at the greatest risk for symptomatic, potentially fatal, and often rash-associated liver toxicity associated with NVP (*J Acquir Immune Defic Syndr* 2004;35:538; *Clin Infect Dis* 2004;38 Suppl 2:S80). Lactic acidosis related to prolonged exposure to nucleoside reverse transcriptase inhibitors appears to occur more frequently in women (*AIDS* 2007;21:2455). Women also may be at greater risk for some metabolic complications of ART, such as central fat deposition, and they appear less likely to have triglyceride elevations (*HIV Med* 2001;2:84; *J Acquir Immune Defic Syndr* 2003;34:58). Women are at greater risk of osteopenia and/or osteoporosis, especially after menopause, and this may be worsened in the setting of HIV and ART (*AIDS* 2006;20:2165). Although data are limited, women may metabolize and respond to specific ARV drugs differently from men, which may result in higher drug concentrations and a greater likelihood of adverse effects (*Annu Rev Pharmacol Toxicol* 2004;44:499; *Pharmacol Res* 2008;58:173; *Gend Med* 2007;4:106). Therefore, close monitoring for adverse drug events is recommended when initiating ARV therapy in women. It is also

important that clinicians recognize barriers to initiating and continuing ARV therapy in women because competing priorities, such as child and family care and issues related to stigma and disclosure, can interfere with ART adherence.

Table 13-1

U. S. Food and Drug Administration Categories for the Use of Prescription Drugs in Pregnancy

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 and 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 in 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

Note: At the time of publication of this guide, the FDA was preparing a revision of drug categories for pregnancy and lactation that will likely do away with the current letter categories

Table 13-2

Pregnancy Categories for Antiretroviral Agents in ARV-Naïve Women

Preferred	Drugs or drug combinations are designated as preferred for use in pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific pharmacokinetic data are available to guide dosing; and no evidence of teratogenic effects on the fetus or established association with teratogenic or clinically significant adverse outcomes for the mother, fetus, or newborn are present
Alternative	Drugs or drug combinations are designated as alternatives for initial therapy in pregnant women when clinical trial data in adults show efficacy but any one or more of the following conditions apply: there is limited experience in pregnancy; there is a lack of data on teratogenic effects on the fetus; or there are dosing, formulation, administration, or interaction issues for that drug or regimen
Not Recommended	Drugs and drug combinations listed in this category are not recommended for therapy in pregnant women because of inferior virologic response, potentially serious safety concerns for the mother or fetus, or pharmacologic antagonism. In addition, some drugs are listed in this category because they are not currently recommended in ARV-naïve adults and adolescents due to limited data. These agents may eventually move to a different category as more data becomes available.
Insufficient Data to Recommend	Although approved for use in adults, the drugs and drug combinations in this category do not have pregnancy-specific pharmacokinetic or safety data available or such data are too limited to make a recommendation for use for pregnancy

Source: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2013*

Note: At the time of publication of this guide, the FDA was preparing a revision of drug categories for pregnancy and lactation that will likely do away with the current letter categories

Table 13-3

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Acyclovir (Zovirax®) **FDA pregnancy category: B**	• 5–10 mg/kg IV q 8 h • 200–800 mg po 3–5x qd	• Toxicities are infrequent • GI intolerance: nausea, vomiting, diarrhea • Renal toxicity, esp. with rapid IV infusion • Dizziness • Transaminase elevation • Pruritus • Headache	Not teratogenic, but has potential to cause chromosomal damage at high doses Antiviral drug with the most reported experience in pregnancy; appears to be safe—no increased risk of birth defects or patterns of defects (*Birth Defects Res A Clin Mol Teratol* 2004;70(4):201)	Can be used in pregnancy for treatment or suppression of HSV infections and treatment of uncomplicated chicken pox or shingles; however, valacyclovir can be considered for convenient dosing and better pharmacokinetics IV acyclovir recommended for severe HSV or VZV if parenteral therapy indicated Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 wk gestation for pregnant women with recurrences of genital herpes to reduce need for Cesarean delivery (*Obstet Gynecol* 2007;109:1489) No known benefit of suppressive therapy for women who are seropositive for HSV-2 without a history of genital lesions

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Albendazole (Albenza®) **FDA pregnancy category: C**	Microsporidiosis: 400 mg po bid x 3 wk	• Diarrhea • Abdominal pain • Elevated transaminase • Hepatotoxicity • Reversible pancytopenia and neutropenia	Teratogenic (skeletal malformations) and embryotoxic in rodent and rabbit studies at exposure levels lower than those estimated with therapeutic human dosing No adequate, well-controlled studies in early human pregnancy A recent randomized trial including albendazole for treatment of soil-transmitted helminth infections in 2nd trimester found no evidence of teratogenicity or other adverse pregnancy effects (*Am J Trop Med Hyg* 2008;79(6):856)	Not recommended for use in 1st trimester. Consider use later in pregnancy only if benefits outweigh potential risks.
Amphotericin B (Fungizone®) **FDA pregnancy category: B**	Usual adult dose: 0.3–1.2 mg/kg IV qd **Fluconazole-resistant candida esophagitis:** 0.3 mg/kg IV qd **Cryptococcal meningitis:** 0.7 mg/kg (plus 5FC)	• Fever and chills (40%– 50%) • Renal tubular acidosis (30%–40%); dose dependent and reversible in absence of prior renal damage and dose <3 g (reduced with hydration and sodium loading) • Hypokalemia (20%) • Hypomagnesemia • Anemia • Phlebitis and pain at infusion site • Hypotension • Nausea, vomiting • Metallic taste • Headache	Animal studies demonstrated no evidence of teratogenicity Extensive clinical use has demonstrated no evidence of teratogenicity	Preferred initial regimen for treatment of serious fungal infections in pregnancy Evaluate neonates born to women on chronic amphotericin B for renal dysfunction and hypokalemia at delivery

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Artemisinin-based combination therapy (Artemether/lumefantrine) **FDA pregnancy category: C**	Artemether/lumefantrine (20 mg/120 mg tab) 4 tabs po as single initial dose; 4 tabs again after 8 h, and then 4 tabs bid (AM and PM) for next 2 d (total course of 24 tabs)	Generally well tolerated with occasional nausea, dizziness, headache, rash	Some preclinical studies found possible teratogenic effects and increased embryolethality with early 1st-trimester exposure to artemesinins in a variety of animal species, including at levels below equivalent human therapeutic dose Some data suggest pregnancy may lower levels of artemether/lumefantrine and dihydroartemisinin; optimal dosing strategies in pregnancy have not been determined	Considered first-line treatment during 2nd and 3rd trimesters for women with uncomplicated *Plasmodium falciparum* and severe malaria
Artesunate **FDA pregnancy category: C**	**U.S. IND protocol (available through CDC):** 4 equal doses of 2.4 mg/kg over 3 d, followed by oral treatment with atovaquone-proguanil, doxycycline, clindamycin, or mefloquine to avoid emergence of resistance **WHO recommendations:** IV artesunate 2.4 mg/kg IV or IM given on admission (time = 0), then 12 h and 24 h, qd in low-transmission area or outside malaria endemic area	Generally well tolerated with bradycardia, nausea, and dizziness occasionally reported	No evidence of physical or neurological abnormalities during development observed with 1st trimester exposure in small studies (*Malar J* 2007;6:15)	Alternative treatment of *P. falciparum* in 2nd and 3rd trimesters along with clindamycin WHO recommends artesunate as a first-line agent in 2nd and 3rd trimesters In 1st trimester, until more evidence becomes available, both artesunate and quinine may be considered

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Atovaquone (Mepron®) **FDA pregnancy category: C**	**PCP treatment or prophylaxis:** 750 mg po bid **PCP prophylaxis:** 1500 mg po qd **Toxoplasmosis treatment:** 1500 mg po bid + pyrimethamine or sulfadiazine	• GI intolerance: nausea, vomiting, diarrhea • Headache • Rash • 7%–9% require d/c because of side effects	Atovaquone did not increase malformations in rats and rabbits, although doses used were limited by toxicity to half the human dose Human data are limited No adverse effects in mothers or newborns found with use of atovaquone in combination with other antimalarials in about 90 pregnant Thai women in 2nd or 3rd trimester (*Trans R Soc Trop Med Hyg* 2003;97(5):592; *Eur J Clin Pharmacol* 2003;59(7):545; *J Infect Dis* 2005;192(5):846)	Alternative regimen for PCP prophylaxis and treatment Third-line treatment and prophylaxis for toxoplasmosis
Atovaquone–proguanil (Malarone®) **FDA pregnancy category: C**	**Malaria treatment:** atovaquone 1000 mg/proguanil 400 mg (4 tabs, single dose) po qd x 3 d **Malaria prevention:** atovaquone 250 mg/proguanil 100 mg po (1 tab) qd, starting 1–2 d before travel and continuing for 1 wk after leaving endemic area	Generally well tolerated with occasional GI intolerance, headache, asthenia, dizziness, and rare cases of severe rash.	Preclinical studies have shown no increased risk of defects Limited human data Plasma levels appear lower in pregnancy	Can be used for malaria prophylaxis for travel to chloroquine-resistant regions Alternative treatment for *P. falciparum* in 2nd and 3rd trimesters

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Azithromycin (Zithromax®) **FDA pregnancy category: B**	**MAC prophylaxis:** 1200 mg po q wk **MAC treatment:** 500 mg or 600 mg po qd + ethambutol +/- rifabutin	• GI intolerance (4%): nausea, diarrhea, abdominal pain • Vaginitis • Reversible hearing loss (more common with 500 mg x 30–90 d) • Elevated transaminase	Animal studies show no harm to fetus Two studies including >300 women found no increased risk of congenital anomalies with azithromycin exposure in pregnancy (*Sex Transm Dis* 2006;33(2):106; *BMC Pregnancy Childbirth* 2006;6:18)	Recommended for MAC prophylaxis or treatment in pregnancy Also used in treatment of Bartonellosis
Boceprevir (Victrelis®) **FDA pregnancy category: X**	800 mg po tid (in combination with peginterferon + ribavirin)	• Headache • Fatigue • Nausea • Elevated LFTs	No human data	Not recommended for use in pregnancy Because goal of HCV treatment is to prevent long-term sequelae, treatment in pregnancy is rarely indicated
Caspofungin (Cancidas®) **FDA pregnancy category: C**	70 mg IV load on day 1, then 50 mg IV qd (infuse over 1 h)	• Generally well tolerated • Histamine-mediated symptoms including rash, facial swelling, pruritus and sensation of warmth have been reported • Rare: fever, phlebitis, nausea, vomiting, headache, eosinophilia, proteinuria, increased alkaline phosphatase, hypokalemia	Embryotoxic: animal data with exposure comparable to human dosing resulted in incomplete ossification of skull, torso, and talus/calcaneus No human data	Avoid in 1st trimester. Use later in pregnancy should be based on consideration of benefit versus potential risk.

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Chloroquine (Aralen®) **FDA pregnancy category: C**	***P. vivax, P. ovale, P. malariae, and chloroquine-sensitive P. falciparum:*** chloroquine phosphate 1 g salt (600 mg base) 1x; then 500 mg salt (300 mg base) 6 h later; then 500 mg at 24 h and 48 h po Chloroquine HCl 160–200 mg (base) IM or IV q 6 h (IV n/a in U.S.)	• Visual disturbances • Hemolysis with G6PD deficiency • GI intolerance • Pruritus • Alopecia • Headache • Confusion • Dizziness • Severe skin rash • QTc prolongation	No evidence of increase in malformations Extensive experience with use in pregnancy	Drug of choice for malaria prophylaxis and treatment of sensitive strains in pregnancy
Cidofovir (Vistide®) **FDA pregnancy category: C**	**CMV retinitis induction:** 5 mg/kg q wk x 2 wk, then q 2 wk; give concurrently with probenecid and hydration **Probenecid regimen:** 2 g given 3 h prior to cidofovir and 1 g given at 2 h and 8 h after infusion (total 4 g) >1 L normal saline 1 or 2 h immediately before cidofovir infusion	• Nephropathy (dose dependent); reduced with hydration and probenecid • Probenecid side effects: chills, fever, headache, rash, nausea (30%–50%) • Uveitis • GI intolerance • Neutropenia • Metabolic acidosis	Embryotoxic and teratogenic (meningomyelocele, skeletal abnormalities) in rats and rabbits No experience with use of cidofovir in human pregnancy	Not recommended for use in pregnancy

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Clarithromycin (Biaxin®) **FDA pregnancy category: C**	**MAC prophylaxis:** 500 mg po bid **MAC treatment:** 500 mg po bid + ethambutol +/- rifabutin	• GI intolerance: diarrhea (4%) • Headache • Reversible dose-related hearing loss • Taste disturbances	Studies in monkeys show growth retardation, cleft palate, embryonic loss Two studies, each with slightly >100 women with 1st-trimester exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although one study noted an increased risk for spontaneous abortion (*Am J Perinatol* 1998;15(9):523; *Pharmacoepidemiol Drug Saf* 2000;9(7):549)	Not recommended in 1st trimester
Clotrimazole (Canesten®, Lotrimin®, Mycelex®) **FDA pregnancy category: C** (troches)	**Oral thrush:** 10 mg troches 5 x/d **Candida vaginitis:** • 100 mg intravaginal tabs bid x 3 d ***or*** • qd x 7 d ***or*** • 1 applicator (5 g) vaginal cream q hs x 7–14d	• GI intolerance: nausea, vomiting • Transaminase elevation • Topical treatment (rare): burning, erythema, pruritus	Embryotoxic in rats and mice. Not teratogenic in mice, rabbits, and rats. No adverse effects or congenital anomalies reported with use of vaginal or topical clotrimazole in pregnancy (*Obstet Gynecol* 1987;69(5):751; *Epidemiology* 1999;10(4):437)	Nystatin is preferred over clotrimazole in management of oral thrush during pregnancy because of minimal systemic absorption Clotrimazole is considered safe for treatment of vaginal candidiasis in pregnancy

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Cycloserine (Seromycin®) **FDA pregnancy category: C**	**TB:** 10–15 mg/kg/d po (maximum daily dose = 1000 mg, but hard to tolerate) Usual dose 500–750 mg po qd, given in 2 divided doses	• Common CNS side effects: anxiety, confusion, somnolence, disorientation, headache, hallucinations, tremor, hyperreflexia, depression (with suicidal ideation), psychotic disturbances • Occasional seizures • Peripheral neuropathy • Fever • Rash	No data available from animal studies No data on use in human pregnancy	Avoid use in pregnancy unless other options not available
Dapsone (Aczone®) **FDA pregnancy category: C**	**PCP prophylaxis:** 100 mg po qd **Treatment of mild to moderate PCP:** 100 mg po qd + trimethoprim x 3 wk **PCP + toxoplasmosis prophylaxis:** 50 mg po qd or 200 mg q wk + leucovorin and pyrimethamine	• Rash • Blood dyscrasias, including methemoglobinemia, sulfhemoglobinemia, and hemolytic anemia (with or without G6PD deficiency) • Nephrotic syndrome • Fever • Nausea, anorexia • Blurred vision • Photosensitivity • Tinnitus • Insomnia • Irritability • Headache (transient) • Rare sulfone syndrome: fever, exfoliative dermatitis, jaundice, adenopathy, methemoglobinemia, anemia	No animal teratogenicity studies conducted Carcinogenic risk in rats Has been used safely for several decades to treat leprosy, malaria, and various dermatologic conditions during pregnancy (*Trop Med Int Health* 2003;8(6):488; *Drug Saf* 2004;27(9):633) Risk of mild maternal hemolysis with long-term therapy and potential risk, though extremely low, of hemolytic anemia in an exposed fetus with G6PD deficiency (*South Med J* 1989;82(5):668)	Alternative for PCP prophylaxis and treatment of mild–moderate PCP (with TMP); also alternative to toxoplasmosis prophylaxis Screening of mother for G6PD deficiency is recommended before use

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Ethambutol (Myambutol®) **FDA pregnancy category: C**	• 15–25 mg/kg po qd (1.6 g max) • 35–50 mg/kg biw (4.0 g max) • 25–30 mg/kg tiw (2.4 g max)	• Optic neuritis: decreased acuity, reduced color discrimination, constricted fields, scotomata (dose related and infrequent with 15 mg/kg) • GI intolerance • Confusion • Precipitation of acute gout	Teratogenic among rodents and rabbits at doses much higher than those used in humans No evidence of teratogenicity in humans	CDC considers ethambutol safe in pregnancy
Ethionamide (Trecator®) **FDA pregnancy category: X**	15–20 mg/kg/d po (max 1 g/d); usually 500–750 mg divided q 24 h, q 12 h, or q 8 h administered w/food or hs	• Common, severe, and dose-dependent GI intolerance: nausea, vomiting, metallic taste, anorexia, abdominal pain • Occasional allergic reaction • Hepatitis • Neurotoxicity • Orthostatic hypotension	Associated with birth defects in multiple animal species No increased risk for defects was noted with doses similar to those used in humans Limited experience In human pregnancy	Avoid use in pregnancy unless other options not available
Famciclovir (Famvir®) **FDA pregnancy category: B**	**Zoster:** 500 mg po q 8 h **Recurrent HSV and HSV suppression:** 125–250 mg po q 12 h	• Headache • Nausea • Fatigue	Carcinogenic but not embryotoxic or teratogenic in animal studies Human data limited	Acyclovir or valacyclovir preferred In pregnancy given limited information on famciclovir

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Fluconazole (Diflucan®) **FDA pregnancy category: C**	**Candida esophagitis:** 200–800 mg po or IV qd **Candida vaginitis:** 150 mg po x 1; 150 mg po q wk for multiple recurrences **Cryptococcal infection:** • 1200 mg po or IV qd +5FC (alternative induction phase at least 2 wk) • Then 400 mg po qd (consolidation phase x 8 wk); • Then 200 mg po qd (maintenance)	• Dose-related GI intolerance: bloating, nausea, vomiting, pain, anorexia, weight loss (8%–11% with dose <400 mg/d; 30% with dose >400 mg/d) • Reversible alopecia (10%–20% of patients receiving 400 mg/d for 3 mo) • Transaminase elevation to >8 x normal • Rare cases of fatal hepatitis and Stevens–Johnson syndrome	Teratogenic in animal studies, with limb and craniofacial abnormalities reported Craniofacial, limb, and cardiac defects have been reported in 4 infants with 1st-trimester exposure to high-dose fluconazole (*Clin Infect Dis* 1996;22:336; *Am J Med Genet* 1997;72:253) Several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, but most of these involved low doses and short-term exposure (*J Antimicrob Chemother* 2008;62(1):172; *Am J Obstet Gynecol* 1996;75:1645)	Avoid in 1st trimester because of potential for teratogenicity Use topical agents in treatment of candida vaginitis in pregnancy
Flucytosine (Ancobon®) **FDA pregnancy category: C**	25 mg/kg q 6 h (monitor levels; goal = 30–80 mcg/mL at steady state)	• GI intolerance: nausea, vomiting, diarrhea • Marrow suppression with leukopenia or thrombocytopenia (dose related with renal failure, serum concentration >100 mg/mL or concurrent amphotericin) • Confusion • Rash • Hepatitis (dose related) • Enterocolitis • Headache • Photosensitivity reaction • Peripheral neuropathy	Teratogenicity reported in animal studies Data limited to 3 case reports of 2nd and 3rd trimester exposure that resulted in no defects in newborns	4% of administered dose biotransformed to 5FU, which has been associated with congenital malformations Use in pregnancy only if benefits outweigh potential risks

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Foscarnet (Foscavir®) **FDA pregnancy category: C**	**CMV retinitis induction:** • 60 mg/kg IV q 8 h **or** • 90 mg/kg IV q 12 h x 14 d **Maintenance:** 90–120 mg/kg IV qd **Acyclovir-resistant HSV or VZV:** • 40 mg/kg IV q 8 h **or** • 60 mg/kg IV q 12 h x 3 wk	• Renal failure: usually reversible; 30% get Cr >2 mg/dL; monitor Cr 1–3 x/wk; d/c if Cr >2.9 mg/dL • Mineral and electrolyte changes: reduced magnesium, phosphorus, ionized calcium, potassium; monitor serum electrolytes 1–2 x/wk and monitor for symptoms of paresthesias • Seizures (10%) • Fever • GI intolerance • Anemia • Genital ulceration • Neuropathy	Skeletal malformation or variation in animal studies No experience with use in early pregnancy A single case report of use in 3rd trimester described normal infant outcome (*Clin Infect Dis* 1999;29(4):937)	Use only if benefits outweigh risks and safer alternatives not available Avoid in 1st trimester if possible Because foscarnet toxicity is primarily renal, monitor amniotic fluid volume by ultrasound weekly after 20 wk gestation to detect oligohydramnios If therapy given near delivery, evaluate electrolyte and renal function in neonate
Fumagillin (Not commercially available in U.S.) **FDA pregnancy category: N/A**	20 mg po tid x 2 wk (not available in U.S.)		Systemic fumagillin associated with increased resorption and growth retardation in rats No data on systemic use in human pregnancy Topical fumagillin has not been associated with embryotoxic or teratogenic effects among pregnant women	Because of antiangiogenic effect of fumagillin, this drug should not be used systemically in pregnant women Topical fumagillin may be considered when therapy with this agent is appropriate (ocular microsporidiosis)

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Furazolidone (No longer available in U.S.) **FDA pregnancy category: C**	100 mg po q 6 h x 7–10 d	• GI intolerance • Yellow to brown discoloration of urine • Allergic reaction • Fever • Hemolysis • Headache	Not teratogenic in animal studies Human data limited to case series that found no association between 1st-trimester use and birth defects	Use in pregnancy only if benefit outweighs potential risk
Ganciclovir (Cytovene®) **FDA pregnancy category: C**	**CMV retinitis induction:** 5 mg/kg IV q 12 h x 2 wk, then maintenance: 5 mg/kg IV qd	• Neutropenia (ANC <500 in 15%–20%); usually occurs early in treatment and responds within 3–7 d to drug holiday or to GCSF • Thrombocytopenia (platelet count <20,000 in 10%); reversible; monitor CBC 2–3 x wk and d/c if ANC <500–750 or platelet count <25,000 • Anemia • Fever • Rash • CNS: headache, seizures, confusion, changes in mental status • Abnormal LFTs (2%–3%).	Teratogenic (in concentrations comparable to those achieved in humans) and embryotoxic: cleft palate, anophthalmia, hydrocephalus, aplastic kidney and pancreas (rabbits); growth retardation Safe use in human pregnancy after organ transplantation has been reported (*Transplantation* 1995;60(11):1353). Use in late pregnancy to treat fetal CMV infection in HIV uninfected women has also been reported (*Semin Perinatol* 2007;31(1):10).	For retinal disease, consider intraocular ganciclovir implants or intravitreous injections in 1st trimester to limit fetal exposure to systemically administered drugs Start systemic antiviral therapy after 1st trimester, generally with oral valganciclovir (see below) For patients with colitis or esophagitis, IV ganciclovir is recommended if symptoms are severe enough to interfere with oral absorption Monitor fetus with fetal movement counts in 3rd trimester and after 20 wk gestation with periodic ultrasound for evidence of significant anemia, manifest as hydrops fetalis Evaluate newborn for bone marrow suppression

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Interferon (Roferon®, Intron®) **FDA pregnancy category: C**	**Treatment of hepatitis:** 3 million units IM or SC tiw + ribavirin Also used at higher doses for treatment of hepatitis B and Kaposi's sarcoma	• Flu-like syndrome • GI intolerance: nausea, vomiting, diarrhea, anorexia • CNS toxicity: delirium; obtundation, depression • Neutropenia • Anemia • Thrombocytopenia • Elevated transaminase • Rash • Alopecia • Proteinuria	Abortifacient in rhesus monkeys when given at 20–500 x human dose Limited case reports of interferon exposure during pregnancy do not suggest an association with birth defects; however, data are too limited to draw conclusions	Not recommended for use in pregnancy because of direct antigrowth and antiproliferative effects (*Neurology* 2005;65(6):807) Because goal of HCV treatment is to prevent long-term sequelae, treatment in pregnancy is rarely indicated
Isoniazid (INH, Tubizid®, Nydrazid®) **FDA pregnancy category: C**	300 mg po qd	• Age-related hepatitis: <20 y (nil); 35 y (6%); 45 y (11%); 55 y (18%); d/c if transaminase levels are >3–5x normal limits • Allergic reactions • Fever • Peripheral neuropathy (especially with preexisting alcoholism, diabetes, pregnancy, malnutrition) • Glossitis	Animal studies show embryocidal effect, but not teratogenic Retrospective analysis of more than 4,900 exposures to INH did not show increased fetal malformations (*Am Rev Respir Dis* 1980;122(1):65)	American Academy of Pediatrics and American Thoracic Society recommend that pregnant women with a positive PPD receive INH if they are HIV infected, have had recent TB contact, or have an X-ray showing old TB, once active disease is ruled out. Start after 1st trimester if possible. Hepatotoxicity caused by INH may occur more frequently in pregnancy and postpartum period; monthly monitoring of liver transaminases is recommended

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Itraconazole (Sporanox®) **FDA pregnancy category: C**	100–400 mg po qd, depending on specific condition	• Headache • GI intolerance: nausea (10%) and vomiting • Rash (8%) • Hypokalemia reported with high doses (600 mg/d) • Adrenal insufficiency • Impotence • Gynecomastia • Leg edema • Elevated transaminase • Rare cases of fatal hepatitis	Teratogenic in rats and mice (encephaloceles, macroglossia, skeletal malformation) FDA has received 14 case reports of malformations following use of itraconazole; 4 were limb defects. Prospective cohort studies of >300 women with 1st-trimester exposure, however, did not show an increased risk of malformation (*Drug Saf* 2009;32(3):239; *Am J Obstet Gynecol* 2000; 183(3): 617).	In general, avoid azole antifungals in 1st trimester because of potential for teratogenicity
Mefloquine (Lariam®) **FDA pregnancy category: C**	**Uncomplicated malaria treatment:** • 1250 mg po x 1 or • 750 mg 1x, then 500 mg 12 h later **Malaria prophylaxis:** 250 mg po q wk; start 1 wk prior to departure to an endemic area and continue for 4 wk after leaving endemic area	• Common CNS side effects: vertigo, light-headedness, nightmares, headache, decreased fine motor function • Visual disturbances • GI intolerance • Sinus bradycardia	Animal studies suggest potential teratogenicity and/or embryotoxicity, but clinical experience has not shown evidence of such effects in humans No evidence of increase in defects Several other large studies found mefloquine to be safe and effective in pregnancy (*J Travel Med* 1998;5(3):121)	Drug of choice for malaria prophylaxis with travel to chloroquine-resistant regions and for continuing prophylaxis after treatment
Nitazoxanide (Alinia®) **FDA pregnancy category: B**	500 mg po q 6–12 h	Generally well tolerated with occasional GI intolerance and headache	No evidence of teratogenicity in animal studies No data on use in human pregnancy	May be considered in pregnancy after 1st trimester in severely symptomatic women

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Nystatin (Bio-Statin®, Mycostatin®, etc.) **FDA pregnancy category: C**	**Oral thrush:** 500,000 units; swish and swallow 5 x/d	GI intolerance: nausea, vomiting, diarrhea	No evidence of congenital defects in animal studies No evidence of congenital defects associated with use in pregnancy	May be used for management of thrush during pregnancy because of low systemic absorption
Paromomycin (Humatin®) **FDA pregnancy category: C**	500–1000 mg po q 6 h	Generally well tolerated with occasional nausea, vomiting, diarrhea, anorexia, cramps, epigastric burning pain	No evidence of teratogenicity in animal studies Limited information in human pregnancy Minimal systemic absorption with oral administration, which may minimize potential risk	May be used in pregnancy after 1st trimester in severely symptomatic women
Peginterferon (PegIntron® [alfa-2B], Pegasys® [alfa-2A]) **FDA pregnancy category: C**	**PegIntron:** 1 mcg/kg SC q wk + ribavirin; dose reduction to 0.5 mcg/kg recommended for ANC <750 or platelet count <50,000 and d/c if ANC <500 or platelet count <25,000 **Pegasys:** 180 mcg SC q wk + ribavirin; reduce dose with hematologic toxicity Peginterferon alfa-2A or alfa-2B + ribavirin is treatment of choice for HCV	• Common: flu-like symptoms, headache, dizziness, fatigue, fever, rigor, injection-site inflammation, depression (29%), insomnia, alopecia, GI intolerance (abdominal pain, anorexia, nausea, vomiting, diarrhea • Occasional: thrombocytopenia, neutropenia, hypo- and hyperthyroidism, elevated LFTs	Abortifacient in rhesus monkeys when given 20–500 x human dose No studies in human pregnancy	Not recommended for use in pregnancy because of direct antigrowth and antiproliferative effects (*Neurology* 2005;*65*(6):807) Because goal of HCV treatment is to prevent long-term sequelae, treatment in pregnancy is rarely indicated

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Pentamidine–aerosolized (NebuPent®) **FDA pregnancy category: C**	**PCP prophylaxis:** 300 mg nebulized q mo	• Asthma reaction (2%– 5%) • Cough (30%)	Systemic pentamidine is embryotoxic but not teratogenic in rats and rabbits Aerosolized pentamidine given to 15 women during the 2nd and 3rd trimesters did not alter pregnancy outcome or cause fetal harm (*Am J Obstet Gynecol* 1992;166:387)	Use for PCP prophylaxis only if alternatives not available. There are concerns about systemic absorption and about adequate drug distribution during pregnancy because of restrictive changes with an enlarged uterus.
Pentamidine–intravenous (Nebupent®, Pentacarinat®, Pentam 300®) **FDA pregnancy category: C**	**PCP treatment:** 3–4 mg/kg IV qd	• Nephrotoxicity (25%), usually reversible with d/c • Hypotension (administer IV over 60 min to decrease risk) • Hypoglycemia (5%– 10%); usually occurs after 5 d of treatment including past treatment and may last days or weeks; may lead to insulin-dependent diabetes • Marrow suppression (leukopenia; thrombocytopenia) • GI intolerance: nausea, vomiting, abdominal pain, anorexia, bad taste • Elevated transaminase • Pancreatitis • Toxic epidermal necrolysis • Fever	Systemic pentamidine is embryotoxic but not teratogenic in rat and rabbit studies; however, it has been shown to be embryocidal Pentamidine is concentrated in placental tissue, but the clinical significance of this is unknown (*Am J Obstet Gynecol* 1989; 160(3): 759-61) No human clinical data on use of IV pentamidine	Use in pregnancy only if benefits outweigh potential risks and recommended alternatives cannot be used

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Posaconazole (Noxafil®) **FDA pregnancy category: C**	**Treatment of invasive fungal infections:** • 200 mg po q 6 h or • 400 mg po q 12 h • Some experts recommend increasing to 400 mg q 8 h for severe infection, lack of clinical response, and/or low posaconazole serum concentrations **Oropharyngeal and esophageal candidiasis refractory to itraconazole and/or fluconazole:** 400 mg q 12 h, with duration of therapy based on clinical response	• Generally well tolerated • Occasional nausea, vomiting, diarrhea, abdominal pain; increased LFTs • Rare cases of adrenal insufficiency, hypersensitivity reaction, QTc prolongation	Has been shown to cause skeletal malformations in rats, but not in rabbits, when given at 3–5 x human exposure No adequate controlled studies	Avoid in pregnancy
Primaquine **FDA pregnancy category: C**	**PCP treatment:** 15–30 mg (base) po qd + clindamycin	• Hemolytic anemia (G6PD deficiency) • Methemoglobinemia • GI intolerance • Neutropenia	No animal studies available No human data available	Generally not used in pregnancy because of risk of maternal hemolysis Potential risk of hemolytic anemia in exposed G6PD-deficient fetus; screen mother for G6PD deficiency before use

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Pyrazinamide **FDA pregnancy category: C**	**Latent TB:** 15 mg/kg/d (2.0 g max) **Active TB:** 20–25 mg/kg/d (2.0 g max) **Intermittent therapy:** 30–50 mg/kg 2–3 x wk (3.0–4.0 g max)	• Nongouty polyarthralgia • Asymptomatic hyperuricemia • Hepatitis (dose related; frequency not increased when given with INH or rifampin; rarely serious) • GI intolerance • Gout	No evidence of increased congenital defects in rodent data Minimal human data available	WHO and International Union Against Tuberculosis and Lung Diseases have recommended routine use of PZA in pregnant women; it has not been recommended for general use during pregnancy in the U.S. because of limited data If PZA not included in initial treatment regimen, minimum duration of TB therapy should be 9 mo Decision to use PZA should take into account gestational age and susceptibility pattern of MTB strain

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Pyrimethamine (Daraprim®) **FDA pregnancy category: C**	**Acute treatment of toxoplasmosis:** 100–200 mg loading dose, then 50–75 mg po qd + sulfadiazine 4–6 g po qd in 4 divided doses for at least 6 wk + leucovorin 10–20 mg po qd **Toxoplasmosis maintenance dose:** After acute treatment, pyrimethamine 25–50 mg po qd + sulfadiazine 2–4 g po qd in 4 divided doses + leucovorin 10–25 mg po qd **Toxoplasmosis prophylaxis:** 50–75 mg po q wk + dapsone + leucovorin 25 mg po q wk	• Folic acid deficiency with megaloblastic anemia and pancytopenia (dose-related and reversed with leucovorin) • Allergic reactions • GI intolerance: nausea, vomiting, anorexia	Teratogenic in animal studies Human data have not suggested an increased risk for defects (*Curr Drug Saf* 2006;1(1):1; *Drug Saf* 2007;30(6):481; *Clin Perinatol* 1994;21:675; *Clin Infect Dis* 1994;18:853)	Recommended as part of treatment regimen for toxoplasmic encephalitis and prophylaxis for patients who cannot tolerate TMP-SMX

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Quinine (Qualaquin®) **FDA pregnancy category: C**	**Uncomplicated malaria:** 650 mg q 8 h x 3–7 d, plus: • doxycycline 100 mg bid x 7 d **or** • clindamycin 450 mg q 8 h x 7 d **or** • pyrimethamine/sulfadoxine 3 tabs on last day of quinine	• GI intolerance • Cinchonism (tinnitus, headache, nausea, abdominal pain, visual disturbances) • Hemolytic anemia with G6PD deficiency • QTc prolongation • Thrombocytopenia • Hepatitis	At high doses, associated with increased risk for birth defects (especially deafness) in some animal species At high doses, associated with increased risk for birth defects (especially deafness) in humans	Use of therapeutic doses in pregnancy considered safe Treatment of choice with a diagnosis of chloroquine-resistant *P. vivax*; with uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with quinine and clindamycin is recommended, particularly in 1st trimester Because of potential for hypoglycemia, monitor glucose levels of pregnant women treated with quinine and their neonates
Ribavirin (Rebetol®) **FDA pregnancy category: X**	T**reatment of hepatitis C:** • **<75 kg:** 400 mg q AM and 600 mg q PM + interferon • **>75 kg:** 600 mg bid + interferon	• Hemolytic anemia (mean Hb decrease 3 g/dL) • Leukopenia • Hyperbilirubinemia • Increased uric acid	Demonstrated to be teratogenic in low doses in multiple animal species (limb abnormalities, craniofacial defects, exencephaly, anophthalmia) No human data available. At this time, inadvertent pregnancy during paternal RBV exposure has not been associated with adverse events (*Am J Gastroenterology* 2001;96:2286).	Use contraindicated during pregnancy and in male partners of pregnant women Women of childbearing potential and men receiving RBV should be counseled about risks and need for consistent contraception during and for 6 mo after use of RBV Pregnancies that occur in women taking RBV should be reported to the Ribavirin Pregnancy Registry (800-593-2214)

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Rifabutin (Mycobutin®) **FDA pregnancy category: B**	• 300 mg po qd • **With unboosted PIs** (e.g., IDV, NFV): 150 mg qd or 300 mg tiw • **With boosted PIs** (e.g., LPV/r, DRV/r, SQV/r, ATV/r) or ATV: 150 mg qod • **With EFV:** 450 mg qd or 600 mg tiw • **With NVP:** standard dose or 300 mg tiw Not recommended with DLV Consider therapeutic drug monitoring with PIs and NNRTI co-administration	• Orange discoloration of urine, tears, sweat • Uveitis with eye pain, photophobia, redness, blurred vision; usually seen with high doses (600 mg/d) or concurrent use of fluconazole or clarithromycin • Hepatitis • GI intolerance • Allergic reactions	Animal data show no increase in birth defects No human data available	Limited experience in pregnancy Many drug interactions, for which dose modifications are recommended (see Table 13-8, p. 500 and Table 13-9, p. 505)
Rifampin (Rifadin®) **FDA pregnancy category: C**	**For TB prophylaxis or active TB:** 10 mg/kg/d (600 mg/d max, but up to 600 mg bid with CNS infections) **With DOT:** 600 mg 2–3 x/wk	• Orange discoloration of urine, tears, sweat • Hepatitis (usually cholestatic changes during first month; frequency not increased when given with INH) • Jaundice (usually reversible with dose reduction and/or continued use) • GI intolerance • Hypersensitivity reactions • Flu-like syndrome with intermittent use characterized by dyspnea, wheezing	Some but not all animal studies show increased risk of cleft palate, spina bifida, embryotoxicity No evidence of human teratogenicity	American Thoracic Society recommends rifampin in combination with INH and ethambutol if treatment for drug-sensitive TB is needed during pregnancy Many drug interactions, including with ARVs Administer prophylactic vitamin K 10 mg to neonate because of potential increased risk of hemorrhagic disease

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Sulfadiazine (Lantrisul®, Neotrizine®, etc.) **FDA pregnancy category: C**	**Acute treatment of toxoplasmosis:** Sulfadiazine 4–6 g/d po in 4 divided doses + pyrimethamine 50–75 mg po qd for at least 6 wk + leucovorin 10–20 mg po qd **Toxoplasmosis maintenance dose:** After acute treatment, sulfadiazine 2–4 g po qd in 4 divided doses + pyrimethamine 25–50 mg po qd + leucovorin 10–25 mg po qd	• Allergic reactions (rash, pruritus) • Crystalluria with renal damage, urolithiasis and oliguria • GI intolerance • Photosensitivity • Hepatitis • Fever • Periarteritis nodosum • Stevens–Johnson syndrome • Serum sickness	At high doses, animals developed cleft palate and bone abnormalities Extensive use in humans without complications except one case of agranulocytosis that was possibly associated (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005)	Theoretical risk of kernicterus in neonate if administered near term
Telaprevir (Incivek®) **FDA pregnancy category: X**	• 750 mg q 8 h • 1125 mg q 8 h (with EFV co-administration) Co-administration recommended only with ATV/r or EFV; not recommended with LPV/r, DRV/r, or FPV/r Must be used in combination with peginterferon and ribavirin	• Rash • Pruritus • Nausea, vomiting • Fever • Anorexia • Dizziness • Anemia • Elevated LFTs	No human data	Not recommended in combination with interferon and ribavirin in pregnancy Because goal of HCV treatment is to prevent long-term sequelae, treatment in pregnancy is rarely indicated
Thalidomide (Thalomid®) **FDA pregnancy category: X**	**Treatment of aphthous ulcers and/or wasting:** 50–200 mg po qd	• Sedation • Rash • Neuropathy • Constipation • Neutropenia (up to 50%)	High potential for birth defects, including absent or abnormal limbs; cleft lip; absent ears; heart, renal, or genital abnormalities Single dose can be associated with teratogenic effects	Contraindicated in pregnancy and in women at risk for pregnancy (not using effective contraception or trying to conceive)

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Trimethoprim–sulfamethoxazole (TMP-SMX) (Bactrim®, Septra®, Cotrim®, Sulfatrim®) **FDA pregnancy category: C**	**PCP prophylaxis:** • 1 DS po qd • 1 SS po qd • 1 DS po tiw **PCP treatment:** 5 mg/kg (based on trimethoprim component) po or IV q 8 h	• Fever • Leukopenia • Rash and/or GI intolerance (25%–50% of patients with HIV); most tolerate readministration of lower dose after 2 wk of d/c • Megaloblastic anemia • Neutropenia • Thrombocytopenia • Hematologic toxicity increased with folate depletion and high doses; treat with leucovorin 3–15 mg q d x 3 d • Reversible hyperkalemia (with high doses) • Photosensitivity • Renal failure • Hemolytic anemia with G6PD deficiency • Hepatitis including cholestatic jaundice • Thrush • Erythema multiforme • Stevens–Johnson syndrome	Cleft palate has been observed in some animals In case-control studies, TMP has been associated with an increased risk of neural tube defects and cardiovascular, urinary tract, and multiple anomalies after 1st-trimester exposure, but folic acid supplementation (up to 6 mg) decreased risk of birth defects (*N Engl J Med* 2000;343(22):1608; *Reprod Toxicol* 2001;15(6):637) In a surveillance study of Michigan Medicaid recipients, 2,296 exposures to TMP-SMX in 1st trimester resulted in a 5.5% incidence of birth defects. This suggests an association with congenital defects (cardiovascular); however, confounding factors such as maternal disease, concurrent drug use, etc., may be involved (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005)	Most authorities consider sulfonamides safe in pregnancy. Clinicians may consider use of supplemental folic acid (>0.4-mg/d routinely recommended) in 1st trimester for pregnant women on TMP-SMX, but use should be limited to 1st trimester. Ultrasound at 18–20 wk recommended to assess fetal anatomy after 1st-trimester exposure Theoretical risk of kernicterus in neonate if administered near term TMP-SMX is recommended for treatment and prophylaxis of PCP and prophylaxis of toxoplasmosis in pregnancy Agent of choice for treatment and secondary prophylaxis for isosporiasis in pregnancy

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Valacyclovir (Valtrex®) **FDA pregnancy category: B**	**Treatment of zoster:** 1000 mg po tid **Recurrent HSV:** 1000 mg po bid **HSV suppression:** 500 mg po bid	• GI intolerance: nausea, vomiting, diarrhea • Headache • Constipation	Not teratogenic in animal studies Use during pregnancy appears to be safe and well tolerated, though data are limited (*JAMA* 2010;304:859)	Can be used for treatment and suppression of genital HSV infections and as treatment for uncomplicated chicken pox or shingles in pregnancy Valacyclovir is converted to acyclovir Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 wk gestation for pregnant women with recurrences of genital herpes to reduce need for Cesarean delivery (*Obstet Gynecol* 2007;109:1489) No known benefit of suppressive therapy for women who are seropositive for HSV-2 without a history of genital lesions

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Valganciclovir (Valcyte®) **FDA pregnancy category: C**	**Induction:** 900 mg po bid w/ food x 3 wks **Maintenance:** 900 mg po qd	• Diarrhea • Nausea • Fever • Bone marrow suppression • Elevated LFTs	Embryotoxic in rabbits and mice; teratogenic in rabbits in concentrations comparable to those achieved in humans: cleft palate, anophthalmia, hydrocephalus, aplastic kidney and pancreas (rabbits); growth retardation No experience reported with use in human pregnancy, but concerns are expected to be same as those for ganciclovir	On basis of limited data, toxicity reports and studies, and ease of use of various drugs, valganciclovir is recognized as treatment of choice during pregnancy Monitor fetus with fetal movement counts in 3rd trimester and periodic ultrasounds after 20 wk gestation for evidence of significant anemia, manifest as hydrops fetalis Evaluate newborn for bone marrow suppression
Voriconazole (Vfend®) **FDA pregnancy category: D**	• 6 mg/kg IV q 12 h x 2 doses (load), then 3–4 mg/kg IV q 12 h infused over 1–2h • **>40 kg:** 200 mg po tid x 1 d (load), then 200–300 mg po bid • **<40 kg:** 100 mg po q 12 h; may be increased to 150 mg po q 12 h Administer on an empty stomach; avoid high-fat food	• Common: abnormal vision, described as blurriness, color changes, enhanced vision (20.6%, but <1% required d/c) • Occasional: LFTs (13%), alkaline phosphatase (4%–8% of patients with hepatitis require d/c); hallucination (4.3%); rash (6%); nausea, vomiting	Teratogenic and embryotoxic in animal studies at doses lower than recommended human doses No adequate controlled studies	Avoid in pregnancy Do not use with RTV (400 mg bid) Check for potential drug-drug interactions (see Table 13-9, p. 505 for specific recommendations) Monitor trough concentrations for invasive fungal infections (goal >1–2 mcg/mL)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix
Source: *Medical Management of HIV Infection*, 16th ed. 2012. Durham, NC: Knowledge Source Solutions

Notes: 1. At the time of publication of this guide, the FDA was preparing a revision of drug categories for pregnancy and lactation that will likely do away with the current letter categories. 2. Unless otherwise noted, all data are taken from FDA labeling.

Table 13-4

Safety of Commonly Used Antimicrobials

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Aminoglycosides **FDA pregnancy category: D**	Fetotoxicity reported in rodent studies	Toxicity to eighth cranial nerve in fetus is well documented with exposure to kanamycin and streptomycin and can potentially occur with other aminoglycosides	If possible, streptomycin should be avoided as part of TB treatment in pregnancy Gentamicin is FDA pregnancy category C, although it has the same potential adverse effects. Use as preferred aminoglycoside if treatment is indicated. Amikacin or capreomycin might be alternatives when an aminoglycoside is required for treatment of MDR TB
Aztreonam **FDA pregnancy category: B**	Animal studies indicate no harm to fetus	No clinical data in pregnancy	Likely to be safe in pregnancy but, because of lack of data, use only if benefits are thought to outweigh potential risk
Cephalosporins **FDA pregnancy category: B**	Not teratogenic or fetotoxic	Extensive pregnancy exposure not associated with birth defects	Usually considered safe to use in pregnancy
Chloramphenicol **FDA pregnancy category: C**	No animal data	A collaborative perinatal project monitored 98 1st- trimester exposures and 348 exposures anytime during pregnancy; no relationship was found between chloramphenicol and congenital malformations (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005)	Although there is no evidence of teratogenicity, chloramphenicol should not be used near term because of potential for development of "gray baby" syndrome and possible infant death due to cardiovascular collapse

Table 13-4 *continued*

Safety of Commonly Used Antimicrobials

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Clindamycin **FDA pregnancy category: B**	No fetal harm demonstrated in rat studies Cleft palate observed in one mouse strain	In a surveillance study of Michigan Medicaid recipients, 647 1st-trimester exposures to clindamycin resulted in a 4.8% incidence of birth defects. Patterns of anomalies do not support an association between clindamycin and congenital effects (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005).	Usually considered safe to use in pregnancy
Erythromycin **FDA pregnancy category: B**	No teratogenic effect in rat studies	In a surveillance study of Michigan Medicaid recipients, 6972 1st-trimester exposures to erythromycin resulted in a 4.6% incidence of birth defects. Patterns of anomalies do not support an association between erythromycin and congenital malformations (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005).	Avoid estolate salt due to hepatotoxicity in 10% of patients. Other forms of erythromycin are usually considered safe to use in pregnancy.
Fluoroquinolones **FDA pregnancy category: C**	Animal data indicate arthropathy that resulted in erosions in joint cartilage in immature animals	Congenital malformation rate was 4.8% in a prospective follow-up study of 666 cases of fluoroquinolone exposure (most during 1st trimester); this did not exceed previously reported background rate (Eur J Obstet Gynecol Reprod Biol 1996;69:83) A registry study of >1100 quinolone exposures during pregnancy found no increase in rate of birth defects (*Pharmacoepidemiol Drug Saf* 2004;13(S1):S206)	Fluoroquinolones can be used in pregnancy as alternative antibiotics when indicated

Table 13-4 *continued*

Safety of Commonly Used Antimicrobials

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Imipenem **FDA pregnancy category: C**	No evidence of teratogenicity Increased embryologic loss has been observed in monkeys at 0.6 x maximal recommended human dose Maternal toxicity observed in pregnant rabbits and monkeys—weight loss, nausea, diarrhea, and death in some cases	Limited data in pregnancy have not shown an increased risk of malformations	Because of limited human data, use only for serious infections when potential benefits outweigh risk
Meropenem **FDA pregnancy category: B**	No evidence of teratogenicity	No clinical data in pregnancy	Because of limited human data, use only for serious infections when potential benefits outweigh risk
Metronidazole **FDA pregnancy category: B**	Animal (rodents) data indicate risk of carcinogenicity	In 4 studies (2 meta-analyses, a population-based case-control study, and a prospective controlled cohort study) no increased risk in birth defects was found (*Teratology* 2001;63:186; *Br J Obstet Gynecol* 1998;105:322; *Br J Clin Pharmacol* 1997; 44:179; *Am J Obstet Gynecol* 1995;172:525)	Most authorities consider use of metronidazole safe in 2nd and 3rd trimesters Use with caution in 1st trimester
Nitrofurantoin **FDA pregnancy category: B**	Not teratogenic or fetotoxic in rat and rabbit studies	In a surveillance study of Michigan Medicaid recipients, 1292 exposures to nitrofurantoin resulted in a 4.0% incidence of birth defects. These data did not support an association between nitrofurantoin and congenital defects (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005).	Most authorities consider use of nitrofurantoin safe in pregnancy

Table 13-4 *continued*

Safety of Commonly Used Antimicrobials

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Penicillins **FDA pregnancy category: B**	Carcinogenicity demonstrated in rats after prolonged subcutaneous administration of penicillin in peanut oil	Several collaborative perinatal project reports involving >12,000 exposures to penicillin derivatives during 1st trimester indicated no association between penicillin derivative drugs and birth defects (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005).	Usually considered safe to use in pregnancy
Tetracyclines **FDA pregnancy category: D**	Teratogenic in animal studies, resulting in retardation of skeletal development and embryotoxicity	Contraindicated in pregnancy due to retardation of skeletal development and bone growth, enamel hypoplasia, and discoloration of fetal teeth. Maternal liver toxicity also reported (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005).	Contraindicated in pregnancy
Vancomycin **FDA pregnancy category: C**	No animal data	Manufacturer has received reports of use during pregnancy without adverse fetal effects	Consider use only when benefit outweighs risk of drug administration

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *Medical Management of HIV Infection*, 16th ed. 2012. Durham, NC: Knowledge Source Solutions

Table 13-5

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
ACNE, SEVERE		
Retinoids (isotretinoin, etretinate) **FDA pregnancy category: X**	Isotretinoin is associated with spontaneous abortion (incidence up to 40%; major malformations (up to 15%); defects in multiple organ systems Etretinate, which is used for treatment of acne and psoriasis, is stored in adipose tissue and has an extremely long half-life. In 30 cases of pregnancy exposure, 30% had congenital defects (*J Gynecol Obstet Biol Reprod* 1993; 22(1):43).	Contraindicated in women who are pregnant, trying to become pregnant, or not using effective contraception. FDA restricted distribution program requires monthly pregnancy tests and recommends two simultaneous forms of effective contraception. Patients taking etretinate are advised not to conceive for at least 2 y following cessation of treatment because of the drug's long half-life: etretinate has been detected in serum up to 3 y after cessation of chronic treatment
ASTHMA: It is safer for pregnant women with asthma to be treated than to have asthma symptoms and exacerbations, with possible maternal and fetal hypoxia		
Rescue therapy	Generally considered safe in pregnancy; no evidence of increased defects	Inhaled short-acting beta-2 agonist is therapy of choice; inhaled albuterol is preferred
Long-term control	Theophylline has more side effects, a narrow therapeutic index, and requires serum monitoring Few data on use of leukotriene receptor antagonists in pregnancy Low- to moderate-dose inhaled steroids effective and considered safe in pregnancy (inhaled budesonide FDA category B) Systemic steroids may increase risk of cleft palate; may also be associated with increased risk of maternal hypertension, glucose intolerance, and infection Inhaled bronchodilators regarded as relatively safe in pregnancy	Treatment depends on severity and response to medications; stepwise approach to therapy is recommended In general, inhaled corticosteroids are first-line treatment, with budesonide preferred, followed by increasing doses of steroids and/or addition of long-acting beta-agonist (e.g., salmeterol) Severe asthma may require regular oral corticosteroid use to achieve adequate control

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
CANCER		
Antimetabolites (e.g., 5-fluorouracil, methotrexate, cytarabine) **FDA pregnancy category: X (most)**	In general, antineoplastic agents given in 1st trimester may have teratogenic effects. In 2nd and 3rd trimesters, they may result in intrauterine growth restriction.	Management of cancer in pregnancy depends on type of malignancy, stage and expected rate of progression, specific treatment needed, and gestational age
Alkylating agents (e.g., busulfan, chlorambucil, cyclophosphamide, mechlorethamine, cisplatin, bleomycin, vinblastine) **FDA pregnancy category: D (most)**	In general, antineoplastic agents given in 1st trimester may have teratogenic effects. In 2nd and 3rd trimesters, they may result in intrauterine growth restriction.	Successful treatment of cancer while continuing with a pregnancy may be possible in individual cases with expert consultation. Other options include deferral of treatment until after delivery (with possible early delivery) and termination of pregnancy.
Tamoxifen **FDA pregnancy category: D**	Little data in human pregnancy; some reports of defects Increased pregnancy loss in some animal studies. Results of animal studies suggest tamoxifen may cause developmental genital-tract abnormalities and that an interval of several years could exist between in utero exposure and clinical manifestations. Similar to DES in structure and activity in experimental systems	Avoid use in pregnancy and in women who are trying to conceive or are not using effective contraception Long-term follow-up recommended for exposed infants for adverse effects, including carcinogenicity

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
GLUCOSE INTOLERANCE/DIABETES: Pregnancy increases risk for glucose intolerance. No definite evidence that pregnant women on PIs are at increased risk for diabetes. Poorly controlled pregestational diabetes is associated with significant increased risk of adverse maternal and fetal outcomes, including worsening of end-organ damage, preeclampsia, congenital anomalies, intrauterine fetal death, excessive fetal growth, etc. Gestational diabetes is associated with increased risk for hypertensive disorders, macrosomia, newborn hyperbilirubinemia, shoulder dystocia and birth trauma, and need for cesarean delivery.		
Oral hypoglycemics	Not well studied in pregnancy Glyburide does not cross placenta; no evidence of adverse maternal and neonatal complications with use of this agent Metformin has been used in pregnancy, but long-term effects of in utero exposure are not well studied	Use of all oral agents for control of type 2 diabetes during pregnancy should be limited and individualized Glyburide may be considered for treatment of gestational and type 2 diabetes mellitus
Insulin	Insulin requirements increase throughout pregnancy	Safe to use in pregnancy
HYPERTENSION: Chronic HTN is associated with potentially significant maternal and fetal adverse outcomes: preterm delivery, intrauterine growth restriction, fetal death, placental abruption, as well as, when severe, maternal cardiac decompensation, renal deterioration, and CNS hemorrhage. HTN in pregnancy defined as SBP ≥140 and/or DBP ≥ 90. Pharmacologic treatment is generally indicated with SBP >150–160 and/or DBP >100–110 (treatment of milder HTN not recommended unless underlying cardiac or renal disease is present, due to concerns about interference with placental blood flow/fetal growth). Distinguish HTN from PEC, which typically appears at >20 wk gestation, is associated with proteinuria and, when severe, with seizures and hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). PEC alone is associated with normal BP prior to pregnancy and resolves after delivery; superimposed PEC is more common in setting of chronic HTN.		
Alpha-2 agonist (methyldopa)	Extensive experience in pregnancy and appears safe; limited effects on uteroplacental blood flow	Methyldopa safe to use in pregnancy and generally considered a first-line agent

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
Alpha and beta blockers **Atenolol – FDA pregnancy category: D** **Metoprolol**	Beta-blockers associated with small-for-gestational-age infants	Labetalol (alpha and beta blocker) better tolerated and considered an alternative to methyldopa IV labetalol considered safer than IV hydralazine and does not decrease placental perfusion Atenolol not recommended In pregnancy. Data on other beta blockers is limited, but they may be considered if benefit outweighs potential risk. Monitor fetal growth
Calcium channel blockers	Limited experience in pregnancy but no evidence of increase in adverse effects or defects	Use if benefit considered to outweigh potential risk. Nifedipine is preferred agent, with most experience.
Diuretics	Concerns have been raised about effects on normal blood volume expansion in pregnancy, but recent meta-analysis found no increase in adverse perinatal effects (*Can Fam Physician* 2009;*55*(1):44)	Considered safe and effective and not contraindicated in pregnancy, except when uteroplacental perfusion is decreased (e.g., PEC, intrauterine growth restriction)
ACE inhibitors (e.g., captopril, enalapril, lisinopril) **FDA pregnancy category:** **C (1st trimester)** **D (2nd and 3rd trimesters)**	Associated with oligohydramnios, pulmonary hypoplasia, skull hypoplasia, fetal and neonatal renal failure and death Use in 1st trimester before development of renal tubular function not associated with defects	Contraindicated in pregnancy, particularly in 2nd and 3rd trimesters If patient becomes pregnant while taking an ACE inhibitor, alternative treatment is recommended; if not possible, fetus should be monitored closely with ultrasound
Angiotensin II receptor blockers **FDA pregnancy category:** **C (1st trimester)** **D (2nd and 3rd trimesters)**	Concerns similar to those for ACE inhibitors	Contraindicated in pregnancy, particularly in 2nd and 3rd trimesters If patient becomes pregnant while taking an ARB, alternative treatment is recommended; if not possible, fetus should be monitored closely with ultrasound

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
LIPID DISORDERS		
HMG-CoA reductase inhibitors (statins) **FDA pregnancy category: X (all)**	Possible increased risk for defects, particularly with atorvastatin, lovastatin, simvastatin, cerivastatin; also potential increased risk for other adverse neonatal outcomes	Contraindicated in pregnancy and should not be administered to women who are trying to become pregnant or not using effective contraception If pregnancy occurs, discontinue statin use. Treatment can resume after delivery; this interruption is not believed to adversely effect overall outcomes.
NAUSEA AND VOMITING: "Morning sickness" is very common, and generally resolves spontaneously toward end of 1st trimester. Hyperemesis gravidarum is at the extreme end of the spectrum and is a common indication for hospital admission during pregnancy; multiple gestation, molar pregnancy are risk factors. N/V first presenting after 9 wk gestation: rule out other conditions (e.g., gastroenteritis, pyelonephritis, hepatitis, pancreatitis, ulcer, drug toxicity/intolerance, acute fatty liver of pregnancy). Hyperemesis has been associated with Wernicke's encephalopathy due to vitamin B1 deficiency, with resultant risk of permanent neurologic disability and low-birth-weight infants. There are concerns about adherence/absorption in women with hyperemesis on ARVs.		
Antihistamine H_1 receptor antagonists (Pyridoxine +/-doxylamine) **Phenothiazines** **Benzamides** **Anticholinergics** **Metoclopramide** **5-hydroxytryptamine-3 inhibitors** (ondansetron) **Corticosteroids**	Good safety data for vitamin B6, doxylamine, phenothiazines, trimethobenzamide; data more limited for other agents but benefits considered to outweigh risk in severe N/V Droperidol associated with prolonged QT interval and potentially fatal arrhythmia Association between use of methylprednisolone use in 1st trimester and oral clefts, though risk is small	Treatment of N/V in pregnancy with ginger has shown beneficial effects and may be considered a nonpharmacologic option Step-wise additive management is recommended: vitamin B6 (pyridoxine), doxylamine, promethazine or dimenhydrinate, metoclopramide or trimethobenzamide, methylprednisolone or ondansetron Use corticosteroids with caution and avoid if possible in 1st trimester IV hydration as needed to prevent/treat dehydration; include dextrose and vitamins, especially thiamine, with prolonged vomiting For severe and/or refractory hyperemesis, particularly with persistent weight loss, consider enteral or parenteral nutrition; enteral nutrition is preferred and may allow continued administration of ARVs

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
PAIN		
Acetaminophen	No evidence of association with birth defects	Considered safe for short-term use in all stages of pregnancy Preferred analgesic/antipyretic during pregnancy
Aspirin	High-dose aspirin is FDA pregnancy category D in 3rd trimester; may increase risk for maternal or newborn hemorrhage, particularly at higher doses. Use of aspirin in 3rd trimester may result in premature closure of ductus arteriosus and may prolong gestation and labor.	Use of aspirin, especially of chronic or intermittent high doses, should generally be avoided in pregnancy; however, low-dose aspirin may be used for thromboprophylaxis in pregnancy in some high-risk conditions (e.g., antiphospholipid syndrome)
Nonsteroidal anti-inflammatory drugs **FDA pregnancy category: C→D** ≥30 wk gestation	3rd-trimester concerns include risk of premature closure of ductus arteriosus, oligohydramnios, possible increased risk of necrotizing enterocolitis or intraventricular hemorrhage, persistent pulmonary hypertension in neonate, and prolonged pregnancy	Generally avoid use of NSAIDs in pregnancy
Narcotics		Narcotic analgesics can be used short term in pregnancy. Avoid use of high doses for prolonged periods near term as neonatal respiratory depression and withdrawal can occur.
PSYCHIATRIC ILLNESS: Inadequate treatment may result in adverse maternal and infant outcomes, including nonadherence to care, increased substance use, premature birth, low-birth-weight infants, etc. Multidisciplinary management recommended. A single medication at a higher dose is recommended over multiple medications. Use nonpharmacologic treatment when feasible (e.g., psychotherapy). Electroconvulsive therapy is safe to use in pregnancy if needed for severe depression. When medication is needed, drugs with fewer metabolites, higher protein binding (decreases placental transfer), and fewer drug interactions are preferred. Select drugs based on history of efficacy and available reproductive safety information.		
Benzodiazepines (Clonazepam, lorazepam, alprazolam) **FDA pregnancy category: D**	Possible small increased incidence of cleft lip/palate; possible neonatal withdrawal syndrome	Do not abruptly withdraw in pregnancy. In general, avoid in pregnancy; use based on risk vs benefit considerations.

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
Nonbenzodiazepine anxiolytics and hypnotics (Buspirone, zolpidem)	Data limited in pregnancy but no increase in defects noted	
Antidepressants (SSRIs, SNRIs, tricyclics, etc.) (Fluoxetine, sertraline, citalopram, nortriptyline, bupropion)	No confirmed increased incidence of birth defects, though some conflicting data for SSRIs; some studies have reported increased risk of cardiac defects, specifically with paroxetine, though absolute risk small Decreased serum concentrations in pregnancy; possible neonatal withdrawal syndrome; unconfirmed association reported with SSRIs and newborn persistent pulmonary hypertension Limited data for bupropion but no evidence of increase in defects	Individualize treatment based on risk vs benefits; avoid use of paroxetine if possible but also avoid abrupt discontinuation (associated with withdrawal symptoms) Consider fetal echocardiography with early-pregnancy exposure to paroxetine
Lithium **FDA pregnancy category: D**	Increased incidence of heart defects; decreased serum concentrations in pregnancy; potential increased risk for lithium toxicity in neonate	Use only if benefits thought to outweigh risks If indicated, use sustained-release formulation Monitor lithium levels Consider fetal echocardiography
Antipsychotics	No confirmed increase in birth defects; possible risk for neuroleptic malignant syndrome and intestinal obstruction in neonate	Minimize doses to limit need to utilize medications for extrapyramidal side effects Atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone) generally better tolerated and may be more effective, but have very limited safety data in pregnancy; avoid routine use Options for typical antipsychotics include haloperidol, trifluoperazine, perphenazine

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
SEIZURE DISORDERS		
Phenytoin **Phenobarbital** **Carbamazepine** **Valproate** **Lamotrigine** **Topiramate** **All FDA pregnancy category D (except lamotrigine: category C)**	Increased incidence in both major and minor malformations associated with all anti-seizure medications; most common major malformations are NTDs, congenital heart and urinary-tract defects, skeletal abnormalities, and cleft palate Valproate associated with higher rates of defects and may have increased placental transfer Lamotrigine may have lower risk of defects In-utero exposure to anti-seizure medications may be linked to impaired cognitive outcomes in childhood Limited human information on fetal risks of newer drugs (gabapentin, felbamate, tiagabine, levetiracetam, pregabalin) Decreased serum concentrations in pregnancy Oral hormonal contraceptive failure before or after pregnancy may be increased due to drug interaction with cytochrome P450-inducing anti-seizure medications (carbamazepine, phenytoin, phenobarbital, felbamate, oxcarbazepine, topiramate), resulting in decreased hormone levels	Several anticonvulsants also used in treatment of bipolar disorder If anti-seizure medications cannot be withdrawn in pregnancy, administer most suitable medication for seizure type. No consensus exists as to which medication is most teratogenic; with exception of valproate, most effective agent for individual patient should be given. Use lowest effective dose; if possible avoid combination therapy to limit risk of teratogenicity Monitor drug levels in plasma throughout pregnancy If possible avoid valproate in pregnant women and in women who are trying to conceive or are not using effective contraception Consider increased preconception folate supplementation (4 mg qd) for women on anti-seizure medications, particularly those on valproate or carbamazepine, to reduce risk of NTDs Oral vitamin K (10mg/d) supplementation in last month of pregnancy recommended in patients on enzyme-inducing anti-epileptic drugs (e.g phenytoin, phenobarbital, carbamazepine) Prenatal surveillance for defects with serum alpha-fetoprotein; fetal echocardiography and detailed ultrasound of fetal anatomy

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
THYROID DISEASE		
Thioamides (for hyperthyroidism; methimazole, propylthiouracil) **FDA pregnancy category: D**	Untreated hyperthyroidism associated with increased risk for preterm delivery, severe preeclampsia, heart failure, low birth weight, possible fetal loss. Neonates may be at risk of hyper- or hypothyroidism due to transplacental passage of antibodies in Graves disease or autoimmune thyroiditis. Recent data suggest no significant increase in defects with either PTU or methimazole	Either PTU or methimazole can be used to treat pregnant women with hyperthyroidism. Beta blockers may be used during pregnancy to ameliorate symptoms of thyrotoxicosis until thioamides decrease thyroid hormone levels. Iodine 131 contraindicated in pregnant women because of risk of fetal thyroid ablation
Levothyroxine (for hypothyroidism)	Untreated hypothyroidism associated with increased risk of preeclampsia and possible fetal growth restriction	Safe to use in pregnancy Treatment of hypothyroidism using levothyroxine in pregnant women is same as for nonpregnant women
VENOUS THROMBOEMBOLISM (TREATMENT OR PROPHYLAXIS)		
Low-molecular-weight heparin (enoxaparin, dalteparin, tinzaparin) **Unfractionated heparin** **Warfarin – FDA pregnancy category: X**	Warfarin has been associated with fetal hemorrhage and anomalies in all three trimesters	LMWH is preferred UFH is alternative; consider transition to UFH at 36 wk gestation Protamine sulfate can be used if rapid reversal of anticoagulant effect is needed Also consider graduated compression stockings in pregnancy and pneumatic compression boots in intrapartum period Warfarin contraindicated in pregnancy

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix. FDA pregnancy categories noted only for those drugs that are category D or X
Source: ACOG

Table 13-6

Alternative/Complementary Medication Concerns in Pregnancy

Substance	Animal Data and Human Experience	Use in Pregnancy, Possible Health Hazards, Comments
Comfrey (herb)	No animal data No human experience in pregnancy	Avoid; possible obstruction of blood flow to liver; may lead to death
Chaparral (herb; used in traditional American Indian medicine)	No animal data No human experience in pregnancy	Avoid; liver disease; may be irreversible
Germander (herb)	No animal data No human experience in pregnancy	Avoid; liver disease; may lead to death
Germanium (mineral)	No animal data No human experience in pregnancy	Avoid; kidney damage; possibly death
L-tryptophan (amino acid)	No animal data No human experience in pregnancy	Avoid; eosinophilic myalgia syndrome, a potentially fatal blood dyscrasia FDA has limited import of L-tryptophan into U.S.
Lobelia (herb; Indian tobacco)	No animal data No human experience in pregnancy	Avoid; respiratory distress, tachycardia, hypotension; possibly coma and death at higher doses
Ma-huang (*Ephedra sinica*)	No animal data No human experience in pregnancy	Avoid; FDA warns of possible health hazards, including high BP, irregular heartbeat, nerve damage, injury, insomnia, tremor, headache, seizure, heart attack, stroke, death FDA has received >500 reports of adverse events, including 8 fatalities (*MMWR* 1996;45:689)
Magnolia-Stephania (herbs)	No animal data No human experience in pregnancy	Avoid; renal failure; possibly irreversible

Table 13-6 *continued*

Alternative/Complementary Medication Concerns in Pregnancy

Substance	Animal Data and Human Experience	Use in Pregnancy, Possible Health Hazards, Comments
Niacin (in doses >500 mg immediate-release or >750 mg sustained-release)	No animal data No human experience in pregnancy	Avoid use of high doses in pregnancy GI symptoms (nausea, vomiting, diarrhea, abdominal cramps); liver disease
St. John's wort (*Hypericum perforatum*)	No animal data No human experience in pregnancy	Meta-analysis suggests St. John's wort more effective than placebo and as effective as low-dose tricyclic antidepressants for short-term management of mild to moderately severe depression (*J Nerv Ment Dis* 1999;187(9):532) Due to lack of data in pregnancy, routine use of St. John's wort cannot be recommended Major drug interaction: indinavir trough concentration decreases by 81% when co-administered with St. John's wort. This interacton applies to all PIs and NNRTIs.
Selenium (in doses >800–1000 mcg/d)	No animal data No human experience in pregnancy	Avoid high doses in pregnancy; possible tissue damage*
Slimming/dieter's tea	No animal data No human experience in pregnancy	Avoid; nausea, diarrhea, vomiting, stomach cramps, chronic constipation, fainting; possibly death

Table 13-6 *continued*

Alternative/Complementary Medication Concerns in Pregnancy

Substance	Animal Data and Human Experience	Use in Pregnancy, Possible Health Hazards, Comments
Vitamin A	Animal data: known teratogen at high doses Human data: Double-blinded randomized trial of low-dose supplementation with vitamin A or beta-carotene (7000 mcg retinol equivalent) in malnourished pregnant women reported a 40% decrease in newborn mortality (*BMJ* 1999;318(7183):570) In a prospective case-controlled study of 423 exposures to 10,000 IU vitamin A during first 9 wk of pregnancy, an increased risk of major malformations was not reported (*Teratology* 1999;59:7)	Until more data are available it is prudent to consume only RDA of 8000 IU, which can be obtained through a balanced diet
Vitamin B6 (in doses >100 mg/d)	No animal data No human experience in pregnancy	Avoid high doses in pregnancy; ataxia, peripheral neuropathy
Willow bark (herb)	No animal data No human experience in pregnancy	Avoid; allergic reaction Although marketed as aspirin-free, contains a precursor of aspirin, with subsequent conversion to aspirin
Wormwood (herb)	No animal data No human experience in pregnancy	Avoid; neurological symptoms, paresthesia, delirium, paralysis

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *Medical Management of HIV Infection*, 16th ed. 2012. Durham, NC: Knowledge Source Solutions

Table 13-7

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS			
Stribild should not be initiated in patients with CrCl <70 mL/min. Use of the following fixed-dose combinations is not recommended in patients with CrCl <50 mL/min: Atripla, Combivir, Stribild, Trizivir, or Epzicom. Use of Truvada is not recommended in patients with CrCL <30 mL/min.			
Abacavir (ABC)/Ziagen	300 mg PO BID	No dosage adjustment necessary	**Child-Pugh Score** / **Dose** 5–6: 200 mg PO BID (use oral solution) >6: Contraindicated
Didanosine EC (ddI)/Videx EC	**Body weight ≥60 kg:** 400 mg PO once daily **Body weight <60 kg:** 250 mg PO once daily	**Dose (once daily)** **CrCL (mL/min)** / **≥60 kg** / **<60 kg** 30–59: 200 mg / 125 mg 10–29: 125 mg / 125 mg <10, HD, CAPD: 125 mg / use ddI oral solution	No dosage adjustment necessary
Didanosine oral solution (ddI)/Videx	**Body weight ≥60 kg:** 200 mg PO BID **or** 400 mg PO once daily **Body weight <60 kg:** 250 mg PO once daily **or** 125 mg PO BID	**Dose (once daily)** **CrCL (mL/min)** / **≥60 kg** / **<60 kg** 30–59: 200 mg / 150 mg 10–29: 150 mg / 100 mg <10, HD, CAPD: 100 mg / 75 mg	No dosage adjustment necessary

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS continued			
Emtricitabine (FTC)/Emtriva	200 mg oral capsule once daily **or** 240 mg (24 mL) oral solution once daily	**Dose** **CrCL (mL/min)** — **Capsule** — **Solution** 30–49 — 200 mg q48h — 120 mg q24h 15–29 — 200 mg q72h — 80 mg q24h <15 or on HD* — 200 mg q96h — 60 mg q24h *On dialysis days, take dose after HD session.	No dosage recommendation
Lamivudine (3TC)/Epivir	300 mg PO once daily **or** 150 mg PO BID	**CrCL (mL/min)** — **Dose** 30–49 — 150 mg q24h 15–29 — 1 × 150 mg, then 100 mg q24h 5–14 — 1 × 150 mg, then 50 mg q24h <5 or on HD* — 1 × 50 mg, then 25 mg q24h *On dialysis days, take dose after HD session.	No dosage adjustment necessary

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS continued			
Stavudine (d4T)/Zerit	**Body weight ≥60 kg:** 40 mg PO BID **Body weight <60 kg:** 30 mg PO BID	**CrCL (mL/min)** / **Dose ≥60 kg** / **Dose <60 kg** 26–50: 20 mg q12h / 15 mg q12h 10–25 or on HD*: 20 mg q24h / 15 mg q24h *On dialysis days, take dose after HD session.	No dosage recommendation
Tenofovir (TDF)/Viread	300 mg PO once daily	**CrCL (mL/min)** / **Dose** 30–49: 300 mg q48h 10–29: 300 mg twice weekly (every 72–96 hours) <10 and not on HD: Not recommended On HD*: 300 mg q7d *On dialysis days, take dose after HD session.	No dosage adjustment necessary
Emtricitabine (FTC) + **Tenofovir** (TDF)/ Truvada	1 tablet PO once daily	**CrCL (mL/min)** / **Dose** 30–49: 1 tablet q48h <30 or on HD: Not recommended	No dosage recommendation

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS continued			
Zidovudine (AZT, ZDV)/ Retrovir	300 mg PO BID	**CrCL (mL/min)** — **Dose** <15 or HD* — 100 mg TID **or** 300 mg once daily *On dialysis days, take dose after HD session.	No dosage recommendation
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS			
Delavirdine (DLV)/Rescriptor	400 mg PO TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz (EFV)/Sustiva	600 mg PO once daily, at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz (EFV) + **Tenofovir** (TDF) + **Emtricitabine** (FTC)/Atripla	1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	No dosage recommendation; use with caution in patients with hepatic impairment.
Etravirine (ETR)/Intelence	200 mg PO BID	No dosage adjustment necessary	*Child-Pugh Class A or B:* No dosage adjustment *Child-Pugh Class C:* No dosage recommendation

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS continued			
Nevirapine (NVP)/Viramune or Viramune XR	200 mg PO BID **or** 400 mg PO once daily (using Viramune XR formulation)	*Patients on HD:* limited data; no dosage recommendation	*Child-Pugh Class A:* No dosage adjustment *Child-Pugh Class B or C:* Contraindicated
Rilpivirine (RPV)/Edurant	25 mg PO once daily	No dosage adjustment necessary	*Child-Pugh Class A or B:* No dosage adjustment *Child-Pugh Class C:* No dosage recommendation
Rilpivirine (RPV) + **Tenofovir** (TDF) + **Emtricitabine** (FTC)/Complera	1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses levels according to CrCl level.	*Child-Pugh Class A or B:* No dosage adjustment *Child-Pugh Class C:* No dosage recommendation
PROTEASE INHIBITORS			
Atazanavir (ATV)/Reyataz	400 mg PO once daily **or** (ATV 300 mg + RTV 100 mg) PO once daily	No dosage adjustment for patients with renal dysfunction not requiring HD *ARV-naïve patients on HD:* (ATV 300 mg + RTV 100 mg) once daily *ARV-experienced patients on HD:* ATV or RTV-boosted ATV not recommended	**Child-Pugh Class** / **Dose** B / 300 mg once daily C / Not recommended RTV boosting is ***not*** recommended in patients with hepatic impairment (Child-Pugh Class B or C).

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
PROTEASE INHIBITORS continued			
Darunavir (DRV)/Prezista	(DRV 800 mg + RTV 100 mg) PO once daily (ARV-naïve patients only) **or** (DRV 600 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	*Mild-to-moderate hepatic impairment:* No dosage adjustment *Severe hepatic impairment:* Not recommended
Fosamprenavir (FPV)/Lexiva	1400 mg PO BID **or** (FPV 1400 mg + RTV 100–200 mg) PO once daily **or** (FPV 700 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	*PI-naïve patients only:* **Child-Pugh Score** — **Dose** 5–9 — 700 mg BID 10–15 — 350 mg BID *PI-naïve or PI-experienced patients:* **Child-Pugh Score** — **Dose** 5–6 — 700 mg BID + RTV 100 mg once daily 7–9 — 450 mg BID + RTV 100 mg once daily 10–15 — 300 mg BID + RTV 100 mg once daily
Indinavir (IDV)/Crixivan	800 mg PO q8h	No dosage adjustment necessary	*Mild-to-moderate hepatic insufficiency becasue of cirrhosis:* 600 mg q8h

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
PROTEASE INHIBITORS continued			
Lopinavir/ ritonavir (LPV/r) Kaletra	400/100 mg PO BID **or** 800/200 mg PO once daily	Avoid once-daily dosing in patients on HD	No dosage recommendation; use with caution in patients with hepatic impairment.
Nelfinavir (NFV)/Viracept	1250 mg PO BID	No dosage adjustment necessary	*Mild hepatic impairment:* No dosage adjustment *Moderate-to-severe hepatic impairment:* Do not use
Ritonavir (RTV)/Norvir	*As a PI-boosting agent:* 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI.
Saquinavir (SQV)/Invirase	(SQV 1000 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	*Mild-to-moderate hepatic impairment:* Use with caution *Severe hepatic impairment:* Contraindicated
Tipranavir (TPV)/Aptivus	(TPV 500 mg + RTV 200 mg) PO BID	No dosage adjustment necessary	*Child-Pugh Class A:* Use with caution *Child-Pugh Class B or C:* Contraindicated

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
INTEGRASE INHIBITORS			
Raltegravir (RAL)/Isentress	400 mg BID	No dosage adjustment necessary	*Mild-to-moderate hepatic insufficiency:* No dosage adjustment necessary *Severe hepatic insufficiency:* No recommendation
Elvitegravir (EVG)/ **Cobicistat** (COBI)/ **Tenofovir** (TDF)/ **Emtricitabine** (FTC)/Stribild (only availabe as a co-formulated product)	1 tablet once daily	EVG/COBI/TDF/FTC **should not be initiated** in patients with CrCl <70 mL/min. Discontinue EVG/COBI/TDF/FTC if CrCl declines to <50 mL/min while patient is on therapy.	*Mild-to-moderate hepatic insufficiency:* No dosage adjustment necessary *Severe hepatic insufficiency:* Not recommended
FUSION INHIBITOR			
Enfuvirtide (T20)/Fuzeon	90 mg subcutaneous BID	No dosage adjustment necessary	No dosage adjustment necessary

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
CCR5 ANTAGONIST			
Maraviroc (MVC)/Selzentry	The recommended dose differs based on concomitant medications and potential for drug-drug interactions.	**CrCl <30 mL/min or on HD** *Without potent CYP3A inhibitors or inducers:* 300 mg BID; reduce to 150 mg BID if postural hypotension occurs *With potent CYP3A inducers or inhibitors:* Not recommended	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* Approved adult dose, but for most PIs lower doses are usually used with RTV boosting

** Prediction based on PK principles. Drugs likely to be removed have a Vd <0.7 L/kg, protein binding <80%, and size <1500 Dalton

Source: *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*

Table 13-8

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

	Drug Categories									
Anti-retroviral Agents[a,b]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Antimyco-bacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Anti-retroviral Agents**	**Others**
ATV +/– RTV	amiodarone dronedarone	lovastatin simvastatin	rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR NVP	alfuzosin irinotecan salmeterol sildenafil for PAH
DRV/r	amiodarone dronedarone	lovastatin simvastatin	rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
FPV +/– RTV	amiodarone dronedarone flecainide propafenone	lovastatin simvastatin	rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH

Table 13-8 *continued*

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

	Drug Categories									
Anti-retroviral Agents[a,b]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Antimyco-bacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Anti-retroviral Agents**	**Others**
LPV/r	amiodarone dronedarone	lovastatin simvastatin	rifampin[d] rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
SQV/r	amiodarone dronedarone dofetilide flecainide lidocaine propafenone quinidine	lovastatin simvastatin	rifampin[d] rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam trazodone	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort garlic supple-ments	none	alfuzosin salmeterol sildenafil for PAH
TPV/r	amiodarone dronedarone flecainide propafenone quinidine	lovastatin simvastatin	rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH

Table 13-8 *continued*

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

	Drug Categories									
Anti-retroviral Agents[a,b]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Antimyco-bacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Anti-retroviral Agents**	**Others**
EFV	none	none	rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St John's wort	other NNRTIs	none
ETR	none	none	rifampin rifapentine[c]	none	none	none	none	St John's wort	unboosted PIs ATV/r, FPV/r, or TPV/r other NNRTIs	carbama-zepine pheno-barbital phenytoin clopido-grel
NVP	none	none	rifapentine[c]	none	none	none	none	St. John's wort	ATV +/– RTV other NNRTIs	ketocon-azole

Table 13-8 *continued*

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

	Drug Categories									
Anti-retroviral Agents[a,b]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Antimyco-bacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Anti-retroviral Agents**	**Others**
RPV	none	none	rifabutin rifampin rifapentine[c]	proton pump inhibitors	none	none	none	St. John's wort	other NNRTIs	carbama-zepine oxcarba-zepine pheno-barbital phenytoin
MVC	none	none	rifapentine[c]	none	none	none	none	St. John's wort	none	none

Table 13-8 *continued*

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

Drug Categories										
Anti-retroviral Agents[a,b]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Antimyco-bacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Anti-retroviral Agents**	**Others**
EVG/ COBI/ TDF/FTC	none	lovastatin simvastatin	rifabutin rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergotamine methylergonovine	St. John's wort	All other ARVs	alfuzosin sildenafil for PAH

[a]DLV, IDV, NFV, and RTV (as sole PI) are not included in this table. Refer to the appropriate FDA package insert for information regarding DLV-, IDV-, NFV-, and RTV (as sole PI)-related drug interactions.

[b]Certain listed drugs are contraindicated on the basis of theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

[c]HIV-infected patients treated with rifapentine have a higher rate of tuberculosis (TB) relapse than those treated with other rifamycin-based regimens. Therefore an alternative agent to rifapentine is recommended.

[d]A high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect and therefore, these dosing strategies should not be used.

[e]Use of oral midazolam is contraindicated. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

Suggested alternatives to:

- **Lovastatin, simvastatin:** Fluvastatin, pitavastatin, and pravastatin (except for pravastatin with DRV/r) have the least potential for drug-drug interactions (see Table 15a). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
- **Rifampin:** Rifabutin (with dosage adjustment, see Tables 15a and 15b)
- **Midazolam, triazolam:** temazepam, lorazepam, oxazepam

Source: *Medical Management of HIV Infection,* 16th ed., 2012. Durham, NC: Knowledge Source Solutions

Table 13-9

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Antifungal agents	Itraconazole	• All PIs: Monitor for toxicities • Itraconazole ≤200 mg/d • EFV, NVP, ETR: ↓ itraconazole possible dose adjustments may be needed • EVG: ↑ itraconazole: itraconazole ≤200 mg/d • MVC: 150 mg bid
	Ketoconazole	• MVC: 150 mg bid
		• LPV/r, TPV/r, FPV/r, DRV/r, RTV: ketoconazole ≤200 mg/d • FPV: ≤400 mg/d
		• NVP: Consider fluconazole as an alternative • RPV AUC ↑ 49%; ketoconazole AUC ↓ 24%; monitor for breakthrough fungal infection
	Voriconazole	• EFV: contraindicated at standard doses • NPV: ↓ voriconazole possible, ↑ NVP possible: monitor for toxicity and antifungal response • All boosted PIs: significant ↓ in voriconazole levels: do not co-administer unless benefit outweighs risk • EVG: ↑ voriconazole: consider drug levels and adjust dose as needed • MVC: 150 mg bid
	Fluconazole	• ETR: AUC ↑ 86%; use with caution • NVP: AUC ↑; monitor for ADR or use alternative • PI/r; EFV, RAL, MVC: Use standard dose • With TPV/r co-administration, do not exceed fluconazole 200 mg/d

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Antifungal agents (*continued*)	Posaconazole	• ATV: concentrations may be increased; monitor for adverse effects • Do not co-administer with unboosted FPV • EFV: ↓ posaconazole level: avoid co-administration unless benefits outweigh risk • EVG: ↑ posaconazole: monitor posaconazole drug levels if co-administered
Anticonvulsants	Phenobarbital Phenytoin Carbamazepine	• Phenobarbital may decrease concentrations of all PIs: consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response • Carbamazepine: may decrease PI levels significantly (except for DRV): consider alternate anticonvulsant or monitor drug levels of both drugs and assess virologic response; DRV: monitor anticonvulsant level and adjust dose as needed • MVC: 600 mg bid if used without strong CYP3A inhibitor • Phenobarbital, carbamazepine, phenytoin: do not co-administer with ETR, RPV; NVP or EFV: ↓ anticonvulsant and ARV: monitor drug levels of both drugs, monitor virologic response and consider alternative anticonvulsant • EVG: ↑ carbamazepine possible: consider alternate anticonvulsant • Phenytoin: all boosted PIs ↓ phenytoin; ↓ ARV level with ATV/r, DRV/r, SQV/r, TPV/r, LPV/r: consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response
	Valproic acid	• LPV/r: AUC ↑ 75%; monitor valproic acid levels and virologic response; monitor for LPV-related toxicity
	Lamotrigine	• LPV/r: lamotrigine AUC ↓ 50%; dose increase of lamotrigine may be needed

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Narcotics/Treatment for Opioid Dependence	Methadone	• NVP, EFV: May significantly decrease methadone concentrations. Monitor for withdrawal symptoms. ↑ methadone dose often needed • RPV: Methadone ↓ 26%: monitor for withdrawal symptoms • TPV/r, LPV/r, SQV/r, DRV/r, ATV/r, SQV/r: May decrease methadone levels and require monitoring for withdrawal symptoms, but clinical significance is unclear
	Oxycodone	• LPV/r: ↑ oxycodone AUC 2.6 fold: monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary
	Buprenorphine	• ATV/r: ↑ buprenorphine 66%: monitor for sedation. Buprenorphine dose reduction may be necessary • TPV/r: ↓ TPV: consider monitoring TPV level

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Antimycobacterial agents	Rifabutin‡	• All PIs with RTV boosting: standard PI dose; Rifabutin dose 150 mg/dg or 300 mg 3x/wk. consider TDM • EFV: RBT 450–600 mg/d or 600 mg 3x/wk • MVC: 300 mg bid; 150 mg bid with PI co-administration • EVG: ↓ EVG: do not co-administer • ETR: rifabutin 300 mg qd, ETR SD; if ETR used with PI/r, rifabutin should not be co-administered • RPV: Contraindicated; do not co-administer
	Rifampin	• All PIs and NNRTIs contraindicated except EFV (600 mg/d) using SDs of rifampin. Monitor virologic response • MVC: co-administration not recommended • RAL: Avoid or use RAL 800 mg bid; monitor virologic response • EVG: ↓ EVG: do not co-administer

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Lipid-lowering agents	Simvastatin Lovastatin	• EVG: do not co-administer • All boosted PIs: Contraindicated • EFV, NVP, ETR: ↓ statin: adjust statin dose according to lipid response
	Atorvastatin	• All PIs may substantially increase levels. Use lowest possible dose of atorvastatin. • TPV/r: do not co-administer • EFV, ETR: May reduce atorvastatin levels; adjust atorvastatin dose according to lipid responses • EVG: titrate statin dose slowly and use lowest dose possible
	Pravastatin	• No dose change with most agents • DRV/r: May ↑ statin AUC 81%: use lowest possible starting dose of pravastatin with careful monitoring • EFV: ↓ statin level: Adjust statin dose according to lipid response
	Rosuvastatin	• ATV/r, LPV/r, DRV/r, SQV/r: titrate rosuvastatin dose carefully and use lowest necessary dose; monitor for toxicities • EVG: ↑ rosuvastatin level: titrate statin dose slowly and use lowest dose possible • RAL, MVC: Interaction unlikely
Calcium channel blockers (CCBs)		• All PIs: ↑ CCB level: Use with caution, titrate CCB dose and monitor closely; ECG monitoring recommended when CCB used with ATV • EFV, NVP: ↓ CCB level possible: titrate CCB dose based on clinical response • EVG: ↑ CCB level possible: co-administer with caution. Monitor for CCB efficacy and toxicity

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Contraceptives (See table 7-4)		
Corticosteroids	Budesonide (systemic)	• All PIs: ↓ PI levels, ↑ glucocorticoids: do not co-administer unless benefits outweigh risks: co-administration can result in adrenal insufficiency, including Cushing's syndrome
	Budesonide (inhaled or intranasal)	• All PI/r: ↑ glucocorticoids (see above recommendation)
	Dexamethasone	• All PIs: ↓ PI levels: use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use • EFV, NVP, ETR: ↓ ARV levels: consider alternate corticosteroid for long-term use. If dexamethasone used, monitor virologic response • RPV: ↓ significant RPV: contraindicated with >1 dose dexamethasone • EVG: ↓ EVG possible: co-administer with caution, monitor HIV virologic response
	Fluticasone (inhaled or intranasal)	• All PI/r: significant ↑ steroid level; do not co-administer unless benefits outweigh risks of systemic corticosteroid adverse effects • EVG: possible ↑ fluticasone: use alternative inhaled steroid especially for long-term use
	Prednisone	• LPV/r: ↑ prednisone ↓ LPV; Monitor virologic response. Do not co-administer unless benefits outweigh risks of systemic corticosteroid adverse effects

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Antidepressants	TCAs	• Boosted PI, EVG may ↑ TCA concentrations; use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels
	Bupropion	• LPV/r, TPV/r: ↓ bupropion: titrate dose based on clinical response • EFV: ↓ bupropion: titrate dose based on clinical response
	Trazodone	• ATV/r, LPV/r, DRV/r, TPV/r, FPV/r: use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects • EVG: possible ↑ trazodone: initiate with lowest dose and titrate carefully • SQV/r: Contraindicated
	Sertraline	• DRV/r, EFV: ↓ sertraline: titrate dose based on clinical response • EVG: ↑ SSRI possible: initiate with lowest dose and titrate based on clinical response

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Miscellaneous	H_2 blockers	• ATV/r: H_2 blocker dose should not exceed a dose equivalent to famotidine 40 mg bid in ART-naïve or 20 mg bid in ART-experienced • Administer ATV/r 400/100 if used with H_2 blocker and TDF • RPV: Administer H_2 blocker 12 h before or 4 h after RPV
	Clopidogrel	• ETR: May decrease efficacy of clopidogrel; avoid co-administration, if possible
	Warfarin	• Monitor INR closely if given with any PI or NNRTI (or EVG); adjust warfarin dose as needed • PI/r and RTV may ↓ INR at steady state
	Antacid	• RPV: ↓ RPV when given simultaneously; give antacids at least 2 hr. before or at least 4 hr. after RPV • ATV/r, TPV/r: give ARV at least 2 hr. before or 1 hr. after antacids or buffered medications • EVG: separate EVG and antacid administration by more than 2 hr.
	Proton Pump Inhibitors (PPIs)	• ATV/r: PPIs should not exceed a dose equivalent to omeprazole 20 mg/d in PI-naïve patients. PPIs should be administered at least 12 hrs. before ATV/r; PPIs are not recommended in PI-experienced patients • DVR/r, TPV/r: ↓ omeprazole; may need to ↑ omeprazole dose • SQV/r: ↑ SQV: monitor for toxicity • RPV: ↓ RPV: contraindicated, do not co-administer

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* RTV 100–200 mg/d may be given with voriconazole. May ↓ voriconazole concentrations. Monitor voriconazole levels.

† Do not coadminister ETR with DRV/r or SQV/r when combined with rifabutin

‡ For treatment of TB, most experts recommend rifabutin 150 mg qd with PI/r. Consider rifabutin therapeutic dose management.

§ Bepridil contraindicated with EFV; clinical significance unknown

Source: *Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents* (http://aidsinfo.nih.gov). Accessed 5/22/2013

Table 13-10

Clinically Pertinent Food-Drug Recommendations

Atazanavir Clarithromycin XL Darunavir Etravirine Itraconazole capsule Ribavirin Rifapentine Ritonavir Tipranavir Valganciclovir	Take with food or within 2 h of a meal
AZT	Can be taken with food to decrease GI side effects
Atovaquone Nelfinavir Rilpivirine	Take with high-fat meal
Efavirenz	Manufacturer recommends taking on empty stomach. Take on empty stomach to minimize risk of CNS side effects.
Didanosine* Indinavir (unboosted)† Isoniazid Itraconazole solution Voriconazole	Take on empty stomach (1 h before or 2 h after a meal)
Grapefruit juice	Increases saquinavir levels 40%–100%, but decreases indinavir AUC by 26%. Unlikely to be clinically significant with boosted PIs.

* No food restriction when ddI is co-administered with TDF, but this combination is generally not recommended due to potential for increased ddI toxicity and higher rates of virologic failure

† No food restriction when IDV is co-administered with RTV

Source: *Medical Management of HIV Infection,* 16th ed., 2012. Durham, NC: Knowledge Source Solutions