

APPENDIX A: SUMMARY OF PRE-CLINICAL AND HUMAN DATA ON OI DRUGS IN PREGNANCY

DRUG	FDA PREG-NANCY CATEGORY	PLACENTAL PASSAGE (NEWBORN/MATERNAL RATIO)	ANIMAL REPRODUCTION STUDIES	CONCERNS IN HUMAN PREGNANCY	RECOMMENDED USE IN PREGNANCY
Acyclovir	B	Yes (1.2-1.4)	Impaired fertility, foetal death, and growth retardation in rats at high doses. No teratogenicity in mice, rats, or 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 in mice later in the neonate with use in later pregnancy.	No experience with human use.	Not recommended. Report exposures during pregnancy to Antiretroviral Pregnancy Registry, (910) 256-4263.
Albendazole	C	Unknown	Teratogenic (skeletal malformations) in rats and rabbits, but not in mice.	No experience, animal data concerning.	Consider in second, third trimester for severe diarrhoea with documented <i>Microsporidia</i> infection.
Amikacin	C	Moderate (0.15-0.5)	Not teratogenic in mice, rats, or rabbits.	Theoretical risk of ototoxicity in foetus; reported with streptomycin but not with amikacin.	Drug resistant TB, 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. May 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. Labelled as contra-indicated in pregnancy.	Therapy of visceral leishmaniasis not responsive to amphotericin B or pentamidine.
Atovaquone	C	Yes, in rats and rabbits (0.18-0.6)	Not teratogenic in rats or rabbits.	Limited experience.	PCP, <i>T. gondii</i> infections.
Azithromycin	B	Low	No effect on fertility; no teratogenicity in rodents.	Moderate experience with use for treatment of <i>Chlamydia trachomatis</i> in pregnancy.	Preferred agent for MAC prophylaxis or treatment (with EMB); <i>Chlamydia trachomatis</i> infection.
Benznidazole	Not FDA approved	Yes, in rats	No specific studies of teratogenicity.	Increase in 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 <i>T. cruzi</i> is diagnosed in pregnancy.
Capreomycin	C	Unknown	Possible increase in skeletal variants in rats.	Limited experience in human pregnancy. Theoretical risk of foetal ototoxicity.	Drug resistant TB.
Caspofungin	C	Yes, in rats and rabbits	Incomplete ossification in rats and rabbits at similar to human	No experience with human use.	Invasive <i>Candida</i> or <i>Aspergillus</i> infections refractory to amphotericin and azoles.

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			doses.		
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 CMV 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 age <18 years not recommended. No increase in anomalies with <200 first trimester exposures.	Severe MAC infections, MDR-TB. (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 noted.	Treatment or secondary MAC prophylaxis if other choices exhausted.
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 <i>Toxoplasma</i> encephalitis.
Clofazimine	C	Yes	Not teratogenic in mice, rats, or rabbits.	Limited experience reported (19 cases). No anomalies noted but red-brown skin discolouration reported in several infants exposed throughout pregnancy.	No current indications.
Cycloserine	C	Unknown	No data available.	No data available.	MDR-TB.
Dapsone	C	Unknown	No animal studies of teratogenicity.	Limited human experience does not suggest teratogenicity. May displace bound bilirubin in the neonate, increasing the risk of kernicterus.	Alternate choice for primary or secondary PCP prophylaxis.
Diphenoxylate/atropine (Lomotil®)	C	Unknown	Increased foetal death in rats at extremely high doses; no teratogenicity.	Limited data do not suggest teratogenicity.	Symptomatic treatment of diarrhoea.
Doxycycline, other tetracyclines	D	Passage in animal studies	Incorporated into foetal bones, teeth with staining. No birth defects in mice, rats, or rabbits.	Risk of hepatic toxicity increased with tetracyclines in pregnancy. Bone and tooth changes contra-indicate use in pregnancy.	None.
Erythromycin	B	Limited passage	No evidence of teratogenicity.	Hepatotoxicity with erythromycin estolate in pregnancy, other forms	Bacterial and chlamydial infections.

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				acceptable. No evidence of teratogenicity.	
EMB	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 TB. Avoid in first trimester if possible.	Active TB, 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 TB.
Famciclovir	B	Unknown	No evidence of teratogenicity in rats or rabbits.	Limited human experience. Report exposures during pregnancy to ARV Registry: (910) 256-0238.	Recurrent genital herpes, 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 4 infants born to 3 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 <i>Candida</i> . 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. May be metabolised 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.	Intravitreal injection probably safe in pregnancy as 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 may be used for ocular infections.
Ganciclovir, valganciclovir	C	Low	Embryotoxic in rabbits and mice. Teratogenic in rabbits: cleft	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

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			palate, anophthalmia, aplastic kidney and pancreas, hydrocephalus.		children.
G-CSF, GM-CSF	C	Yes	Not teratogenic in rats or rabbits.	Case reports of use in human pregnancy without adverse effects.	Treatment of leukopaenia.
Imiquimod	B	Low, in rabbits	No teratogenicity in rats or rabbits.	No experience with use in human pregnancy.	Given 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 and mice. Not teratogenic in monkeys, mice, rats, or rabbits.	Over 30 cases of use of alfa-interferon in pregnancy reported; 14 in first trimester without increase in anomalies. Possible increased risk of intrauterine growth retardation.	Treatment of HCV should be delayed until after delivery if possible.
INH	C	Yes, high	Not teratogenic in rodents, rabbits.	Possible increased risk of hepatotoxicity during pregnancy. Prophylactic pyridoxine, 50mg/day, should be given to prevent neurotoxicity. Prophylactic vitamin K recommended at birth to prevent haemorrhagic disease.	Active TB; 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, or monkeys except inner ear changes in multiple species.	Hearing loss in 2.3% of 391 children after long term <i>in utero</i> therapy.	Drug resistant TB.
Ketoconazole	C	Low in animals	Teratogenic (VSD, cleft palate) in rats. Increased foetal death in mice, rabbits.	Inhibits androgen and corticosteroid synthesis, may impact foetal male genital development. Case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy.	None.
3TC	C	High	No evidence of teratogenicity in multiple species.	No evidence of teratogenicity with nearly 1,000 first trimester	Hepatitis B therapy, only as part of a combination ARV regimen.

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				exposures to ARV doses.	
Loperamide	B	Unknown	Not teratogenic in rats, rabbits.	No increase in birth defects among infants born to 89 women with first trimester exposure.	Symptomatic treatment of diarrhoea.
Miltefosine	Not FDA approved	Unknown	Embryotoxic in rats and rabbits. Complete embryoletality in rabbits at doses of 6mg/kg/day.	No experience with human use.	Not recommended.
Metronidazole	B	Yes	Multiple studies do not suggest teratogenesis; one study with positive findings in rodents and guinea pigs.	Studies in several hundred women with first trimester exposure do not show increase in birth defects.	Anaerobic bacterial infections, bacterial vaginosis, trichomoniasis, giardiasis, amebiasis.
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 <i>T. cruzi</i> diagnosed in pregnancy.
Nitazoxamide	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 or rabbits.	4 case reports with use in early pregnancy and normal outcomes.	Symptomatic treatment of diarrhoea.
p-aminosalicylic acid (PAS)	C	Unknown	Occipital bone defects in one study in rats. Not teratogenic in rabbits.	Possible increase in limb and 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 TB.
Paromomycin	C	Unknown	Not teratogenic in mice or rabbits.	Poor oral absorption makes toxicity and 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 or rabbits with systemic use.	Limited systemic absorption with aerosol use. Limited experience with systemic use in pregnancy.	Alternate therapy for PCP, leishmaniasis.
Podophyllin, podofilox	C	Unknown	Increased embryonic and foetal deaths in rats and mice but not teratogenic.	Case reports of maternal and foetal deaths after use of podophyllin resin in pregnancy are concerning. No clear increase in birth defects with first trimester exposure.	Since 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 of cleft palate in mice, rabbits, and	Human data inconsistent in finding increased risk of cleft palate. Risk of growth retardation, low	Adjunctive therapy for severe PCP. Multiple other non-HIV related indications.

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			hamsters; dose-dependent increase in genital anomalies in mice.	birth weight may be increased with chronic use. Monitor blood sugars with use in third trimester.	
Primaquine	C	Unknown	Not available.	Limited experience with use in human pregnancy. Theoretical risk of haemolytic anaemia if foetus has G6PD deficiency.	Alternate therapy for PCP.
PZA	C	Unknown	Not teratogenic in mice.	Limited experience with use in human pregnancy.	Active TB.
Pyrimethamine	C	Unknown	Teratogenic in mice, rats, and hamsters (cleft palate, neural tube defects, limb anomalies).	Limited human data have not suggested an increased risk of birth defects. Folate antagonist, use with leucovorin.	Treatment and secondary prophylaxis of TE; alternate treatment of PCP.
Ribavirin	X	Unknown	Dose-dependent risk of 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 in 9 women without incident. Contra-indicated in first trimester because of consistent teratogenicity in animals.	Contra-indicated in early pregnancy. No clear indications in pregnancy.
Rifabutin	B	Unknown	Not teratogenic in rats or rabbits.	No specific concerns for pregnancy.	Treatment or prophylaxis of MAC, active TB.
RIF	C	Yes (0.12-0.33)	Teratogenic in mice (cleft palate), rats (spina bifida) but not in rabbits.	No clear teratogenicity in humans. Vitamin K recommended at birth to prevent haemorrhagic disease of the newborn.	Active TB.
Streptomycin	D	Unknown	No teratogenicity in mice, rats, or guinea pigs.	Possible increased risk of deafness and VIII nerve damage; no evidence of other defects.	Alternate therapy for active TB.
Sulfadiazine	B	Yes (0.7-0.9)	Sulfonamides teratogenic in some animal studies.	No clear teratogenicity in humans. Potential for increased jaundice, kernicterus if used near delivery.	Secondary prophylaxis of TE.
TDF	B	0.17 in monkeys	No evidence of birth defects in rats, rabbits, or monkeys at high doses. Decreased foetal weights and increased bone porosity were seen in monkeys with long-term exposure <i>in utero</i> to doses 25x usual human dose. Chronic administration in immature animals of	No experience with human use.	Not recommended. Report exposures during pregnancy to ARV Registry, (910) 256-0238.

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			multiple species at 6-50x human doses have led to dose-specific bone changes ranging from decreased mineral density to severe osteomalacia and fractures.		
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 PCP.
Trimetrexate	D	Yes	Teratogenic in rats, 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 may increase with increasing maternal dose.	Use in pregnancy should be avoided if possible, may be used for PCP if refractory/intolerant to TMP-SMX and pentamidine.
Valacyclovir	B	Yes	Not teratogenic in mice, rats, or rabbits.	Experience with valacyclovir in pregnancy limited. Prodrug of acyclovir, which is considered safe for use in pregnancy.	Alternate agent for HSV, varicella infections in pregnancy.
Voriconazole	D	Unknown	Embryotoxic in rats and rabbits. Teratogenic in rats (cleft palate, hydronephrosis, ossification defects).	No experience with human use.	Not recommended.