TABLE 2. Summary of pre-clinical and human data on opportunistic infection drugs during pregnancy

Drug	FDA pregnancy category	Placental passage (newborn/ maternal ratio)	Animal reproduction studies	Concerns about human pregnancy	Recommended use during pregnancy
Acyclovir	B	Yes (1.2–1.4)	Impaired fertility, fetal death, growth retardation in rats at high doses. No teratogenicity in mice, rats, rabbits at human levels	Large experience in pregnancy (>700 first-trimester exposures reported to registry); well-tolerated	Treatment of frequent or severe symptomatic herpes outbreaks or varicella; use for prevention of recurrences at term investigational
Adefovir	C	Unknown	Embryotoxic in mice, caused thymic lymphoid tissue destruction later in the neonate with use in later pregnancy in mice	No experience with human use	Not recommended; report exposures during pregnancy to Antiretroviral Pregnancy Registry (800-258-4263)
Albendazole	C	Unknown	Teratogenic (skeletal malformations) in rats and rabbits but not in mice	No experience; animal data concerning	Consider in second and third trimester for severe diarrhea with documented microsporidia infection
Amikacin	C	Moderate (0.15–0.5)	Not teratogenic in mice, rats, or rabbits	Theoretical risk for ototoxicty in fetus; reported with streptomycin but not amikacin	Drug resistant tuberculosis, severe MAC infections
Amphotericin B	B	Yes (0.4–1.0)	No effect on fertility, no teratogenicity in rats or rabbits	No studies. No evidence of teratogenicity; might be preferred over fluconazole in first trimester	Documented invasive fungal disease
Antimonials, pentavalent	Not FDA approved	Unknown	Antimony not teratogenic in rats, chicks, or sheep	One case report of use in human pregnancy in second trimester with good outcome. Labeled as contraindicated in pregnancy	Therapy of visceral leishmaniasis not responsive to amphotericin B or pentamidine
Atovaquone	C	Yes, in rats, rabbits (0.18-0.6)	Not teratogenic in rats or rabbits	Limited experience	*Pneumocystis jiroveci* pneumonia, *Toxoplasma gondii* infections
Azithromycin	B	Low	No effect on fertility, no teratogenicity in rodents	Moderate experience with use for treatment of *Chlamydia trachomatis* in pregnancy	Preferred agent for *Mycobacterium avium* complex (MAC) prophylaxis or treatment (with ethambutol); *chlamydia trachomatis* infection
Benznidazole	Not FDA approved	Yes, in rats	No specific studies of teratogenicity	Increase chromosomal aberrations in children receiving treatment; uncertain significance. No human pregnancy data	Not indicated in chronic infections; seek expert consultation if acute infection or symptomatic reactivation of *T. cruzi* diagnosed in pregnancy
Capreomycin	C	Unknown	Possible increase in skeletal variants in rats	Limited experience in human pregnancy; theoretical risk for fetal ototoxicity	Drug resistant tuberculosis
Caspofungin	C	Yes, in rats and rabbits	Incomplete ossification in rats and rabbits at similar to human doses	No experience with human use	Invasive *Candida* or *Aspergillus* infections refractory to amphotericin and azoles
Cephalosporins	B	Yes, moderate to high	No teratogenicity in rodents or rabbits	No evidence of teratogenicity in humans	Bacterial infections; alternate treatment for MAC
Cidofovir	C	Unknown	Embryotoxic and teratogenic (meningocele, skeletal abnormalities) in rats and rabbits	Unknown risk; animal studies concerning	Alternate treatment or secondary prophylaxis of life-threatening or sight-threatening cytomegalovirus infections
Ciprofloxacin, other quinolones	C	Yes, in rabbits	Arthropathy in immature animals; not embryotoxic or teratogenic in mice, rats, rabbits, or monkeys	Because of cartilage changes in immature animals, use in pregnant women and children aged <18 years not recommended; no increase in anomalies with >200 first trimester exposures	Severe MAC infections; multidrug resistant tuberculosis (Anthrax)
Clarithromycin	C	Unknown	Teratogenic in one strain of rats (cardiovascular defects) and mice (cleft palate); not teratogenic in rabbits or monkeys; intrauterine growth retardation in monkeys	Animal data concerning; limited human experience. No increase in anomalies in 156 infants with first trimester exposure but increased rate of first trimester spontaneous abortions	Treatment or secondary MAC prophylaxis if other choices exhausted

TABLE 2 (*Continued*). Summary of pre-clinical and human data on opportunistic infection drugs during pregnancy

Drug	FDA pregnancy category	Placental passage (newborn/ maternal ratio)	Animal reproduction studies	Concerns about human pregnancy	Recommended use during pregnancy
Clindamycin	B	Yes (0.5)	No effect on fertility; no teratogenicity in rodents	No concerns specific to pregnancy	Treatment of anaerobic bacterial infections; alternate agent for secondary prophylaxis of toxoplasma encephalitis
Clofazimine	C	Yes	Not teratogenic in mice, rats, or rabbits	Limited experience reported (19 cases); no anomalies noted but red-brown skin discoloration reported in several infants exposed throughout pregnancy	No indications
Cycloserine	C	Unknown	No data available	No data available	Drug resistant tuberculosis
Dapsone	C	Unknown	No animal studies of teratogenicity	Limited human experience does not suggest teratogenicity; might displace bound bilirubin in the neonate, increasing the risk for kernicterus	Alternate choice for primary or secondary *Pneumocytis jiroveci* pneumonia (PCP) prophylaxis
Diphenoxylate/ atropine (Lomotil®)	C	Unknown	Increased fetal death in rats at extremely high doses; no teratogenicity	Limited data do not indicate teratogenicity	Symptomatic treatment of diarrhea
Doxycycline, other tetracyclines	D	Passage in animal studies	Incorporated into fetal bones, teeth with staining; no birth defects in mice, rats, or rabbits	Risk for hepatic toxicity increased with tetracyclines in pregnancy; bone and tooth changes contraindicate use in pregnancy	None
Erythromycin	B	Limited passage	No evidence of teratogenicity	Hepatotoxicity with erythromycin estolate in pregnancy; other forms acceptable; no evidence of teratogenicity	Bacterial and chlamydial infections
Ethambutol	B	Yes (0.75)	Teratogenic, at high doses, in mice (cleft palate, exencephaly, vertebral abnormalities), rats (vertebral abnormalities), and rabbits (monophthalmia, cleft lip, palate)	No evidence of teratogenicity in 320 cases of human use for treatment of tuberculosis; avoid in first trimester if possible	Active tuberculosis and MAC treatment
Ethionamide	C	Unknown	Increased rate of defects (omphalocele, exencephaly, cleft palate) in rats, mice, and rabbits with high doses; not seen with usual human doses	Limited human data; avoid in first trimester if possible	Active tuberculosis
Famciclovir	B	Unknown	No evidence of teratogenicity in rats or rabbits	Limited human experience; report exposures during pregnancy to Registry (888-669-6682)	Recurrent genital herpes and primary varicella infection
Fluconazole	C	Unknown	Abnormal ossification, structural defects in rats, and mice at high doses	Case reports of rare pattern of craniofacial, skeletal abnormalities in four infants born to three women with prolonged exposure during pregnancy; no increase in defects seen in several series after single dose treatment	Only for documented systemic disease, not prophylaxis; not for treatment of vaginal or oral *Candida*; consider use of amphotericin B in first trimester
Flucytosine	C	Yes, in rats	Facial clefts and skeletal abnormalities in rats; no defects in mice or rabbits	No reports of use in first trimester of human pregnancy; might be metabolized to 5-fluorouracil, which is teratogenic in animals and possibly in humans	Use after first trimester if indicated for life-threatening fungal infections
Fomivirsen	C	Unknown	No animal studies	No data in human pregnancy	Intravitreous injection probably safe in pregnancy at minimal systemic levels
Foscarnet	C	Unknown	Teratogenic (skeletal abnormalities) in rats and rabbits	No data in human pregnancy	Treatment or secondary prophylaxis of life-threatening or sight-threatening CMV infection
Fumagillin	Not approved	Unknown	Caused complete litter destruction or growth retardation in rats, depending on when administered	No data in human pregnancy	Topical solution might be used for ocular infections

TABLE 2 (*Continued*). Summary of pre-clinical and human data on opportunistic infection drugs during pregnancy

Drug	FDA pregnancy category	Placental passage (newborn/ maternal ratio)	Animal reproduction studies	Concerns about human pregnancy	Recommended use during pregnancy
Ganciclovir, valganciclovir	C	Low	Embryotoxic in rabbits and mice; Teratogenic in rabbits (cleft palate, anophthalmia, aplastic kidney and pancreas, hydrocephalus)	Case reports of safe use in human pregnancy after transplants	Treatment or secondary prophylaxis of life-threatening or sight-threatening CMV infection. Preferred agent for therapy in children
Granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor	C	Yes	Not teratogenic in rats and rabbits	Case reports of use in human pregnancy without adverse effects	Treatment of leuckopenia
Imiquimod	B	Low, in rabbits	No teratogenicity in rats and rabbits	No experience with use in human pregnancy	Because of lack of experience, other treatment modalities such as cryotherapy or trichloroacetic acid recommended for wart treatment during pregnancy
Interferons: alfa, beta, gamma	C	Unknown	Abortifacient at high doses in monkeys, mice; not teratogenic in monkeys, mice, rats, or rabbits	Approximately 30 cases of use of interferon-alfa in pregnancy reported; 14 in first trimester without increase in anomalies; possible increased risk for intrauterine growth retardation	Treatment of hepatitis C should be delayed until after delivery if possible
Isoniazid	C	Yes, high	Not teratogenic in rodents and rabbits	Possible increased risk for hepatotoxicity during pregnancy; prophylactic pyridoxine, 50 mg/day, should be given to prevent neurotoxicity; prophylactic vitamin K recommended at birth to prevent hemorrhagic disease	Active tuberculosis; prophylaxis for exposure or skin test conversion
Itraconazole	C	Unknown	Teratogenic in rats (skeletal defects) and mice (encephalocele, macroglossia) at high doses	Case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy; no increase in defect rate noted among 156 infants born after first trimester itraconazole exposure	Only for documented systemic fungal disease, not prophylaxis
Kanamycin	D	Yes	Club feet in mice; no defects in rats, rabbits and monkeys except inner ear changes in multiple species	Hearing loss in 2.3% of 391 children after long term in utero therapy	Drug resistant tuberculosis
Ketoconazole	C	Low in animals	Teratogenic (VSD, cleft palate) in rats; increased fetal death in mice and rabbits	Inhibits androgen and corticosteroid synthesis; might impact fetal male genital development; case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy	None
Lamivudine	C	High	No evidence of teratogenicity in multiple species	No evidence of teratogenicity with approximately 1,000 first-trimester exposures to antiretroviral doses	Hepatitis B therapy, only as part of a combination antiretroviral regimen
Loperamide	B	Unknown	Not teratogenic in rats and rabbits	No increase in birth defects among infants born to 89 women with first trimester exposure	Symptomatic treatment of diarrhea
Miltefosine	Not FDA approved	Unknown	Embryotoxic in rats and rabbits; complete embryolethality in rabbits at doses of 6 mg/kg body weight/day	No experience with human use	Not recommended
Metronidazole	B	Yes	Multiple studies do not indicate teratogenesis; one study with positive findings in rodents and guinea pigs	Studies in several hundred women with first trimester exposure do not indicate increase in birth defects	Anaerobic bacterial infections, bacterial vaginosis, trichomoniasis, and giardiasis, amebiasis

TABLE 2 (*Continued*). Summary of pre-clinical and human data on opportunistic infection drugs during pregnancy

Drug	FDA pregnancy category	Placental passage (newborn/ maternal ratio)	Animal reproduction studies	Concerns about human pregnancy	Recommended use during pregnancy
Nifurtimox	Not FDA approved	Unknown	Not teratogenic in mice and rats	Increase chromosomal aberrations in children receiving treatment; uncertain significance; no experience in human pregnancy	Not indicated in chronic infection; seek expert consultation if acute infection or symptomatic reactivation of *T. cruzi* diagnosed in pregnancy
Nitazoxanide	Approved for use in children	Unknown	No data	No experience in human pregnancy	Experimental agent for cryptosporidiosis
Octreotide	B	Yes (0.5)	Not teratogenic in rats and rabbits	Four case reports with use in early pregnancy and normal outcomes	Symptomatic treatment of diarrhea
Para-aminosalicylic acid (PAS)	C	Unknown	Occipital bone defects in one study in rats; not teratogenic in rabbits.	Possible increase in limb, ear anomalies in one study with 143 first trimester exposures; no specific pattern of defects noted, several studies did not find increased risk	Drug resistant tuberculosis
Paromomycin	C	Unknown	Not teratogenic in mice and rabbits	Poor oral absorption makes toxicity, teratogenicity unlikely.	Experimental agent for cryptosporidiosis
Penicillin	B	High	Not teratogenic in multiple animal species	Vast experience with use in human pregnancy does not suggest teratogenicity	Syphilis, other susceptible bacterial infections
Pentamidine	C	High in rats	Embryocidal but not teratogenic in rats and rabbits with systemic use	Limited systemic absorption with aerosol use; limited experience with systemic use in pregnancy	Alternate therapy for *Pneumocystis jiroveci* pneumonia and leishmaniasis
Podophyllin, podofilox	C	Unknown	Increased embryonic and fetal deaths in rats and mice but not teratogenic	Case reports of maternal and fetal deaths after use of podophyllin resin in pregnancy are concerning; no clear increase in birth defects with first trimester exposure	Because alternative treatments for genital warts in pregnancy are available, use not recommended; inadvertent use in early pregnancy is not indication for abortion
Prednisone	B	Minimal	Dose dependent increased risk for cleft palate in mice, rabbits, and hamsters; dose dependent increase in genital anomalies in mice	Human data inconsistent in finding increased risk for cleft palate; risk for growth retardation; low birthweight might be increased with chronic use; monitor blood sugars with use in third trimester	Adjunctive therapy for severe *Pneumocystis* pneumonia; multiple other non-HIV related indications
Primaquine	C	Unknown	Not available	Limited experience with use in human pregnancy; theoretical risk for hemolytic anemia if fetus has G6PD deficiency	Alternate therapy for *Pneumocystis* pneumonia
Pyrazinamide	C	Unknown	Not teratogenic in mice	Limited experience with use in human pregnancy	Active tuberculosis
Pyrimethamine	C	Unknown	Teratogenic in mice, rats, and hamsters (cleft palate, neural tube defects, and limb anomalies)	Limited human data have not suggested an increased risk for birth defects; folate antagonist, use with leucovorin	Treatment and secondary prophylaxis of toxoplasmic encephalitis; alternate treatment of *Pneumocystis* pneumonia
Ribavirin	X	Unknown	Dose dependent risk for multiple defects (craniofacial, CNS, skeletal, anophthalmia) in rats, mice, and hamsters starting at doses below those used in humans	Reports of treatment during second half of pregnancy among nine women without incident; contraindicated in first trimester because of consistent teratogenicity in animals	Contraindicated in early pregnancy; no clear indications in pregnancy
Rifabutin	B	Unknown	Not teratogenic in rats and rabbits	No specific concerns for pregnancy	Treatment or prophylaxis of MAC, active tuberculosis
Rifampin	C	Yes (0.12–0.33)	Teratogenic in mice (cleft palate) and rats (spina bifida) but not in rabbits	No clear teratogenicity in humans; vitamin K recommended at birth to prevent hemorrhagic disease of the newborn	Active tuberculosis
Streptomycin	D	Unknown	No teratogenicity in mice, rats, and guinea pigs	Possible increased risk for deafness and VIII nerve damage; no evidence of other defects	Alternate therapy for active tuberculosis

TABLE 2 (*Continued*). Summary of pre-clinical and human data on opportunistic infection drugs during pregnancy

Drug	FDA pregnancy category	Placental passage (newborn/ maternal ratio)	Animal reproduction studies	Concerns about human pregnancy	Recommended use during pregnancy
Sulfadiazine	B	Yes (0.7-0.9)	Sulfonamides teratogenic in some animal studies	No clear teratogenicity among humans; potential for increased jaundice, kernicterus if used near delivery	Secondary prophylaxis of toxoplasmic encephalitis
Tenofovir	B	0.17 in monkeys	No evidence of birth defects in rats, rabbits, or monkeys at high doses; decreased fetal weights and increased bone porosity were observed in monkeys with long term exposure in utero to doses 25 times usual human dose; chronic administration in immature animals of multiple species at 6–50 times human doses have led to dose-specific bone changes ranging from decreased mineral density to severe osteomalacia and fractures	No experience with human use	Not recommended; report exposures during pregnancy to Antiretroviral Pregnancy Registry (800-258-4263)
Trimethoprim-sulfamethoxazole (TMP/SMX)	C	Yes (~1.0)	Teratogenic in rats and mice (cleft palate)	Possible increase in congenital cardiac defects, facial clefts with first trimester use. Potential for increased jaundice, kernicterus if used near delivery	Treatment and prophylaxis of *Pneumocystis* pneumonia
Trimetrexate	D	Yes	Teratogenic in rats and rabbits (visceral, ocular, skeletal, cardiovascular, CNS defects) at low doses	Similar drugs, methotrexate and aminopterin, are abortifacient and associated with embryopathy including "clover-leaf skull, limb defects, developmental delay, sometimes with neural tube defects; frequency might increase with increasing maternal dose	Use in pregnancy should be avoided if possible; might be used for *Pneumocystis* pneumonia if refractory/intolerant to TMP/SMX and pentamidine
Valacyclovir	B	Yes	Not teratogenic in mice, rats, and rabbits	Experience with valacyclovir in pregnancy limited; prodrug of acyclovir, which is considered safe for use in pregnancy	Alternate agent for herpes simplex virus and varicella infections in pregnancy
Voriconazole	D	Unknown	Embryotoxic in rats, rabbits. Teratogenic in rats (cleft palate, hydronephrosis, ossification defects)	No experience with human use	Not recommended

TABLE 3. Cytology and histology terms for Papanicolou smears and cervical, vaginal, and anal tissue samples

Cytology (Bethesda System 2001)	Tissue histology (Dysplasia system)	Tissue histology (Intraepithelial neoplasia system)
Negative for intraepithelial lesion or malignancy	Normal	Normal
Unsatisfactory	Unsatisfactory	Unsatisfactory
Atypical squamous cells—undetermined significance	No term	No term
Atypical squamous cells- cannot exclude high-grade squamous intraepithelial lesion (HSIL)	No term	No term
Low-grade squamous intraepithelial lesion	Mild	CIN I
HSIL	Moderate Severe CIS (carcinoma in situ)	CIN II CIN III CIN III
Carcinoma	Carcinoma	Carcinoma