# XIV: Pharmacologic Considerations in HIV-infected Pregnant Patients

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## I. LIST OF TABLES



## II. INTRODUCTION

The decision to administer drugs to a pregnant woman is largely based on the therapeutic benefit to the mother and/or fetus versus the perceived risk to the developing fetus. Clinicians are usually advised to avoid prescribing drugs for pregnant patients since human safety data in pregnancy are lacking for many medications. However in some clinical situations the benefits far outweigh the risks. These are important considerations when selecting agents to treat patients with human immunodeficiency virus (HIV), to prevent its transmission, and to prevent associated opportunistic infections.

There is limited information concerning the safety of many antiretrovirals in pregnancy. Mutagenicity and teratogenicity studies in animals are the basis for most safety in pregnancy data. Animals are administered doses 5- to 20-times higher that those given to humans; clinical applicability is not always evident.

It is now standard care to treat for HIV-infected patients with an "antiretroviral cocktail" making it increasingly difficult to assess the safety of a single antiretroviral agent. More prospective clinical data are needed. Clinicians are

encouraged to report all in utero exposures to The Antiretroviral Pregnancy Registry (1-800-258-4263), a collaborative effort between the National Institutes of Health, Centers for Disease Control and pharmaceutical companies: Outcome data compiled from the Registry are used to monitor birth defects.

The Food and Drug Administration (FDA) has developed a classification system to help clinicians choose agents safe for use in pregnancy. (Tables 14-1, 14-2, 14-3, and 14-6)

## III. RISKS OF ANTIRETROVIRAL DRUGS IN PREGNANCY

Certain antiretroviral agents should be avoided during pregnancy, either because of effects inherent to the drug itself, or the potential for dangerous interactions. Administration of efavirenz to pregnant cynomolgus monkeys is associated with anenecephaly, unilateral anophthalmia, microopthalmia and cleft palate in newborns[1]. Hydroxyurea produces mutagenesis and teratogenesis in many animal species; it should not be given during pregnancy[2].

Antiretroviral therapy is often complicated by side effects in relatively healthy HIV-infected nonpregnant adults which could be exacerbated in pregnancy or put the fetus at risk. Protease inhibitors, for example, have been associated with the development of glucose intolerance and even diabetes mellitus. Hyperglycemia in pregnancy leads to increased risk of macrosomia, fetal distress, pre-eclampsia and stillbirth[3]. In patients taking indinavir, 10% develop indirect bilirubinemia (i.e., > 2.5%) and nephrolithiasis has been reported in 5-15%[4]. Any of these adverse effects will complicate a pregnancy.

Because many patients turn to so-called complimentary or alternative therapies, it is important to take a complete medication history, including over-the-counter drugs and nutritional supplements . St John's wort lowers trough indinavir drug concentrations (Cmin) by 81% when administered concurrently [Lancet 2000; 355(9203): 547-8]. Because St John's wort induces cytochrome P450 3A enzymes, it will likely decrease levels of other protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Therefore, St John's wort should not be taken with antiretroviral medications. Since safety data for herbal alternative therapies are scarce, these agents should be avoided during pregnancy. Table 14-6 summarizes data on alternative therapies to avoid during pregnancy.

## IV. BENEFITS OF ANTIRETROVIRAL DRUGS IN PREGNANCY: DRUGS TO CONSIDER

One example in which the benefit far outweighs the risk of drug administration during pregnancy is evident in the use of zidovudine (AZT) in preventing perinatal HIV transmission (ACTG study 076)[5]. Administration of AZT to the pregnant HIV-infected mother after the first trimester, during labor, after labor

and to the newborn reduced the perinatal acquisition of HIV. In addition, uninfected infants exposed to AZT in this study and followed to a median age of 3.9 years, have not shown a significant difference in growth, neurological development or immune status when compared to uninfected infants exposed to placebo[6]. The use of AZT during pregnancy and delivery has become the standard of care in the United States; however due to its high cost, its administration during pregnancy is not feasible in developing countries.

The HIVNET 012 trial compared the administration of one dose of nevirapine given orally to the mother during labor followed by one dose of nevirapine to the infant within 72 hours after birth to the administration of AZT during labor followed by AZT to the infant for 7 days. The 14-16 week post delivery data showed that while both regimens were well tolerated, 25.1% of infants in the AZT arm and 13.1% of infants in the nevirapine arm were infected with HIV (p=0.0006)[7]. Although long-term safety data are not currently available for nevirapine, this regimen may provide a simple and inexpensive regimen to prevent perinatal transmission of HIV in less developed countries. The current guidelines state that pregnancy per se should not preclude use of optimal therapeutic regimens. Therefore pregnant women should be treated according to standard guidelines for antiretroviral therapy in adults, with sustained reduction of viral load as the primary objective. (*MMWR* 1998; 47[RR-2])

## V. PHARMACOKINETICS OF ANTIRETROVIRAL DRUGS IN PREGNANCY

Although many physiologic changes occur during pregnancy, few trials have been conducted to evaluate their clinical significance on the pharmacokinetics of commonly used drugs. Physiologic changes that may affect drug pharmacokinetics include: delayed gastric emptying, decreased intestinal motility, increased volume of distribution (an average increase of 8L), increased renal blood flow (by 25-50%) and glomerular filtration rate (by 50%)[8, 9, 10]. The serum half-life of nevirapine is reduced from 66 hours in non-pregnant women to 45 hours in pregnant women; this decrease is not likely to be clinically significant[11]. Pregnancy does not change the pharmacokinetics of AZT, 3TC and ddI.[12, 13, 14]

The absorption and pharmacokinetics of many of the anti-HIV drugs are affected by food. Table 14-5 lists pertinent food-drug interactions that are probably as valid for pregnant women as for a non-gravid population.

Table 14-1, on the following pages, provides a quick reference on dosing recommendations, FDA Pregnancy Risk Classification, animal teratogenicity and human experience in pregnancy for the most commonly prescribed drugs in the treatment of HIV infection.

**Table 14-1: Antiretrovirals**

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| ***Nucleoside Reverse Transcriptase Inhibitor (NRTIs)*** | | | | | | |
| **Abacavir (Ziagen®)** | **300 mg bid** | Hypersensitivity reaction-fever, rash, fatigue, malaise, GI symptoms and arthralgias (noted in 2-3% of patients). **Mandatory discontinuation with hypersensitivity reaction. Do not rechallenge (2 deaths reported upon rechallenge);** rare cases of lactic acidosis and severe hepatomegaly with steatosis. | C | Rodent studies demonstrated placental passage, anasarca, skeletal malformation at 1000 mg/kg dose (35 times human therapeutic levels) during organogenesis. However rabbits receiving 8.5 times human therapeutic levels did not have fetal malformation. | Based on ex vivo data, placental transfer was 32-66% (Infect Dis Obstet Gynecol, 1998 6 (6): 244-6). | Inadequate data to recommend routine use during pregnancy. |
| **Zidovudine (Retrovir®, AZT)** | **300 mg po bid, or 200 mg po tid. PACTG protocol dosing: Prenatal: 100 mg 5x per day (alternatively 300 mg twice a day) beginning at weeks 14-34; Intrapartum 2mg/kg IV for first hour then 1mg/kg IV until birth. Infant received 2mg/kg po q6h for the first 6 weeks of life beginning 8-12 hrs after birth** | GI intolerance, malaise; headache (in 5-10%); bone marrow suppression (anemia and neutropenia seen more commonly with late stage AIDS); myalgia; myopathy; transaminase elevation; fingernail discoloration; rare cases of lactic acidosis and severe hepatomegaly with steatosis. | C | Rodent studies of doses that resulted in serum levels 350 times higher than levels in humans demonstrated maternal toxicity and fetal malformations. Vaginal squamous tumors seen in 13% of rodents exposed to high dose AZT. | Human studies demonstrated 85% placental passage. No maternal toxicities or fetal defects noted with AZT during pregnancy. Long-term toxicity data (up to 3.9 years) for infants exposed to AZT in utero and post partum did not show an increased risk of adverse effects or developmental abnormalities. | The only nucleoside analog with extensive clinical data on safety and efficacy during pregnancy. When feasible all antiretroviral regimens for the prevention of perinatal transmission should include AZT. |

*Table continues . . .*

**TABLE 14-1: ANTIRETROVIRALS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Stavudine (Zerit®, D4T)** | **Wt > 60kg dose: 40 mg po bid. Wt < 60kg dose: 30 mg po bid** | Peripheral neuropathy (in 5-15% of patients); transaminase elevation (in 8% of patients); rare cases of lactic acidosis and severe hepatomegaly with steatosis. | C | Studies in rhesus monkeys demonstrated 76% placental passage. Not teratogenic in rodent, but decreased sternal bone calcium developed. Carcinogenic studies not completed. | Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. | Use as an alternative for patients unable to tolerate AZT-containing regimens. ***Note:*** Due to the antagonism between AZT and d4T, they should never be used together as a part of a HAART regimen. |
| **Didanosine (Videx, DDI)** | **Wt > 60kg dose: 400 mg po qd (tabs) or 500 mg po qd (powder). Wt < 60kg dose: 250 mg po qd (tabs) or 334 mg po qd (powder). Total daily dose may also be taken in two divided doses** | GI intolerance (diarrhea, mouth sores), peripheral neuropathy in (5-12% of patients); pancreatitis (in 1-9% of patients with 6% cases fatal); transaminase elevation; rare cases of lactic acidosis and severe hepatomegaly with steatosis. | B | Not teratogenic or carcinogenic in rodent studies. | Human studies demonstrated 35% (range 23-59%) placental passage. In 8 patients studied, no toxicities were observed in mothers, infants. (5th Conference Retroviral Oppor Infect 1998 Feb 1-5; 121 (Abst. No 226). Due to the small number of patients no firm conclusion can be made. PACTG 249 Phase I study showed that ddI was well tolerated by mother and fetus when started at weeks 26-36. | GI side effects may limit use. The pediatric powder formulation is better tolerated (for every 4Gm of ddI, mix with 200 cc of Maalox®). |

*Table continues . . .*

**Table 14-1: Antiretrovirals**

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Lamivudine, (Epivir, 3TC)** | **150 mg po bid** | Generally very well tolerated; occasional headache; nausea; diarrhea; abdominal pain; and insomnia; rare cases of lactic acidosis and severe hepatomegaly with steatosis. | C | Not teratogenic or carcinogenic in rodent studies. | Human studies demonstrated 100% placental passage. In a multicenter trial 39 pregnant patients received AZT and 3TC; mild anemia and aspartate aminotransferase elevations were noted in 60% of the neonates. Long term outcome is not known (Infect Dis Obstet Gynecol 1998; 6(6):237-43). PETRA Safety Data. | PETRA trial demonstrated that AZT+3TC starting at 36 wks plus 1week of AZT+3TC postpartum to mother and infant or AZT+3TC during labor plus 1 week AZT+3TC postpartum to mother and infant resulted in a 42% and 37% reduction of transmission rates, respectively. AZT and 3TC given during labor only was not effective.(1999; 6th COROI Abst.S-7) |

*Table continues . . .*

**Table 14-1: Antiretrovirals** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Zalcitabine, (Hivid®; Dideoxycytidine, ddC)** | **0.75 mg po tid** | High incidence of peripheral neuropathy (17-31% of patients); stomatitis, aphthous ulcers; hepatitis; rare cases of pancreatitis reported; rare cases of lactic acidosis and severe hepatomegaly with steatosis. | C | Studies in rhesus monkey demonstrated 30-50% placental passage. Carcinogenic in rodent studies resulting in thymic lymphoma. Teratogenic in rodent studies resulting in hydrocephalus. | Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. | ddC is not recommended as part of any HAART regimen due to sub-optimal virologic response and toxicity, therefore use in the prevention of perinatal transmission is not recommended. |
| ***Non-nucleoside Reverse Transcriptase Inhibitor (NNRITs)*** | | | | | | |
| **Efavirenz (Sustiva®)** | **600 mg po q hs** | Morbilliform rash in 15-27% of patients with 1-2% requiring discontinuation; one case of Steven Johnson Syndrome reported; CNS effects (confusion, depersonalization, abnormal dreams) usually seen on day 1 in up to 52% of patients and resolves in 2-4 weeks; transaminase elevation in 2-3% of patients, hyperlipidemia | C | Placental passage of 100% seen in cynomalgus monkeys, rats and rabbits. Teratogenicity demonstrated in cynomalgus monkeys resulting in anencephaly, anophthalmia, microphthalmia. No data on carcinogenicity. | No data | Due to the teratogenicity data in the cynomalgus monkeys most experts agree that **Efavirenz should be avoided during pregnancy.** |

*Table continues . . .*

**Table 14-1: Antiretrovirals**

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Nevirapine (Viramune)** | **200 mg po qd for 14 days then 200 mg po bid** | Rash in 17% of patients (7% discontinued due to rash, many patient require hospitalization) Stevens Johnson Syndrome reported; transaminase elevation; severe hepatitis; fever; nausea; headache | C | Not teratogenic in rodent studies. No data on carcinogenicity. | Placental passage of 100% in humans. In HIVNET 006 trial (nevirapine 200 mg given to 21 HIV-infected pregnant patients) nevirapine was well tolerated and no fetal defects were noted (AIDS 1999 March 11; 13(4): 479-86.). | In HIVNET 012 administration of single-dose nevirapine given to mother during labor and to infants within 72 hours of delivery was compared with administration of AZT during labor and AZT for 7 days to infants. The 14-16 week data showed that 25.1% of infants in the AZT and 13.1% of infants in the nevirapine arm were infected (p=0.0006)(Lancet 1999 Sep 4; 354 (9181): 795-802.) The nevirapine regimen represents a simple and inexpensive therapy for the prevention of perinatal transmission. |

*Table continues . . .*

**TABLE 14-1: ANTIRETROVIRALS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Delavirdine (Rescriptor®)** | **400 mg po tid** | Rash in 18% of patients (4.3% discontinued due to rash, usually does not require discontinuation unless mucous membrane involvement); rare erythema multiforme or Stevens-Johnson syndrome; headache | C | Placental passage of 4-15% in late-term rodent studies. Teratogenic in rodent studies resulting in ventricular septal defects. Maternal toxicity, embryotoxicity and decrease pup survival seen with doses five times the human dose. No data on carcinogenicity. | Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. | Due to the availability of more potent NNRTIs (e.g., nevirapine) use of delavirdine is generally not recommended. |
| ***PROTEASE INHIBITORS (PIS)*** | | | | | | |
| **Ritonavir (Norvir®)** | **600 mg po bid** | Severe GI intolerance (N/V/D; abdominal pain, common with 600 mg bid dosing); taste perversion; asthenia; circumoral and peripheral paresthesias; lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation; (increased incidence seen with Hep B and C co-infection); elevated CPK and uric acid. | B | Placental passage of 115% mid-term and 15-64% late-term demonstrated in rodent studies. In human placental perfusion model, ritonavir showed little accumulation in the fetal compartment and no accumulation in placental tissue. Not teratogenic but cryptochidism reported in rodents studies. No data on carcinogenicity. | Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. | Use may be limited by GI intolerance. Dose of ritonavir may be lowered if used with another protease inhibitor (e.g., ritonavir 400 mg /saquinavir 400 mg BID) |

*Table continues . . .*

**Table 14-1: Antiretrovirals**

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Saquinavir (Invirase® Fortovase®)** | **Invirase® 600 mg po tid (not recommended as sole PI); Fortovase® 1200 mg po tid** | GI intolerance (nausea, diarrhea, abdominal pain); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation | B | Placental passage in humans unknown. Placental passage in rat and rabbit is minimal. No teratogenicity reported in rodent studies. No data on carcinogenicity. | Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. | Fortovase® 1200 mg tid is not a practical regimen due to the high pill burden and resulting marginal drug levels. Used in combination with ritonavir, allows for an acceptable alternative PI regimen (see above for dosing). |
| **Indinavir (Crixivan®)** | **800 mg tid** | Nephrolithiasis +/- hematuria in 5-15% of patients (48oz of fluid recommended to decrease incident); indirect hyperbilirubinemia (> or = 2.5 mg/dl in 10-15% of patients); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation | C | Placental passage is significant in rats, but low in rabbits. Not teratogenic in rodent studies (but extra ribs have been reported). Incidence of hyperbilirubinemia in neonatal Rhesus monkeys approximately 4-fold above controls. No data on carcinogenicity. | Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. | Due to theoretical concerns of hyperbilirubinemia and nephrolithiasis, **Indinavir should be avoided during pregnancy.** |

*Table continues . . .*

**TABLE 14-1: ANTIRETROVIRALS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Nelfinavir (Viracept®)** | **750 mg po tid or 1250 mg po bid** | Diarrhea (treatable with imodium or pancrealipase); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation | B | Placental passage unknown. Not teratogenic in rodent studies. No data on carcinogenicity. | Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. | The combination of AZT, 3TC and nelfinavir has been well tolerated during pregnancy [personal communication with Jean Anderson, MD]. |
| **Amprenavir (Angenerase®)** | **1200 mg po bid** | GI intolerance most common (N/V/D); oral paresthesias; headache; rash (in 11% of patients); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation | C | Placental passage unknown. Rat studies, using half the human dose, resulted in thymic elongation and incomplete ossification of bones. Rabbit studies using one-twentieth of human therapeutic doses were associated with abortions and skeletal abnormalities. | No data | There is not sufficient data to date to support use of amprenavir in pregnancy. |

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients**

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Trimethoprim-Sulfamethoxazole (Bactrim, Septra, Cotrim, Sulfatrim)** | **PCP prophylaxis: 1 DS po qd, 1SS po qd, 1 DS po TIW**<br>**PCP treatment: 5mg/kg (based on the trimethoprim component) po or IV q 8h** | Fever; leukopenia; rash and/or GI intolerance (in 25-50% of HIV-infected persons, most patients tolerate readministration of lower dose after 2 weeks of discontinuation); megaloblastic anemia; neutropenia; thrombocytopenia. Hematologic toxicity increased with folate depletion and high doses-treat with leucovorin 3-15 mg qd x 3 days. Reversible hyperkalemia (with high doses); photosensitivity; renal failure; hemolytic anemia with G6PD deficiency; hepatitis including cholestatic jaundice; thrush; erythema multiforme; Stevens Johnson syndrome | C | Cleft palate has been observed in some animals. | In a surveillance study of Michigan Medicaid recipients, 2,296 exposures to sulfamethoxazole/trimethoprim in the first trimester resulted in a 5.5% incidence of birth defects. This incidence suggests an association between the drug and congenital defects (cardiovascular), however other factors such as mother's disease, concurrent drug use, and chance, may be involved[15]. | Most authorities consider sulfonamides safe in pregnancy. **Sulfonamides may cause kernicterus in neonates, therefore should be avoided in pregnant women at term.** |

*Table continues . . .*

**TABLE 14-2: COMMONLY USED ANTIMICROBIALS FOR THE TREATMENT AND PREVENTION OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED PATIENTS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Azithromycin (Zithromax®)** | **MAI prophylaxis: 1200 mg po q week;** **MAI treatment: 500 mg po qd (in combination with ethambutol and/or rifabutin)** | GI intolerance (4%); diarrhea; nausea; abdominal pain; vaginitis; reversible hearing loss (more common with 500 mg x 30-90 days); increased transaminases | B | Animal studies show no harm to the fetus. | Azithromycin and erythromycin were compared for the treatment of chlamydia in pregnancy. The authors recommended using azithromycin due to efficacy and better tolerability. Effect on the fetus was not evaluated. (Obstet Gyn 1998 Feb; 91 (2): 165-8.) | The benefit of azithromycin administration for MAI prophylaxis or treatment outweighs the risks of congenital malformations. |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Clarithromycin (Biaxin®)** | **MAI prophylaxis: 500 mg po bid**<br>**MAI treatment: 500 mg po bid (in combination with ethambutol and/or rifabutin.)** | GI intolerance (4%); diarrhea; headache; reversible dose-related hearing loss; taste disturbances | C | Studies in monkeys show growth retardation, cleft palate and embryonic loss | The Teratogen Information Service in Philadelphia reported that the outcome of 34 first or second trimester exposures were similar to those expected in the non-exposed population. The 122 pregnancies exposed to clarithromycin in the 1st trimester did not have increased major or minor malformations when compared to matched controls. Incidence of spontaneous abortion was higher in clarithromycin-exposed group compared to controls (14% vs 7%) (p=0.04)(Schick B et al. Reprod Toxicology 1996; 10:162) | The benefit from clarithromycin administration for MAI prophylaxis or treatment outweighs the risks of congenital malformations. |

*Table continues . . .*

**TABLE 14-2: COMMONLY USED ANTIMICROBIALS FOR THE TREATMENT AND PREVENTION OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED PATIENTS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Pyrazinamide** | **15-30 mg/kg/day in 2-4 divided doses; usually 500 mg po tid** | Non-gouty polyarthralgia; asymptomatic hyperuricemia; hepatitis (dose related, frequency not increased when given with INH or rifampin, rarely serious); GI intolerance; gout | C | No animal data available. | No human data available. | **Due to insufficient data pyrazinamide should be avoided.** INH, rifampin and ethambutol are recommended as first line agents. |
| **Isoniazid (INH, Tubizid®, Nydrazid®)** | **300 mg po qd** | Age-related hepatitis- < 20 years old-nil/35 yrs old-6%/45 yrs old-11%/ 55 yrs old-18%; drug should be discontinued if transaminase levels are greater or equal to 3-5 x normal limits; allergic reactions; fever; peripheral neuropathy (especially with pre-existing alcoholism, diabetes, pregnancy, malnutrition); glossitis | C | C-Animal studies show embryocidal effect, but not teratogenic. | Retrospective analysis of more than 4900 exposures to INH did not show increased fetal malformations. (Snider DE et al. Am Rev Respir Dis 1980; 122:65-79) | The American Academy of Pediatrics and the American Thoracic Society recommend that pregnant women with a positive PPD should receive INH if HIV-positive, have had recent TB contact, or have an X-ray showing old TB; start after 1st trimester if possible. |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Rifampin (Rifadin)** | **600 mg po qd** | 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 | C | Animal data show congenital malformations-cleft palate, spina bifida, and embryotoxicity. Isolated cases of fetal abnormalities reported. Administration in last weeks of pregnancy may cause postnatal hemorrhage. | Several reviews have evaluated treatment of TB in pregnancy. All concluded that rifampin was not teratogenic and recommended use of the drug with INH and ethambutol if necessary (Am Rev Respir Dis 1986; 134:355-63). | The American Thoracic Society recommends rifampin in combination with INH and ethambutol if treatment for TB is needed during pregnancy. |
| **Rifabutin (Mycobutin®)** | **300 mg po qd (dose is decreased to 150 mg when used with protease inhibitor e.g., indinavir or nelfinavir)** | Orange discoloration of urine, tears, sweat; uveitis with eye pain, photophobia, redness and blurred vision-usually seen with high doses (600mg/day or concurrent use of fluconazole or clarithromycin); hepatitis; GI intolerance; allergic reactions | B | Animal data showed skeletal abnormalities. | No human data available. | For MAI prophylaxis azithromycin is preferred; for MAI treatment clarithromycin + ethambutol is recommended in pregnancy. Rifabutin cannot be routinely recommended in pregnancy due to the lack of data. |

*Table continues . . .*

**TABLE 14-2: COMMONLY USED ANTIMICROBIALS FOR THE TREATMENT AND PREVENTION OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED PATIENTS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Ethambutol (Myambutol®)** | **15-25 mg/kg po qd** | Optic neuritis (decreased acuity, reduced color discrimination, constricted fields, scotomata-dose related and infrequent with 15mg/kg); GI intolerance; confusion, precipitation of acute gout | B | Teratogenic in animal studies | No congenital defects have been reported. In 38 patients exposed to ethambutol during pregnancy, no increased risk of birth defects observed (including embryonic optic nerve). (Chest 1974; 66:20-4) | The CDC considers ethambutol safe in pregnancy |
| **Atovaquone (Mepron®)** | **750 mg po bid** | GI intolerance (nausea, vomiting and diarrhea); headache; rash. 7-9% required discontinuation due to side effects | C | Not teratogenic in rat studies. Maternal and fetal toxicities (decreased fetal weight, early fetal resorption and post-implantation fetal loss) reported in rabbits | No human data available | Not recommended for PCP treatment due to poor clinical efficacy. Not recommended for PCP prophylaxis due to high cost, poor GI tolerance and lack of safety data in pregnancy. Preferred regimens for PCP prophylaxis include trimethoprim/sulfamethoxazole and dapsone. |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Hydroxyurea (Hydrea®, Droxia®)** | **500 mg po bid** | Dose-dependent leukopenia, anemia and thrombocytopenia; GI intolerance (N/V/D, constipation), stomatitis; rash; alopecia | D | Hydroxyurea is teratogenic in several animal studies; anomalies include nervous system, palate, skeleton, neural tube and cardiac defects. | Eight case reports of hydroxyurea exposure during pregnancy did not demonstrate teratogenicity, however the data are too limited to draw any conclusions[15]. | **Contraindicated due to high incidence of teratogenicity in animal studies and limited human experience.** |
| **Amphotericin B (Fungizone®)** | **0.5-1.2 mg/kg IV qd** | 40-50% incidence of fever and chills; 30-40% incidence of renal tubular acidosis-dose dependent and reversible in absence of prior renal damage and dose < 3 Gm (reduced with hydration and sodium loading); 20% incidence of hypokalemia; hypomagnesemia; anemia; phlebitis and pain at infusion site; hypotension; nausea; vomiting; metallic taste; headache | B | Animal studies demonstrated amphotericin to be harmless in pregnancy | The Collaborative Perinatal Project identified 9 1st trimester exposures to amphotericin and found no adverse fetal effect [15]. | Many authorities feel that amphotericin can be used in pregnancy for the treatment of serious fungal infections. |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Flucytosine (Ancobon®)** | **25 mg/kg q6h (monitor levels)** | GI intolerance (N/V/D); marrow suppression with leukopenia or thrombocytopenia (dose related with renal failure, serum concentration > 100mcg/ml or concurrent amphotericin); confusion; rash; hepatitis (dose related); enterocolitis; headache; photosensitivity reaction | C | Teratogenicity reported in animal studies. | Three case reports of second and third trimester exposure resulted in no defects in the newborns, however no conclusion can be drawn[15]. | 4% of administered dose converts to 5FU in the fungal organism. 5FU has been associated with congenital malformations. Its use with amphotericin for the treatment of cryptococcal meningitis did not result in added efficacy (ACTG 159, NEJM 1997; 337:15) **Avoid in pregnancy.** |
| **Nystatin** | **500,000 units 5x/day** | GI intolerance (N/V/D) | B | No animal data | 489 first trimester exposures to nystatin were observed in a Michigan Medicaid recipients surveillance study. No association between nystatin and congenital defects was observed[15]. | Due to low systemic absorption nystatin may be used in the management of thrush during pregnancy |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Clotrimazole** | **10 mg troches 5x/day** | GI intolerance (N/V); transaminase elevation | C | Embryotoxic in rats and mice. Not teratogenic in mice, rabbits and rats. | 2,624 exposures to clotrimazole were observed in the first trimester in a Michigan Medicaid recipients surveillance study. No association between clotrimazole and congenital defects were observed[15]. | Due to low systemic absorption nystatin is preferred over clotrimazole in the management of thrush during pregnancy. |
| **Fluconazole (Diflucan®)** | **100-800 mg po qd** | Dose-related GI intolerance including bloating, nausea, vomiting, pain, anorexia, weight loss (8-11% with dose < 400mg/day, 30% with dose > 400mg/day); reversible alopecia in 10-20% of receiving >/= 400mg/day for 3 months; transaminase elevation to > 8 x normal, rare cases of fatal hepatitis and Stevens Johnson Syndrome. | C | Teratogenic in animal studies. | Craniofacial, limb and cardiac defects have been reported in 3 infants with 1st trimester exposure to high dose fluconazole (CID 1996; 22:336-40). The risk of low dose intermittent use has not been fully evaluated but appears to be low. In a prospective follow up of 226 patients exposed to low dose fluconazole, teratogenicity was not reported . (Am J Obstet Gyn 1996; 175:1645-50) | **Contraindicated in the 1st trimester due to potential for teratogenicity.** |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Itraconazole (Sporanox®)** | **200-400 mg po qd** | Headache; GI intolerance-nausea (10%) and vomiting; rash (8%); hypokalemia reported with high doses (600mg per day); adrenal insufficiency; impotence; gynecomastia; leg edema; transaminase elevation, rare cases of fatal hepatitis | C | Teratogenic in rats and mice (encephaloceles, macroglossia and skeletal malformation). | FDA has received 14 case reports of malformations following use of itraconazole, 4 were limb defects. However in another report of 80 exposures to single-dose itraconazole or fluconazole no malformations were reported (Rosa F et al. Presented at the Ninth International Conference of the Organization of Teratology Information Services, May 2-4, 1996, Salt Lake City, Utah). | Contraindicated in the 1st trimester due to potential for teratogenicity. |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Pyrimethamine (Daraprim®)** | **<u>Acute treatment of Toxoplasmosis</u> Pyrimethamine 50-100 mg po qd (in combination with Sulfadiazine 4-8 Gm po qd in four divided doses for 6 weeks);**<br>**<u>Toxoplasmosis maintenance dose:</u> Sulfadiazine 2-4 Gm po qd in four divided dose (plus pyrimethamine 25-75 mg po qd after acute treatment).**<br>**<u>Toxoplasmosis prophylaxis:</u> 50-75 mg po q week (in combination with dapsone 100 po qd) / administer with leucovorin** | Folic acid deficiency with megaloblastic anemia and pancytopenia (dose-related and reversed with leucovorin); allergic reactions; GI intolerance (nausea, anorexia, vomiting) | C | Teratogenic in animal studies. | No adverse fetal effects were reported in two reviews of treatment of toxoplasmosis in pregnancy (CID 1994; 18:853-62; Clin Peritonol 1994;21:675-88). If pyrimethamine is used during pregnancy, concomitant leucovorin (folinic acid) supplementation (25 mg/day) is recommended, especially during the 1st trimester. | When use in pregnancy is indicated, leucovorin 25mg po qd should be administered concomitantly to prevent hematologic toxicity. |

*Table continues . . .*

**TABLE 14-2: COMMONLY USED ANTIMICROBIALS FOR THE TREATMENT AND PREVENTION OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED PATIENTS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Sulfadiazine** | **Acute treatment of Toxoplasmosis: Sulfadiazine 4-8 Gm po qd in four divided doses (in combination with Pyrimethamine 50-100 mg po qd for 6 weeks);**<br>**Toxoplasmosis maintenance dose: Pyrimethamine 25-75 mg po qd (plus Sulfadiazine 2-4 Gm po qd in four divided dose after acute treatment)** | Allergic reactions-rash, pruritus; crystalluria with renal damage, urolithiasis and oliguria; GI intolerance; photosensitivity; hepatitis; fever; periarteritis nodosum, Stevens-Johnson Syndrome; serum sickness | C | At high doses, animals developed cleft palate and bone abnormalities. | Extensive use in humans without complication except one case of agranulocytosis that was possibly associated[15]. | **Due to the potential of kernicterus in the newborn, sulfa drugs should be avoided near term.** May be used in the 2nd and 3rd trimester without complications. |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Aerosolized pentamidine** | **PCP prophylaxis- 300 mg nebulized q month** | Asthma reaction reported in 2-5% of patients; cough seen in 30% of patients | | | Aerosolized pentamidine given to 15 women during the 2nd and 3rd trimesters did not alter pregnancy outcome or cause fetal harm (Am J Obstet Gyn 1992; 166:387). | CDC and manufacturer advise against the use of pentamidine during pregnancy due to the lack of data, however some feel that aerosolized pentamidine may be considered safe due to minimal systemic absorption (CID 1995; 21 suppl 1:S24) |

*Table continues . . .*

**TABLE 14-2: COMMONLY USED ANTIMICROBIALS FOR THE TREATMENT AND PREVENTION OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED PATIENTS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Intravenous pentamidine** | **PCP treatment- 3-4 mg/kg IV qd** | Nephrotoxicity-seen in 25% (usually reversible with discontinuation); hypotension (administer IV over 60 min to decrease risk); hypoglycemia-seen in 5-10% (usually occurs after 5 days of treatment including past treatment, may last days or weeks) may lead to insulin dependent diabetes; marrow suppression (leukopenia; thrombocytopenia); GI intolerance with nausea, vomiting, abdominal pain, anorexia and bad taste; transaminase elevation; pancreatitis; toxic epidermal necrolysis; fever | C | Not teratogenic in rat studies, however has been shown to be embryocidal | Spontaneous abortion reported, but causal relationship has not been established. | **Both manufacturer and CDC advise against the use of intravenous pentamidine in pregnancy.** |
| **Primaquine** | **15-30 mg (base) po qd (in combination with Clindamycin for the treatment of PCP)** | Hemolytic anemia (G6PD deficiency); methemoglobinemia; GI intolerance; neutropenia | C | No animal studies available. | No human data available | Theoretical concern is hemolytic anemia in G6PD deficient fetus. Should screen for G6PD deficiency in mother prior to use |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Albendazole (Albenza®)** | **400-800 mg bid x 3 weeks** | Diarrhea; abdominal pain; transaminase elevation; hepatotoxicity; reversible pancytopenia and neutropenia | C | Teratogenic and embryotoxic in rodent and rabbit studies. | No human data available | **Contraindicated in pregnancy.** |
| **Dapsone** | **100 mg po qd (PCP prophylaxis)** | Rash; blood dyscrasias including methemoglobinemia and sulfhemoglobinemia and hemolytic anemia (with or without G6PD deficiency); nephrotic syndrome; fever, nausea, anorexia; blurred vision; photosensitivity; tinnitis; insomnia; irritability; headache (transient); rare "sulfone syndrome"-fever, exfoliative dermatitis, jaundice, adenopathy; methemoglobinemia and anemia | C | No animal teratogenicity studies conducted. Carcinogenic risk in rats. | No adverse effects reported. (Drug Saf 1993;8:295-311). | Dapsone has been used extensively in the treatment of malaria and for chemoprophylaxis of leprosy without producing major fetotoxicity or causing birth defects. Recommend screening for G6PD deficiency in mother prior to use. |

*Table continues . . .*

**TABLE 14-2: COMMONLY USED ANTIMICROBIALS FOR THE TREATMENT AND PREVENTION OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED PATIENTS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Acyclovir (Zovirax®)** | **5-10 mg/kg IV q8h; 200-800 mg po x3-5 times per day** | GI intolerance (nausea and vomiting; diarrhea); renal toxicity (esp with rapid IV infusion); dizziness; transaminase elevation; itching, headache. Toxicities are infrequent. | C | Not teratogenic but potential to cause chromosomal damage at high doses. | Birth defects reported in 23 out of 1002 exposures however this was not statistically different from the expected rate. (Glaxo Wellcome, Acyclovir Pregnancy Registry, 1996) | CDC recommends use of acyclovir for life threatening disease but does NOT advocate use for treatment or prophylaxis of genital herpes. |
| **Valacyclovir (Valtrex®)** | **1000 mg po tid (for Zoster); 500 mg po bid (for recurrent HSV)** | GI intolerance-nausea, vomiting, diarrhea; headache; constipation | B | Not teratogenic in animal studies | No human data available but likely to be similar to acyclovir. | Recommendation is likely to be similar to acyclovir since valacyclovir is converted to acyclovir. However it may be more prudent to use acyclovir in pregnancy due to more extensive pregnancy data. |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Famciclovir (Famvir®)** | **500 mg po q8h (for zoster); 125 mg q12h (HSV)** | Headache; nausea; fatigue | B | Carcinogenic, but not embryotoxic or teratogenic in animal studies. | No human data | Until more data are available, it may be prudent to use acyclovir in pregnancy. |
| **Ganciclovir (Cytovene®)** | **CMV retinitis-**<br>**Induction: 5mg/kg IV q12h x 2 weeks then Maintenance: 5 mg/kg IV qd** | Neutropenia (ANC < 500 in 15-20%; usually early in treatment and responds within 3-7 days to drug holiday or to G-CSF); thrombocytopenia (platelet count < 20,000 in 10%, reversible). Monitor CBC 2-3/week and discontinue if ANC < 500-750 or platelet count < 25,000; anemia; fever; rash; CNS-headache, seizures, confusion, changes in mental status; abnormal liver function tests (2-3%) | C | Teratogenic and embryogenic; growth retardation; aplastic organ in animal studies. | No human data | Most authorities recommend the use of foscarnet for treatment of CMV infection during pregnancy due to the potential teratogenic effect of ganciclovir. |

*Table continues . . .*

**TABLE 14-2: COMMONLY USED ANTIMICROBIALS FOR THE TREATMENT AND PREVENTION OF OPPORTUNISTIC INFECTIONS IN HIV-INFECTED PATIENTS** *(continued)*

| *DRUG NAME* | *DOSING* | *ADVERSE EFFECTS* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Cidofovir (Vistide®)** | **CMV retinitis**<br>**Induction: 5mg/kg q week x 2 weeks then q2 weeks (give concurrently with probenecid and hydration)** | Nephropathy-dose dependent, reduced with hydration and probenecid. (Side effect of probenecid includes chills, fever, headache, rash and nausea in 30-50% of patients); uveitis; ocular hypotony; GI intolerance; neutropenia; metabolic acidosis | C | Carcinogenic in animal studies | No human data available. | Due to lack of data on cidofovir during pregnancy, most authorities recommend the use of foscarnet for the treatment of CMV infection in pregnancy. |
| **Foscarnet (Foscavir®)** | **CMV retinitis**<br>**Induction: 90 mg/kg IV q12h;**<br>**Maintenance: 90-120 mg/kg IV qd.** | Renal failure (usually reversible; 30% get serum creatine (Cr) > 2mg/dl; (Monitor Cr 1-3 times per week and discontinue if Cr > 2.9 mg/dl); Mineral and electrolyte changes-reduced magnesium, phosphorus, ionized calcium, potassium (monitor serum electrolytes 1-2 times per week and monitor for symptoms of paresthesias); seizures (10%); fever; GI intolerance; anemia; genital ulceration; neuropathy | C | Skeletal malformation or variation in animal studies. | No human data available | Some experts recommend that foscarnet should be used as first line treatment for sight-threatening CMV retinitis in pregnant women. Due to high incidence of nephrotoxicity, antepartum testing of the fetus and close monitoring of the aminiotic fluid to observe for fetal nephrotoxicity is recommended. |

*Table continues . . .*

**Table 14-2: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients** *(continued)*

| *Drug Name* | *Dosing* | *Adverse Effects* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|---|---|
| **Ribavirin (Rebetrol®)** | **Treatment of Hepatitis C (in combination with interferon): < 75kg-400 mg q am and 600 mg q pm. > 75kg-600 mg bid** | Hemolytic anemia (mean hgb decrease is 3 gm/dl); leukopenia; hyperbilirubinemia; increased uric acid. | X | Ribavirin has been demonstrated teratogenic in rodents (and in all animals data tested), but not in primates when given during the first trimester | No data available | **Both the CDC and the manufacturer consider the use of ribavirin contraindicated during pregnancy.** |
| **Interferon (Roferon®, Intron®)** | **Treatment of Hepatitis C (in combination with ribavirin): 3 million units 3x/week.** | Flu-like syndrome; GI intolerance (N/V/D, anorexia); CNS toxicity (delirium; obtundation and depression); neutropenia, anemia, thrombocytopenia, increased transaminase; rash; alopecia; proteinuria | C | Abortifacient in Rhesus monkeys when given 20-500 times the 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 a conclusion. | Due to the antiproliferative properties of interferon, it should be used cautiously in pregnancy. |

**TABLE 14-3: SAFETY OF COMMONLY USED ANTIMICROBIALS**

| *DRUG NAME* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|
| **Metronidazole** | B | Animal (rodents) data show risk of carcinogenicity. | The use of metronidazole in pregnancy is controversial; most studies show no risk). | The manufacturer and CDC consider use of metronidazole **contraindicated** during 1st trimester. However most authorities feel metronidazole is safe in the 2nd and 3rd trimester. |
| **Clindamycin** | B | No fetal harm demonstrated in rat studies. Cleft palate observed in one mouse strain. | In a surveillance study of Michigan Medicaid recipients, 647 exposures to clindamycin during the first trimester resulted in a 4.8% incidence of birth defects. These data do not support an association between clindamycin and congenital effects[15]. | Clindamycin is considered to be safe in the 2nd and 3rd trimesters of pregnancy. |
| **Penicillins** | B | Carcinogenicity demonstrated in rats after prolonged subcutaneous administration of penicillin in peanut oil. | Several collaborative perinatal project reports involving over 12,000 exposures to penicillin derivatives during the 1st trimester indicated no association between penicillin derivative drugs and birth defects[15]. | Penicillins are usually considered safe to use during pregnancy. |
| **Cephalosporins** | B | Not teratogenic or fetotoxic. | Extensive pregnancy exposure was not associated with birth defects. | Cephalosporins are usually considered safe to use during pregnancy. |
| **Erythromycin** | B | No teratogenic effect in rat studies. | In a surveillance study of Michigan Medicaid recipients, 6,972 patients exposed to erythromycin during the first trimester resulted in a 4.6% incidence of birth defects. These data do not support an association erythromycin and congenital malformations. | **Avoid estolate salt** (due to hepatotoxicity in 10% of patients). The CDC recommends the use of erythromycin for the treatment of chlamydia during pregnancy. |

*Table continues . . .*

**Table 14-3: Safety of Commonly Used Antimicrobials** *(continued)*

| *Drug Name* | *FDA Class* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|---|
| **Tetracyclines** | D | Teratogenic in animal studies resulting retardation of skeletal development and embryotoxicity. | Tetracyclines are contraindicated in pregnancy due to retardation of skeletal development and bone growth, enamel hypoplasia, and discoloration of teeth of fetus. Maternal liver toxicity has also been reported. | **Contraindicated** |
| **Fluoroquinolones** | C | Animal data demonstrated arthropathy in immature animals resulting in erosions in joint cartilage. | In a prospective follow-up study conducted by the European Network of Teratology Information Services (ENTIS), 666 cases of fluoroquinolone exposure (the majority during the 1st trimester) showed a congenital malformation rate of 4.8%. From previous epidemiologic data, this rate did not exceed the background rate.(Eur J Obstet Gyn Reprod Bio 1996; 69:83-9) | Based on animal data and the availability of alternative antimicrobial agents, **the use of fluoroquinolones during pregnancy is contraindicated**. |
| **Aminoglycoside** | D | Fetotoxicity reported in rodent studies | Eighth cranial nerve toxicity in the fetus is well documented with exposure to kanamycin and streptomycin and can potentially occur with other aminoglycosides. | **Consider use only in life-threatening infections when no alternative is available**. Gentamicin is classified by the FDA as "C" (although it has the same potential adverse effects.) |
| **Imipenem** | C | Animal studies (monkeys) show increased embryogenic loss. | No data in humans. | Due to the lack of human data, use only in life-threatening infections |
| **Meropenem** | B | No risk | No data in humans | Due to the lack of human data, use only in life-threatening infections |

*Table continues . . .*

**TABLE 14-3: SAFETY OF COMMONLY USED ANTIMICROBIALS** *(continued)*

| *DRUG NAME* | *FDA CLASS* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|---|
| **Chloramphenicol** | C | No animal data | A collaborative perinatal project monitored 98 exposures during the first trimester and 348 exposures anytime during pregnancy. No relationship between chloramphenicol and malformations were found[15]. | **Although apparently non-toxic to the fetus, chloramphenicol should not be used near term due to the potential of cardiovascular collapse (Gray Baby Syndrome).** |
| Aztreonam | B | Animal studies show no harm to the fetus. | No human data available | Likely to be safe in pregnancy, but due to the lack of data, use only if absolutely needed. |
| Methenamine | C | No animal data | In a surveillance study of Michigan Medicaid recipients, 209 exposures to methenamine during the first trimester resulted in a 3.8% incidence of birth defects. This data did not support an association between methenamine and congenital defects. | The benefit of methenamine therapy is not likely to be worth the risk of use during pregnancy. |
| Nitrofurantoin | B | Not teratogenic or fetotoxic in rat and rabbit studies | In a surveillance study of Michigan Medicaid recipients, 1,292 exposures to nitrofurantoin resulted in a 4.0% incidence of birth defects. These data did not support an association between nitrofurantoin and congenital defects[15]. | Most authorities feel that use of nitrofurantoin is safe during pregnancy. |
| Vancomycin | C | No animal data | The manufacturer has received reports of vancomycin use during pregnancy without adverse fetal effects. | Consider use only when the benefit outweighs the risk of drug administration. |

*Table continues . . .*

**Table 14-3: Safety of Commonly Used Antimicrobials** *(continued)*

| *Category* | *Pregnancy Risk Factor* |
|---|---|
| **A** | Controlled studies in women fail to demonstrate a risk to the fetus in the 1st trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote. |
| **B** | Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women *or* animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the 1st trimester (and there is no evidence of a risk in later trimesters). |
| **C** | Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women *or* studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. |
| **D** | There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). |
| **X** | Studies in animals or human beings have demonstrated fetal abnormalities *or* there is evidence of fetal risk based on human experience *or* both, *and* the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are *or* may become pregnant. |

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS**

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS/RECOMMENDATION* |
|---|---|---|---|---|---|---|
| ***NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS*** | | | | | | |
| **AZT (Zidovudine) (Retrovir®)** | Ganciclovir | Pharmacodynamic interaction/Additive toxicity. | Enhanced bone marrow toxicity. | Delayed | Moderate | May require decreased dose of AZT: Switch to alternative antiretroviral or use concomitant G-CSF. Monitor CBC frequently. |
| | Acetaminophen | Competitive inhibition of glucuronidation | May rarely result in granulocytopenia and hepatotoxicity | Delayed | Minor | Intermittent use of acetaminophen is considered safe. Adverse effects not consistently reported. |
| | Stavudine | In vitro and in vivo antagonism | Decreased antiviral efficacy | Immediate | Major | Concomitant administration not recommended |
| | Rifampin | Enzymatic induction resulting in increased glucuronidation of AZT | Increased clearance of AZT | Delayed | Moderate | Monitor for antiretroviral failure (e.g., increased viral load). May require increasing the dose of AZT. |
| **ddI (Didanosine) (Videx®)** | Oral Ganciclovir | Unknown | ddI AUC increased by 70% with concomitant dosing | Delayed | Moderate | Monitor for ddI toxicity (e.g., peripheral neuropathy, pancreatitis). Dose reduction may be required. |
| | Indinavir Ritonavir Delavirdine | Increase in gastric pH due to the buffer in ddI formulation | Decreased absorption of indinavir, ritonavir and delavirdine | Immediate | Moderate | Separate administration time by at least 2 hours |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **ddI (Didanosine) (Videx®)** *(continued)* | Dapsone | Increase in gastric pH due to the buffer in ddI formulation | Decreased absorption of dapsone | Immediate | Moderate | Separate administration time by at least 2 hours. |
| | Itraconazole Ketoconazole | Increase in gastric pH due to the buffer in ddI formulation | Decreased absorption of antifungal agent | Immediate | Major | Separate administration time by at least 2 hours. Fluconazole may be preferred as an alternative azole antifungal. |
| | Ciprofloxacin (Fluoroquinolone) Tetracyclines | Chelation of fluoroquinolones and tetracyclines by the divalent cation in ddI | Significant decrease in antibiotic absorption results in sub therapeutic levels | Immediate | Major | Administer quinolones or tetracyclines 2 hours before or 6 hours after ddI administration. |
| | Pentamidine Ethambutol | Pharmacodynamic interaction / additive toxicity | May increase the risk of pancreatitis | Delayed | Moderate | Avoid in patients with current alcohol use. Use caution when administering to patients with a history of alcoholism. |
| | DDC,D4T,INH, Cisplatin, Disulfiram Vincristine, Gold | Pharmacodynamic interaction/Additive toxicity | May increase the risk of peripheral neuropathy. | Delayed | Moderate | Avoid co-administration or give with careful monitoring for symptoms of peripheral neuropathy. Incidence of peripheral neuropathy increases with low CD4 count. |
| | Methadone | Unknown | ddI levels decreased by 41%, methadone levels remains unchanged. | Delayed | Moderate | Consider ddI dose increase. |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **DDC (Zalcitabine) (Hivid®)** | DDI,D4T,INH Cisplatin, Disulfiram, Vincristine, Gold- | Pharmacodynamic interaction/ Additive toxicity | May increase the risk of peripheral neuropathy. | Delayed | Moderate | Avoid or give with careful monitoring of symptoms of peripheral neuropathy. Peripheral neuropathy increases with low CD4 count. |
| **D4T (Stavudine) (Zerit®)** | DDC,DDI,INH Cisplatin, Disulfiram, Vincristine, Gold | Pharmacodynamic interaction/Additive toxicity | May increase the risk of peripheral neuropathy | Delayed | Moderate | Avoid or give with careful monitoring of symptoms of peripheral neuropathy. Peripheral neuropathy increases with low CD4 count. |
| | Methadone | Unknown | D4T drug levels decreased by 27%. Methadone levels unchanged | Delayed | Mild | Clinical significance unknown, no dose adjustment needed. |
| | Zidovudine | In vitro and in vivo antagonism | Decreased efficacy of the combination therapy | Immediate | Major | Concomitant administration not recommended due to antagonism. |
| **3TC (Lamivudine) (Epivir®)** | Bactrim | Trimethoprim competitively inhibits renal tubular secretion. | Lamivudine AUC increased by 44% | Immediate | Minor | No dosage adjustment required due to the safety profile of 3TC. |
| **Abacavir (Ziagen®)** | | | | | | No known drug interactions |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| ***NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS*** | | | | | | |
| **Nevirapine (Viramune®) (NVP)** | Ethinyl estradiol (Oral contraceptive) | Induction of hepatic metabolism | May decrease ethinyl estradiol AUC | Delayed | Major | Although there are no data on this interaction, patients should be aware of the potential interaction. Alternative birth control method **recommended**. |
| | Methadone | Induction of hepatic metabolism | May substantially decrease methadone AUC | Delayed | Moderate | **Opiate withdrawl** may occur. May need increased dose of methadone (some patients may required doses of greater than 150 mg per day) |
| | Ketoconazole | Induction of hepatic metabolism by nevirapine. Inhibition of hepatic metabolism by Ketoconazole | Ketoconazole levels decreased by 63%. Nevirapine levels increased by 15-30%. | Delayed | Moderate | **Co-administration not recommended.** Ketoconazole dose may need to be increased. |
| | Rifampin/ Rifabutin | Induction of hepatic metabolism | Nevirapine levels decreased by 37% with rifampin and 16% with rifabutin | Delayed | Major | Co-administration not recommended with rifampin. Rifabutin may be a preferred alternative agent. |
| | Clarithromycin | Induction of hepatic metabolism by nevirapine | Clarithromycin AUC decreased by 30%, but active hydroxy-metabolite is increased. | Delayed | Minor | No dose modification needed. Use standard dose of nevirapine and clarithromycin |
| | | Inhibition of hepatic metabolism by clarithromycin. | Nevirapine AUC increased by 26% | Immediate | Minor | |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Nevirapine (Viramune®) (NVP)** *(continued)* | Saquinavir | Induction of hepatic metabolism | Saquinavir AUC decreased by 25% | Delayed | Moderate | Avoid concurrent use. |
| | Ritonavir | Induction of hepatic metabolism | Ritonavir AUC decreased by 11%. | Delayed | Minor | Use standard doses. |
| | Indinavir | Induction of hepatic metabolism | Indinavir AUC decreased by 28% | Delayed | Minor | Clinical trials demonstrated efficacy with standard dose. Some experts recommend increasing the indinavir dose to 1000 mg q8h. |
| | Nelfinavir | Induction of hepatic metabolism | Nelfinavir levels increase by 10%. | Delayed | Minor | Use standard doses. |
| **Delavirdine (Rescriptor®) (DLV)** | Indinavir | Inhibition of hepatic metabolism | Indinavir AUC increased by 40% | Immediate | Moderate | May reduce indinavir dose to 600 mg q8h |
| | Nelfinavir | Inhibition of hepatic metabolism by delavirdine | Nelfinavir AUC increased by 2 fold | Immediate | Moderate | Monitor for neutropenia and complication for the first few months. Insufficient data for dosing recommendation. |
| | | Induction of hepatic metabolism by nelfinavir. | Delavirdine AUC decreased by 50% | Delayed | | |
| | Ritonavir | Inhibition of hepatic metabolism | Ritonavir AUC increased by 70%. No effect on delavirdine concentration. | Immediate | Minor | No data on dosage. |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **Delavirdine (Rescriptor®) (DLV)** *(continued)* | Saquinavir | Inhibition of hepatic metabolism | Invirase C min increased by six - fold | Delayed | Minor | Beneficial interaction. No dosage adjustment needed. Monitor transaminases. |
| | ddI and antacid | Decrease delavirdine absorption due to antacid content in ddI | Delavirdine AUC decreased by 41% | Immediate | Moderate | Separate administration by at least 1 hour. |
| | Simvastatin/ Lovastatin | Inhibition of hepatic metabolism | Increased serum levels of simvastatin and lovastatin | Immediate | Moderate | **Avoid concurrent administration**. Consider alternatives such as atorvastatin, pravastatin, cerivastatin, fluvastatin. Monitor for adverse effects due to limited clinical data. |
| | H2 blockers, Proton pump inhibitors (e.g., omeprazole) | Decreased delavirdine absorption due to increased gastric pH | May decrease delavirdine concentration | Immediate | Moderate | Though not thoroughly evaluated, the **manufacturer does not recommend** long-term concurrent administration. |
| | Terfenadine, Astemizole, Cisapride | Inhibition of hepatic metabolism | Increased levels of terfenadine, astemizole, cisapride | Immediate | Major | **Concurrent administration contraindicated** due to potential for serious cardiac arrhythmias. |
| | Midazolam, Triazolam | Inhibition of hepatic metabolism | Midazolam and triazolam AUCs increased | Immediate | Major | **Concurrent administration contraindicated** due to potential for prolonged sedation. Lorazepam and Temazepam may be safe alternatives. |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Delavirdine (Rescriptor®) (DLV)** *(continued)* | Ergot Alkaloid | Inhibition of hepatic metabolism | Possible acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities | Immediate | Major | **Concurrent administration contraindicated.** |
| | Sildenafil | Inhibition of hepatic metabolism | Potential increase in sildenafil drug levels | Immediate | Moderate | **Caution** with concurrent use. Do not exceed 25 mg sildenafil in a 48-hour period. |
| | Clarithromycin | Inhibition of hepatic metabolism | Clarithromycin levels increased by 100%. and delavirdine levels increased by 44%. | Immediate | Minor | May require dose adjustment. |
| | Rifampin | Induction of hepatic metabolism | Delavirdine Cmin decreased below the level of detection. | Delayed | Major | **Concurrent administration contraindicated** due to sub-therapeutic level of delavirdine |
| | Rifabutin | Inhibition of hepatic metabolism by delavirdine | Rifabutin AUC increased by 100% | Immediate | Moderate | **Concurrent administration contraindicated** due to sub-therapeutic level of delavirdine |
| | | Induction of hepatic metabolism by rifabutin | Delavirdine AUC decreased by 80% | Delayed | Major | |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **Efavirenz (Sustiva®) (EFV)** | Fortovase® (Saquinavir soft gel) | Induction of hepatic metabolism | Fortovase® AUC decreased by 60%. Efavirenz AUC decreased by 12% | Delayed | Moderate | Avoid using Fortovase® monotherapy with efavirenz.<br>If ritonavir/saquinavir/efavirenz regimen used, dose Fortovase 800 mg bid. |
| | Nelfinavir | Inhibition of hepatic metabolism | Nelfinavir AUC increased by 21% | Immediate | Minor | May be a beneficial pharmacokinetic interaction. No dose adjustment needed. |
| | Amprenavir | Induction of hepatic metabolism | Amprenavir AUC decreased by 36% | Delayed | Moderate | Clinical significance not known. Recommended empiric dose of amprenavir 1200 mg q8h + efavirenz 600 mg qhs is reasonable.<br>Amprenavir 1200 mg q12h + ritonvir 200 mg q12h + efavirenz 600 mg qhs resulted in a 5-fold increase in amprenavir level. May consider decreasing the dose of amprenavir to 600 mg q12h when used with ritonavir and efavirenz. |
| | Indinavir | Induction of hepatic metabolism | Indinavir AUC decreased by 31% | Delayed | Moderate | May need to increase indinavir dose to 1000 mg q8h. |
| | Ritonavir | Dual Inhibition of hepatic metabolism | Efavirenz AUC increased by 21%.<br>Ritonavir AUC increased by 17%. | Immediate | Minor | No adjustment needed. May be able to reduce dose of ritonavir to 500 mg bid if GI intolerance occurs. |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Efavirenz (Sustiva®) (EFV)** *(continued)* | Ergot Alkaloid | Inhibition of hepatic metabolism | Potential acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities | Immediate | Major | **Concurrent administration contraindicated.** |
| | Midazolam, Triazolam | Inhibition of hepatic metabolism | AUCs of midazolam and triazolam increased | Immediate | Major | **Concurrent administration contraindicated** due to potential for prolonged sedation. Lorazepam and Temazepam may be safe alternatives |
| | Terfenadine, Astemizole, Cisapride | Inhibition of hepatic metabolism | Levels of terfenadine, astemizole, cisapride increased | Immediate | Major | **Concurrent administration contraindicated** due to potential for serious cardiac arrhythmia. |
| | Clarithromycin | Induction of hepatic metabolism | Clarithromycin AUC decreased by 39% | Immediate | Moderate | Incidence of rash increased to 46% with concurrent administration. No interaction with azithromycin, a better alternative. |
| | Ethinyl estradiol (oral contraceptive) | Inhibition of hepatic metabolism | Ethinyl estradiol AUC increased by 37% | Immediate | Minor | No dose changes recommended. Clinical significance of interaction unknown. No data on progesterone component of oral contraceptive available. Alternative form of birth control recommended. |
| | Rifabutin | Induction of hepatic metabolism | Rifabutin AUC decreased by 35%. No effect on Efavirenz AUC | Delayed | Moderate | If concurrent administration required, increase dose of rifabutin to 450 mg or 600 mg po qd. |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| | Rifampin | Induction of hepatic metabolism | Efavirenz AUC decreased by 26%. No change in rifampin levels. | Delayed | Moderate | **Concurrent administration contraindicated.** Rifabutin dose adjusted to 450-600 mg qd is a better alternative to rifamycin. |
| ***Protease Inhibitors*** | | | | | | |
| **Indinavir (Crixivan®) (IDV)** | DDI | Impairment of indinavir absorption by ddI buffer | Decreases absorption of indinavir | Immediate | Moderate | Separate indinavir and ddI doses by at least 1 hour. |
| | Simvastatin/ Lovastatin | Inhibition of hepatic metabolism. | Increased serum levels of simvastatin and lovastatin | Immediate | Moderate | **Avoid concurrent administration.** Possible alternatives include atorvastatin, pravastatin, cerivastatin, fluvastatin. Monitor for adverse effect due to limited clinical data with these agents |
| | Rifabutin | Inhibition of hepatic metabolism by indinavir | Rifabutin AUC increased by 2 fold. | Immediate | Moderate | Decrease rifabutin dose by half (150mg once a day). |
| | | Induction of hepatic metabolism by rifabutin. | Indinavir AUC decreased by 32% | Delayed | Moderate | May need to increase indinavir dose to 1Gm po tid. |
| | Rifampin | Induction of hepatic metabolism | Indinavir AUC decreased by 90% | Immediate | Major | **Concurrent administration contraindicated.** |
| | Sildenafil | Inhibition of hepatic metabolism. | Sildenafil AUC increased by 2 to 11 fold. | Immediate | Major | **Caution** with concurrent use, Do not exceed 25 mg of sildenafil in a 48-hour period. |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Indinavir (Crixivan®) (IDV)** *(continued)* | Terfenadine Astemizole Cisapride | Inhibition of hepatic metabolism | Drug levels increased by 3-fold or greater. | Immediate | Major | **Concurrent administration contraindicated** due to potential for cardiac arrhythmias. Alternative antihistamines include loratidine, fexofenadine or cetirizine. Alternative pro-kinetic agent includes metoclopramide. |
| | Ergot Alkaloid | Inhibition of hepatic metabolism | Potential acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities | Immediate | Major | **Concurrent administration contraindicated.** |
| | Ketoconazole Itraconazole | Inhibition of hepatic metabolism | Indinavir AUC increased by 70%. | Immediate | Moderate | Dose indinavir at 600mg Q8h. |
| | Midazolam, Triazolam | Inhibition of hepatic metabolism | AUCs of midazolam and triazolam are increased. | Immediate | Major | **Concurrent administration contraindicated** due to potential for prolonged sedation. |
| | Nelfinavir | Inhibition of hepatic metabolism. | Indinavir AUC increased by 50%<br>Nelfinavir AUC increased by 80% | Immediate | Minor | Limited dosing data using indinavir 1200 mg bid + nelfinavir 1250 mg bid. |
| | Amprenavir | Inhibition of hepatic metabolism | Amprenavir AUC increased by 26%.<br>Indinavir AUC increased by 38%. | Immediate | Minor | No dose adjustment recommended. |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **Indinavir (Crixivan®) (IDV)** *(continued)* | Ritonavir | Inhibition of hepatic metabolism | Indinavir AUC increased by 2 to 5-fold. | Immediate | Minor | Interaction allows indinavir to be given twice-daily (400 mg bid, 600 mg bid or 800 mg bid). Most experience has been with co-administration of 400 mg of indinavir and 400 mg of ritonavir twice-daily. Other dosing regimens studied include indinavir 600 mg bid + ritonavir 200mg bid or indinavir 800mg bid + ritonavir 100 or 200 mg bid. |
| | Saquinavir | Inhibition of hepatic metabolism | Saquinavir AUC increased 4- to 7-fold<br>No effect on Indinavir level | Immediate | Moderate | In vitro antagonism. Avoid co-administration. |
| **Saquinavir (Invirase®) (Fortovase®) (SQV)** | Ritonavir | Inhibition of hepatic metabolism | Saquinavir AUC increased by 20-fold. | Immediate | Minor | Dual protease inhibitor combination with the most clinical experience. Recommended doses: ritonavir 400 mg bid and saquinavir 400 mg bid |
| | Indinavir | Inhibition of hepatic metabolism | Saquinavir AUC increased 4- to7- fold<br>No effect on indinavir | Immediate | Moderate | In vitro antagonism. Avoid co-administration |
| | Nelfinavir | Inhibition of hepatic metabolism | Fortovase® AUC increased by 3 to 5-fold. Nelfinavir AUC increased by 20% | Immediate | Minor | Recommended doses are nelfinavir 750mg tid and Fortovase® 800mg tid. |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Saquinavir (Invirase®) (Fortovase®) (SQV)** *(continued)* | Amprenavir | Induction of hepatic metabolism | Saquinavir level decreased by 18%. Amprenavir level decreased by 36%. | Delayed | Minor | Insufficient data to recommend dose adjustment. |
| | Ketoconazole | Inhibition of hepatic metabolism | Saquinavir level increased by 3-fold. | Immediate | Minor | Beneficial pharmacokinetic interaction. Use standard doses. |
| | Midazolam, Triazolam | Inhibition of hepatic metabolism | Midazolam and triazolam AUCs increased | Immediate | Major | **Concurrent administration contraindicated** due to potential for prolonged sedation. |
| | Terfenadine Astemizole Cisapride | Inhibition of hepatic metabolism | Drug levels increased by 3-fold or greater. | Immediate | Major | **Concurrent administration Contraindicated** due to potential for cardiac arrhythmias. Alternative antihistamines include loratidine, fexofenadine or cetirizine. Alternative pro-kinetic agent includes metoclopramide. |
| | Ergot Alkaloid | Inhibition of hepatic metabolism | Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities | Immediate | Major | **Concurrent administration contraindicated.** |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **Saquinavir (Invirase®) (Fortovase®) (SQV)** *(continued)* | Simvastatin/ Lovastatin | Inhibition of hepatic metabolism. | Simvastatin and lovastatin serum level increased | Immediate | Moderate | **Avoid co-administration.** Recommended alternatives include atorvastatin, pravastatin, cerivastatin, fluvastatin. Monitor for adverse effects due to limited clinical data with these agents |
| | Rifabutin/ Rifampin | Induction of hepatic metabolism | Rifabutin and rifampin decrease AUC of saquinavir by 40% and 80% respectively. | Delayed | Major | **Concurrent administration contraindicated.** |
| | Sildenafil | Inhibition of hepatic metabolism. | Sildenafil AUC increased by 2- to 11-fold. | Immediate | Major | **Caution** with concurrent use. Do not exceed 25 mg of sildenafil in a 48-hour period |
| **Ritonavir (Norvir®) (RTV)** | Metronidazole | Alcohol in ritonavir liquid may precipitate a disulfiram-like reaction. | Unexpected nausea | Immediate | Moderate | Warn patient of the alcohol content in ritonavir liquid. |
| | Ethinyl estradiol (Oral contraceptive) | Induction and increase in glucuronosyl transferase activity. | Ethinyl estradiol level decreased by 40% | Delayed | Major | Warn patient of interaction. Recommend another method of contraception. |
| | Sildenafil | Inhibition of hepatic metabolism. | Sildenafil AUC increased by 2 to 11- fold. | Immediate | Major | **Caution** with concurrent use. Do not exceed 25 mg of sildenafil in a 48 hour period |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Ritonavir (Norvir®) (RTV)** *(continued)* | Theophylline | Induction of glucuronosyl transferase activity. | Theophylline AUC dcreased by 43% | Delayed | Moderate | Monitor theophylline levels; dose may need to be increased if subtherapeutic. |
| | Ketoconazole | Inhibition of hepatic metabolism | Ketoconazole AUC increased more than 3-fold. | Immediate | Moderate | May need to decrease ketoconazole dose. |
| | Rifabutin | Inhibition of hepatic metabolism | Rifabutin AUC increased 4-fold | Immediate | Moderate | Concurrent use of rifabutin and ritonavir is contraindicated by the manufacturer. Some experts recommend one-fourth the dose (150mg every other day) of rifabutin if needed, however no data support this recommendation. |
| | Rifampin | Induction of hepatic metabolism | Ritonavir AUC decreased by 35% | Delayed | Moderate | Monitor for therapeutic efficacy of ritonavir. May need to increase ritonavir dose. There may be an increase in liver toxicity |
| | Ergot Alkaloid | Inhibition of hepatic metabolism | Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities | Immediate | Major | **Concurrent administration contraindicated.** |
| | Terfenadine Astemizole Cisapride | Inhibition of hepatic metabolism | Drug level increased by 3-fold or greater. | Immediate | Major | **Concurrent administration contraindicated** due to potential for cardiac arrhythmias. Alternative antihistamines include loratidine, fexofenadine or cetirizine. Alternative pro-kinetic agents include metoclopramide. |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **Ritonavir (Norvir®) (RTV)** *(continued)* | Benzodiazepines | Inhibition of hepatic metabolism | Prolonged sedation due to accumulation of benzodiazepine | Delayed | Major | **Concurrent administration of zolpidem, lorazepate, midazolam, diazepam, estazolam, flurazepam and triazolam is contraindicated.** Alternative benzodiazepine that can be used : temazepam and lorazepam. |
| | Antiarrhythmics | Inhibition of hepatic metabolism | AUC of antiarrhythmics increased | Immediate | Major | **Concurrent administration of propafenone, quinidine, flecainide, amiodarone, bepridil, encainide is contraindicated.** |
| | Methadone | Induction of hepatic metabolism | Methadone levels decreased by 37%. | Delayed | Moderate | Monitor for withdraw symptoms; may require dose increase of methadone. |
| | Ketoconazole | Inhibition of hepatic metabolism | Ketoconazole levels increased by 3-fold. | Immediate | Moderate | Use with caution; do not exceed 200 mg ketoconazole per day. |
| | Antidepressant/ Antipsychotic | Inhibition of hepatic metabolism | Antidepressant and antipsychotic AUCs are increased | Immediate | Major | **Concurrent administration of buproprion, pimozide, nefazadone and clozapine is contraindicated.** Fluoxetine can be used. Desipramine may be used but dose may have to be reduced if used concurrently with ritonavir. |
| | Simvastatin/ Lovastatin | Inhibition of hepatic metabolism. | Increased simvastatin and lovastatin serum levels. | Immediate | Moderate | **Avoid co-administration.** Alternatives include atorvastatin, pravastatin, cerivastatin, fluvastatin. Monitor for adverse effect due to limited clinical data. |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Ritonavir (Norvir®) (RTV)** *(continued)* | Opioid analgesic | Inhibition of hepatic metabolism | Prolong sedation and possible respiratory depression | Immediate | Major | **Concurrent administration of meperidine and propoxyphene is contraindicated.** Oxycodone can be used. |
| | NSAID | Inhibition of hepatic metabolism | NSAID AUCs may be increased | Immediate | Major | **Concurrent administration of Piroxicam is contraindicated.** ASA can be used. |
| | Saquinavir | Inhibition of hepatic metabolism | Saquinavir AUC increased by 20-fold. | Immediate | Minor | Dual protease inhibitor with the most clinical experience. Recommended doses: ritonavir 400mg bid and Fortovase® or Invirase® 400 mg bid. |
| | Indinavir | Inhibition of hepatic metabolism | Indinavir AUC increased by 2 to 5-fold. | Immediate | Minor | Interaction allows indinavir to be dosed twice-daily (400 mg bid, 600 mg bid or 800 mg bid) which reduces renal stones caused by indinavir. Most experience has been with indinavir 400 mg bid and ritonavir 400 mg bid. Other dosing regimens include indinavir 600 mg bid + ritonavir 200mg bid or indinavir 800mg bid + ritonavir 100 or 200 mg bid. |
| | Nelfinavir | Inhibition of hepatic metabolism | Nelfinavir AUC increased by 1.5 fold. | Immediate | Minor | Ongoing clinical trials are using ritonavir 400mg bid and nelfinavir 500 mg or 750 mg bid. |
| | Amprenavir | Inhibition of hepatic metabolism | Amprenavir AUC increased by 2.5-fold. | Immediate | Minor | Insufficient data for dose recommendation. May be able to use a lower dose of amprenavir. |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **Nelfinavir (Viracept®) (NFV)** | Ketoconazole | Inhibition of hepatic metabolism | Nelfinavir AUC increased by 35% | Immediate | Minor | No dose adjustment needed. |
| | Fluconazole | Inhibition of hepatic metabolism | Nelfinavir AUC increased by 30% | Immediate | Minor | May be beneficial. No dose adjustment needed. |
| | Simvastatin/ Lovastatin | Inhibition of hepatic metabolism. | Simvastatin and lovastatin serum levels increased. | Immediate | Moderate | **Avoid co-administration:** Alternatives include atorvastatin, pravastatin, cerivastatin, fluvastatin. Monitor for adverse effects due to limited clinical data |
| | Rifampin | Induction of hepatic metabolism | Nelfinavir AUC decreased by 82% | Delayed | Major | **Concurrent administration contraindicated.** |
| | Rifabutin | Induction of hepatic metabolism by rifabutin | Nelfinavir AUC decreased by 32% | Delayed | Moderate | If co-administration required, increase nelfinavir to 1000mg po tid. |
| | | Inhibition of hepatic metabolism by nelfinavir | Rifabutin levels increased 3-fold | Immediate | Moderate | If co-administration required, decrease rifabutin to 150 mg po qd. |
| | Benzodiazepines | Inhibition of hepatic metabolism | Prolonged sedation due to accumulation of benzodiazepine. | Immediate | Major | **Midazolam and triazolam are contraindicated.** Alternative benzodiazepines include temazepam and lorazepam. |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Nelfinavir (Viracept®) (NFV)** *(continued)* | Ergot Alkaloid | Inhibition of hepatic metabolism | Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities | Immediate | Major | **Concurrent administration contraindicated.** |
| | Terfenadine Astemizole Cisapride | Inhibition of hepatic metabolism | Drug levels increased by 3-fold or greater. | Immediate | Major | **Concurrent administration contraindicated** due to potential cardiac arrhythmia. Recommended alternative antihistamine: loratidine, fexofenadine or cetirizine. Alternative pro-kinetic agent: metoclopramide |
| | Ethinyl Estradiol (oral contraceptive) | Induction of hepatic metabolism | Ethinyl estradiol AUC decreased by 47% | Delayed | Major | Advise patient to use **alternative method of contraception.** |
| | Sildenafil | Inhibition of hepatic metabolism. | Sildenafil AUC increased by 2-11 fold. | Immediate | Major | **Caution** with concurrent use. Do not exceed 25 mg of sildenafil in a 48 hour period |
| | Indinavir | Inhibition of hepatic metabolism. | Indinavir AUC increased by 50% Nelfinavir AUC increased by 80% | Immediate | Minor | Limited data for dosing IDV 1200mg bid + NFV 1250 mg bid. |
| | Saquinavir | Inhibition of hepatic metabolism | Fortovase® AUC increased by 3-5 fold. Nelfinavir AUC increased by 20% | Immediate | Moderate | Dose nelfinavir 750mg tid and Fortovase 800mg tid. |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **Nelfinavir (Viracept®) (NFV)** *(continued)* | Amprenavir | Inhibition of hepatic metabolism | Nelfinavir AUC increased by 15%, Amprenavir AUC increased by 50%. | Immediate | Minor | No dose adjustment. Insufficient data to recommend a dosage adjustment. |
| | Ritonavir | Inhibition of hepatic metabolism | Nelfinavir AUC increased by 1.5 fold. Increase in nelfinavir M8 metabolite. | Immediate | Moderate | Ongoing clinical trials are using ritonavir 400mg bid and nelfinavir 500 mg or 750 mg bid. |
| **Amprenavir (Angenerase®) (APV)** | Rifampin | Induction of hepatic metabolism | Amprenavir AUC decreased by 80% | Delayed | Major | **Concurrent administration contraindicated.** |
| | Rifabutin | Induction of hepatic metabolism | Amprenavir AUC decreased by 14%. Rifabutin AUC increased by 204% | Delayed | Moderate | Decrease rifabutin dose by one-half: Dose rifabutin 150mg qd. No change in amprenavir dose. |
| | Ketoconazole | Inhibition of hepatic metabolism | Amprenavir AUC increased by 32%. Ketoconazole AUC increased by 44%. | Immediate | Minor | May be beneficial. No dose adjustment needed. |
| | Clarithromycin | Inhibition of hepatic metabolism | Amprenavir AUC increased by 18% | Immediate | Minor | No dose adjustment needed. |
| | Ethinyl Estradiol (oral contraceptive) | Induction of hepatic metabolism | Potential decreases in ethinyl estradiol level. | Delayed | Major | Advise patient of potential risk and to use an alternative contraceptive method. |

*Table continues . . .*

**TABLE 14-4: DRUG INTERACTIONS OF ANTIMICROBIALS** *(continued)*

| *PRIMARY DRUG* | *INTERACTING DRUG* | *MECHANISM OF INTERACTION* | *EFFECT* | *TIME COURSE* | *SEVERITY* | *COMMENTS* |
|---|---|---|---|---|---|---|
| **Amprenavir (Angenerase®) (APV)** *(continued)* | Sildenafil | Inhibition of hepatic metabolism. | Sildenafil AUC increased by 2-11 fold. | Immediate | Major | **Caution** with concurrent use. Do not exceed 25 mg of sildenafil in a 48-hour period |
| | Simvastatin/ Lovastatin | Inhibition of hepatic metabolism. | Simvastatin and lovastatin levels increased. | Immediate | Moderate | Avoid concurrent administration. Alternative agents include atorvastatin, pravastatin, cerivastatin, fluvastatin. Monitor for adverse effects due to limited clinical data. |
| | Saquinavir | Induction of hepatic metabolism. | Saquinavir level decreased by 18%. Amprenavir level decreased by 36%. | Delayed | Minor | No dose adjustment. Insufficient data for dose recommendation |
| | Indinavir | Inhibition of hepatic metabolism. | Amprenavir AUC increased by 33%. Indinavir AUC decreased by 38%. | Immediate | Minor | No dose adjustment. |
| | Nelfinavir | Inhibition of hepatic metabolism. | Nelfinavir AUC increased by 15%, Amprenavir AUC increased by 50%. | Immediate | Minor | No dose adjustment. Insufficient data for dose recommendation. |
| | Ritonavir | Inhibition of hepatic metabolism. | Amprenavir AUC increased 2.5-fold. | Immediate | Minor | Insufficient data for dose recommendation. |

*Table continues . . .*

**Table 14-4: Drug Interactions of Antimicrobials** *(continued)*

| *Primary Drug* | *Interacting Drug* | *Mechanism of Interaction* | *Effect* | *Time Course* | *Severity* | *Comments* |
|---|---|---|---|---|---|---|
| **Amprenavir (Angenerase®) (APV)** *(continued)* | Efavirenz | Induction of hepatic metabolism | Amprenavir AUC decreased by 36%. Efavirenz AUC increased by 15% | Delayed | Moderate | Further studies needed for dosage recommendation. |
| | Bepridil | Inhibition of hepatic metabolism | Bepridil AUC Increased | Immediate | Major | **Concurrent administration contraindicated.** |
| | Ergot Alkaloid | Inhibition of hepatic metabolism | Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities | Immediate | Major | **Concurrent administration contraindicated.** |
| | Midazolam, Triazolam | Inhibition of hepatic metabolism | AUCs of midazolam and triazolam are increased. | Immediate | Major | **Concurrent administration contraindicated** due to potential for prolonged sedation. Lorazepam and Temazepam may be safe alternatives |
| | Terfenadine Astemizole Cisapride | Inhibition of hepatic metabolism | Cardiotoxic drug level increased by 3-fold or greater. | Immediate | Major | **Concurrent administration contraindicated** due to potential for cardiac arrhythmias. Alternatives include loratidine, fexofenadine or cetirizine. Alternative prokinetic agent includes metoclopramide. |

**AUC=** Area Under the Concentration Time Curve
**Cmax=** Peak serum concentration
**Cmin=** Trough serum concentration

**Time course:** *Delayed* = maximal interaction occurring at 14 days
*Immediate* = interaction occurring immediately.

**Severity:** *Major* = Do not co-administer; contraindicated.
*Moderate* = Can be co-administered with caution and possible dose adjustment.
*Minor* = Can be co-administered

**TABLE 14-5: CLINICALLY PERTINENT FOOD-DRUG INTERACTIONS**

***GANCICLOVIR CAPSULE/ ITRACONAZOLE CAPSULE / NELFINAVIR / RITONAVIR:***
Should be taken with food or within 2 hours of eating.

***AZT :***
Can be taken with food to decrease GI side effects.

***SAQUINAVIR (FORTOVASE® AND INVIRASE®) / ATOVAQUONE:***
Should be administered with a high fat meal

***EFAVIRENZ / AMPRENAVIR:***
High fat meal should be avoided

***DIDANOSINE / INDINAVIR / ITRACONAZOLE SOLUTION:***
Should be taken on an empty stomach (1 hour before or 2 hours after meals).

***GRAPEFRUIT JUICE:***
Increases saquinavir levels 40-100% but decreases indinavir AUC by 26%.

**TABLE 14-6: DRUGS OF SPECIAL CONSIDERATION IN WOMEN**

| *DRUG NAME* | *FDA CLASS* | *COMMENTS* |
|---|---|---|
| **Terbutaline** | B | Terbutaline has produced significant increases in birth weights (Briggs et al, 1998). Follow-up studies did not show increased adverse fetal outcomes (Acta Obstet Gynecol Scand Suppl 1982; 108:67-70.) |
| **Ritodrine** | B | The manufacturer reports that ritodrine administration after the 20th week of gestation has not been associated with an increase in fetal abnormalities. |
| **Methergine** | C | Indicated for postpartum uterine bleeding. According to the manufacturer, oral methylergonovine 0.2 milligram 3-to 4-times daily may be administered to nursing mothers for a MAXIMUM of 1 week postpartum to control uterine bleeding |
| ***Pain Medication*** | | |
| **Acetaminophen** | B | Acetaminophen is considered safe for short term use in all stages of pregnancy |
| **Aspirin** | C | **Avoid in pregnancy.** However if absolutely needed, doses of 80 mg per day may be used. Avoid full dose aspirin in third trimester due to potential for bleeding complication in the newborn and prolongation of gestation and labor. |
| **Non-steroidal anti-inflammatory drugs (NSAIDs)** | C | **Avoid in pregnancy.** Due to the prostaglandin synthesis inhibition, constriction of ductus arteriosus has been reported. Persistent pulmonary hypertension in the newborn has occurred when NSAIDs were used in 3rd trimester or near term. NSAIDs have been shown to inhibit labor and prolong pregnancy. |
| **Narcotic analgesic** | B | Narcotic analgesics can be used short term in . pregnancy. **Avoid the use of high doses for prolong periods near term as neonatal withdrawal can occur.** |

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**Table 14-7: Alternative/Complimentary Medication to Avoid in Pregnancy**

| *Drug Name* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|
| **Vitamin A** | A known teratogen at high doses in animal data. | A double-blind randomized trial of low dose supplementation with Vitamin A or beta carotene (7,000 mcg retinol equivalent) in malnourished pregnant women reported a 40% decrease in newborn mortality (BMJ 1999 Feb 27; 318 (7183): 570-5). In a prospective case controlled study of 423 exposures to 10,000 IU vit A during the first 9 weeks. An increased risk of major malformations was not reported. (Teratology 1999 Jan; 59(1): 7-11) | Further research is needed to recommend Vitamin A intake.<br>**Until more data are available it is prudent to consume only the recommended dietary allowance of 8,000 IU (which can be obtained by a balanced diet).** |
| **Vitamin B6** *(in doses above 100 mg a day)* | None | None | **Avoid use of high doses in pregnancy.**<br>**Possible health hazard: ataxia and peripheral neuropathy.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |

*Table continues . . .*

**TABLE 14-7: ALTERNATIVE/COMPLIMENTARY MEDICATION TO AVOID IN PREGNANCY** *(continued)*

| *DRUG NAME* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|
| **Niacin** *(in doses above 500mg immediate-release or 750mg sustained-release)* | None | None | **Avoid use of high doses in pregnancy.**<br>**Possible health hazard: GI symptoms (N/V/D, abdominal cramps); liver disease.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Selenium** *(in doses of greater than 800-1000 mcg per day)* | None | None | **Avoid use of high doses in pregnancy.**<br>**Possible health hazard: Tissue damage.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Ma-huang (Ephedra Sinica)** | None | None | **Avoid use in pregnancy.**<br>**The FDA warns against using Ma-huang (Ephedra Sinica) due to possible health hazards including: high blood pressure, irregular heartbeat, nerve damage, injury, insomnia, tremor, headache, seizure, heart attack, stroke, and death (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). Over 500 reports of adverse events including 8 fatalities have been reported to the FDA. (MMWR August 16,1996).** |
| **St John's Wort (Hypericum perforatum)** | None | None | Meta-analysis of St John's wort suggests that it was more effective than placebo and as effective as low dose tricyclic antidepressants for short-term management of mild-to-moderately severe depression. (J Nervous and Mental dis 1999; 187 (9), 532-538). **Due to the lack of data in pregnancy the routine use of St John's Wort cannot be recommended.**<br>**Major drug interaction:** Indinavir trough concentration (Cmin) decreases by 81% when co-administered with St John's wort. |

*Table continues . . .*

**Table 14-7: Alternative/Complimentary Medication to Avoid in Pregnancy** *(continued)*

| *Drug Name* | *Animal Data* | *Human Experience in Pregnancy* | *Comments* |
|---|---|---|---|
| **Chaparral herb (traditional American Indian medicine)** | None | None | **Avoid use in pregnancy.**<br>**Possible health hazard: liver disease, possibly irreversible.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Comfrey herb** | None | None | **Avoid in pregnancy.**<br>**Possible health hazard: obstruction of blood flow to liver, possibly leading to death.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Slimming/ dieter's tea** | None | None | **Avoid in pregnancy.**<br>**Possible health hazard: nausea, diarrhea, vomiting, stomach cramps, chronic constipation, fainting, possibly death.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Germander herb** | None | None | **Avoid in pregnancy.**<br>**Possible health hazard: liver disease, possibly leading to death.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Lobelia herb (Indian tobacco)** | None | None | **Avoid in pregnancy.**<br>**Possible health hazard: respiratory distress, tachycardia, hypotension, and possibly coma and death at higher doses.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Magnolia-Stephania herb** | None | None | **Avoid in pregnancy.**<br>**Possible health hazard: renal failure which may be irreversible.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |

*Table continues . . .*

**TABLE 14-7: ALTERNATIVE/COMPLIMENTARY MEDICATION TO AVOID IN PREGNANCY** *(continued)*

| *DRUG NAME* | *ANIMAL DATA* | *HUMAN EXPERIENCE IN PREGNANCY* | *COMMENTS* |
|---|---|---|---|
| **Willow bark herb** | None | None | **Avoid in pregnancy.**<br>**Possible health hazard: allergic reaction (marketed as aspirin-free product, although it actually contains a precursor of aspirin with subsequent conversion to aspirin.)** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Wormwood herb** | None | None | **Avoid in pregnancy.**<br>**Possible health hazard: neurological symptoms, paresthesia, delirium and paralysis.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **Germanium mineral** | None | None | **Avoid in pregnancy.**<br>**Possible health hazard: kidney damage, possibly death.** (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |
| **L-tryptophan amino acid** | None | None | **Avoid in pregnancy.**<br>**Possible heath hazard: eosinophilic myalgia syndrome, a potentially fatal blood dyscrasia. (FDA has limited its import into the US)**. (FDA Statement before Senate Committee on Labor and Human Resources, Oct 21, 1993). |

## REFERENCES

[1] Sustiva (Efavirenz) Capsules Product Monograph. Wilmington: DE: DuPont Pharmaceutical; 1998.

[2] Shepard TH, Catalog of Teratogenic *Agents. 7th ed. Baltimore, MD: JHU, Press. 1992:* 206-7.

[3] Ndiaye O, Gbaguidi A, Ba M et al. Newborn infant with macrosomia: etiologic factors and perinatal complications. *Dakar Med* 1997: 42(2): 159-61.

[4] Crixivan (Indinavir) Capsules Product Monograph. West Point; Pa: Merck & Co; 1998.

[5] Connor E and Mofenson L. Zidovudine for the reduction of perinatal human immunodeficiency virus transmission: Pediatric AIDS Clinical Trials Group Protocol 076-results and treatment recommendations. *Pediatric Infect. Dis J*, 1995; 14:536-41.

[6] Hanson C, Antonelli TA; Sperling RS et al. Lack of tumors in infants with perinatal HIV exposure and fetal neonatal exposure to zidovudine. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999 Apr 15;20(5):463-7

[7] Guay LA, Musoke P; Fleming T et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomized trial. *Lancet* 1999 Sep 4; 354(9181): 795-802.

[8] Dunihoo DR. Maternal physiology. In: Dunihoo DR, editor. *Fundamentals of Gynecology and Obstetrics.* Philadelphia: J.B. Lippincott Co. 1992: 280-4

[9] Parry E, Shields R, Turnbull A. Transit time in the small intestine in pregnancy. *J Obstet Gynaecol Br Commonw* 1970; 77:900-1.

[10] Davidson JM, Hytten FE. Glomerular filtration during and after pregnancy. *J Obstet Gynaecol* 1974; 81: 588-95.

[11] Mirochnick M; Fenton T; Gagnier P et al. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1- infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. *J Infect Dis* 1998 Aug;178(2):368-74.

[12] Pharmacokinetic and antiretroviral acitivity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring.

[13] Schuman P; Kauffman R; Crane LR et al. Pharmacokinetics of zidovudine during pregnancy. Int Conf AIDS. 1990 Jun 20-23; 6 (2): 94 (abstract no. F.B.17)

[14] Wang Y; Liningston E; Patil S et al. Pharmacokinetics of didanosine in antepartum and postpartum human immunodeficiency virus-infected pregnant women and their neonates: an AIDS clinical trial group study. *JID* 1999 Nov; 180(5): 1536-41.

[15] Briggs, Freeman and Yaffe; *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risks,* Williams and Wilkins.