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Antiviral and antiretroviral use in pregnancy

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The history of antiviral and antiretroviral therapy is recent compared with many other medical therapies, including traditional antibiotics in pregnancy. Given the proliferation of these recent agents, there are few long-term data on which to base decisions of management in pregnancy. Accessing up-to-date information is critical to optimizing the safety of care for mothers and their infants. The general avoidance of unnecessary medications in the first trimester is still prudent, and judicious use of these medications in later pregnancy is sensible.

Exposure to medications in pregnancy can be toxic to a fetus in a gestational age-dependent manner [1]. Medications that are teratogenic at certain stages in the first trimester may be safe later in pregnancy, and medications later in pregnancy may have metabolic effects that interfere with neonatal function. Determination of safe medications for use in pregnancy must take into consideration the relative need for the use of certain medications and the possibility of inadvertent exposure in early pregnancy because of unplanned pregnancies.

This article reviews the most commonly used antiviral and antiretroviral agents and places particular emphasis on the issues regarding use in pregnancy.

Cyclic amines

Amantadine and rimantadine are related drugs used in the treatment of influenza A. Mechanism of action of these drugs is not well understood, but it is believed that they likely act as membrane fusion inhibitors and as RNA-dependent RNA polymerase inhibitors [2,3]. Amantadine is excreted unchanged in the urine, whereas rimantadine is metabolized in the liver. The main described side effects are central nervous system based, including insomnia, impaired thinking, and confusion [4]. Information in pregnancy is limited, but amantadine has shown teratogenic and embryotoxic effects when given in high doses to rats. No adequate human studies have been conducted. Infants exposed to amantadine in pregnancy

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have had cardiovascular abnormalities. It is listed as a Food and Drug Administration (FDA) category C drug [5,6].

Neuraminidase inhibitors

Neuraminidase inhibitors are active against both influenzae A and B. Their mechanism of action involves a crucial step in the life cycle of influenzae A and B. A viral surface glycoprotein (hemagglutinin) binds to sialic acid residues on respiratory epithelial surface glycoproteins, which is necessary for the initiation of infection. After the virus replicates, it is also attached to the host cell the same way until neuraminidase cleaves this link and frees the new virions. Zanamivir and oseltamivir are sialic acid analogs that competitively inhibit the viral neuraminidase [7,8]. Zanamivir is inhaled as a dry powder (2×5 mg inhalations twice daily for 5 days) and oseltamivir is an oral drug given as 75 mg orally twice a day for 5 days. The major side effects are nausea and vomiting, but there has been some concern with respiratory distress associated with zanamivir [9,10]. There are limited pregnancy data, with animal studies showing minor skeletal alterations in rats when pregnant rats are given zanamivir, and there are similar findings in pregnant rabbits given oseltamivir. These drugs are FDA category C, because there are no human data [11,12]. Given the relatively limited indications, it may be prudent to avoid these drugs in pregnancy.

Nucleosides

The main nucleoside antiviral agents currently available are acyclovir, valacyclovir, famciclovir, and ribaviron. Indications for the use of these medications in pregnancy included treatment of serious herpes zoster infections, primary herpes simplex infections and for prophylaxis at term for women with recurrent herpes simplex. In rare cases with HIV-infected or immunocompromised pregnant women, treatment of cytomegalovirus (CMV) infection with ganciclovir or foscarnet may be indicated. There are currently no usual indications for CMV therapy in pregnancy, even for prevention of vertical transmission [13].

Acyclovir

Acyclovir is a synthetic purine nucleoside. The drug is phosphorylated by virally encoded thymidine kinase, which results in acyclovir triphosphate. This product competitively inhibits viral DNA polymerase, which effectively interferes with viral replication. The mechanism of action results in mammalian non–herpes virus-infected cells being spared the effects of the drug [14]. Acyclovir is active against herpes simplex viruses types 1 and 2, varicella zoster virus, and Epstein-Barr virus. It is effective in vitro against CMV [15]. The usual oral dosage ranges from 200 mg five times per day for herpes simplex virus infections to 800 mg five times per day for varicella zoster infections [16]. Of note, the bioavailability of oral

acyclovir is only 20%, which has led to the development of other compounds, including valacyclovir and famciclovir, designed to achieve better dosing regimens [16].

The indications for use of acyclovir in pregnancy include life-threatening maternal infections, such as varicella pneumonia or disseminated herpes simplex infection [17–19]. Treatment of severe varicella infection is often warranted for maternal symptom relief [20]. The use of acyclovir near term to suppress recurrence of genital herpes also has been evaluated and is currently considered a clinical option to decrease neonatal exposure to virus at delivery and increase the likelihood of a vaginal delivery [21–24]. Acyclovir, 400 mg three times a day, from 36 weeks' gestation to delivery has been shown by pharmacokinetic studies in pregnancy to be required to achieve suppression in pregnancy [25]. The manufacturer (GlaxoSmithKline) has closed its acyclovir and valacyclovir pregnancy registries. A total of 1129 cases of acyclovir exposure in pregnancy—with 712 in the first trimester—were detailed, with no increased risk of congenital defects reported [26]. Acyclovir is found in breast milk at levels approximating those in maternal plasma [27]. Of note, neonatal treatment with acyclovir is relatively commonplace in infants with suspected herpes simplex or herpes zoster infection [28]. Although acyclovir seems to be relatively safe in neonates, caution regarding use in an infant who is dehydrated is warranted because of renal clearance of the drug [14].

Valacyclovir

Valacyclovir is the valine ester of acyclovir. It acts as an oral prodrug, which is converted in vivo to acyclovir. The subsequent action of the drug is then identical to acyclovir. Valacyclovir's indications for use in pregnancy are the same as those for acyclovir, but because acyclovir has a longer history of use in pregnancy, it is the most commonly recommended. The pharmacokinetics of valacyclovir in pregnancy have been evaluated in late pregnancy: at 500 mg twice a day it is comparable to 400 mg three times a day of acyclovir [25]. The acyclovir/valacylovir registry by GlaxoSmithKline contained 56 pregnancies (14 in the first trimester) but showed no evidence of increased risk of congenital defects [26].

There are few specific toxicity data on valacyclovir in pregnancy. Although valacyclovir seems to be a generally well-tolerated drug, a report on high doses in HIV-infected nonpregnant persons being treated for CMV disease showed shorter survival rates for patients on valacyclovir. This effect seemed to be caused by thrombotic microangiopathy [29]. This level of toxicity has not been reported from other studies of the drug in non–HIV-infected individuals.

Famciclovir

Famciclovir is a 2-aminopurine analog. It is a prodrug that is converted in vivo to penciclovir, the active metabolite. Penciclovir is then monophosphorylated by virally encoded thymidine kinase and converted to penciclovir triphosphate, which then preferentially inhibits the viral DNA polymerase. Penciclovir triphosphate has

lower affinity for the viral DNA polymerase than acyclovir but has a longer intracellular half-life. It is active against herpes simplex viruses type 1 and 2 and varicella zoster virus. Use in hepatitis B and Epstein-Barr viral infections is under investigation [30].

Famciclovir is well absorbed orally and results in 77% bioavailability. It is converted to its active form in the liver and then is cleared renally [30]. Generally, famciclovir seems to be a well-tolerated drug, but minimal data are available on toxicity in pregnancy. Indications for use in pregnancy are limited, because for any of the indications for treatment of herpes simplex or varicella zoster infections, acyclovir would be the first choice treatment because of more human safety data in pregnancy. A study was conducted on 18 men in whom exposure to famciclovir showed no adverse effects on semen parameters [31].

Ganciclovir

Ganciclovir is an acyclic analog of the nucleoside guanosine. It is converted intracellularly by a viral kinase to ganciclovir triphosphate, which competitively inhibits the DNA polymerase. It is also incorporated into viral DNA, which gives it a second route of disruption of DNA synthesis [32]. It is mainly used for treatment of CMV infections in immunocompromised patients. Ganciclovir is used primarily as an intravenous formulation, because oral bioavailability is poor (6%) [33]. Few data exist regarding safety in pregnancy. Animal data suggest embryotoxicity in mice and rabbits [34,35]; however, limited data in human exposure in a transplant patient showed no adverse effects [36]. It seems that the drug can cross the human placenta, so the possibility of toxicity exists [37]. Late pregnancy data are not available, but neonatal studies of the use of ganciclovir in CMV-infected infants are proceeding that will provide helpful data. Currently, the main toxicity seen in these studies is bone marrow suppression, which seems to be reversible. Of importance, early data suggest an improvement or stabilization of hearing loss in CMV-infected infants [38].

Ribavirin

Ribavirin is a nucleoside analog with activity against RNA viruses. It has been used clinically in children as an aerosol to treat respiratory syncytial virus [39]. As an oral agent, it has been used for treatment of chronic hepatitis C alone and in combination with interferon-alpha [40,41]. More recently it was used for the treatment of severe acute respiratory syndrome (SARS), with debatable efficacy [42].

There are no standard indications for use in pregnancy, but inadvertent use in the context of hepatitis C infection therapy or treatment of life-threatening infections, such as SARS, may occur. Experimental animal data suggest mutagenic activity. Hamsters treated with ribavirin developed defects in limbs, eyes, and brain. Rats developed defects of the brain and eyes [43,44]. These data have prompted ribavirin to be considered a potential human teratogen and it is recommended that pregnancy be strictly avoided for women on this medication. A small series of nine

pregnant women were treated with ribavirin for severe measles, and no adverse infant outcomes were reported. Of note, these exposures occurred after the first trimester [45].

Interferon

Alpha interferons are naturally occurring proteins that have antiviral properties. Interferon-alpha is produced by fetal tissues and may play a role in pregnancy maintenance [46]. Interferons have been used in many situations for treatment of neoplasms, chronic hepatitis C, and other immunopathic diseases. Of note, a new form of interferon, PEG interferon, is a modified form in which polyethylene glycol is covalently bound to the compound to slow its inactivation and excretion. Currently, PEG interferon and ribavirin are front-line therapy for hepatitis C, and although reproductive-age women are instructed to prevent pregnancy while on the therapy, inadvertent pregnancies occur [40,41,47,48]. General toxicity from the interferons includes pyrexia, leukopenia, hypotension, fatigue, and anorexia. Depression can be a significant side effect in some people [49,50]. Interferon is a large molecule, and limited studies suggest that it is likely unable to cross the placenta [51]. Animal data regarding use of interferon gamma-1b in monkeys at 100 times the human dose suggest that it acts as an abortifacient [50]. A few case reports exist regarding successful pregnancies in women who have been treated with interferon for chronic myeloid leukemia and hepatitis C through pregnancy [47,48,51,52].

Foscarnet

Foscarnet is a pyrophosphate analog that binds reversibly near the pyrophosphate binding site of DNA polymerase. It is used for the treatment of ganciclovir-resistant CMV infections in immunocompromised persons [27]. Foscarnet has poor bioavailability, so is administered intravenously. It is excreted through the kidneys and is associated with nephrotoxicity with crystal salt deposition [53]. It is also associated with hypocalcemia and hypophatemia. Other side effects include nausea, genital ulcerations, and seizures [54]. Data regarding use in pregnancy are limited. Administration of foscarnet to rats seems to result in hypoplasia of dental enamel [55]. A single case report of foscarnet treatment in a pregnant patient at 32 weeks' gestation did not indicate any apparent adverse effects in the infant [56]. Use in pregnancy should be reserved for life-threatening infections in the mother, for which foscarnet is the only reasonable treatment.

Antiretroviral therapy in pregnancy

Antiretroviral therapy in pregnancy is becoming an increasingly important issue worldwide as the population of women with HIV infection dramatically increases.

As of 2002, research determined that 19.2 million women were infected with HIV, which represented 50% of adult persons with the infection [57]. In 2002 alone, there were 2 million new infections in women [57]. Although these demographics are not replicated in western countries, the incidence of HIV infection in women in Canada has increased greatly, with 26% of all new infections in women [58]. Given the magnitude of this disease at the health, social, and economic levels, it becomes even more crucial to understand the impact that therapies can have. Research has established that highly active antiretroviral therapies are capable of increasing the life span of individuals infected with HIV [59], but these are complicated drug regimens with significant short- and long-term toxicities [60,61]. The use of antiretroviral therapies also has allowed for the dramatic prevention of mother-to-child transmission of HIV in antenatally treated women from a baseline of 25% to less than 1% [62,63].

General principles of antiretroviral therapy in pregnancy recommend that treatment for the pregnant woman be provided for her health needs as per adult treatment recommendations. It is also recommended that antiretroviral therapy be given to women to decrease the risk of transmission of HIV from mothers to infants based on data that support the effectiveness of this approach and ensure that treatment minimizes the risk of antiretroviral resistance development. It is also important to consider the possibility of unplanned pregnancy in treatment regimens given to reproductive-age women [64,65].

Basic principles of highly active antiretroviral therapy (HAART) therapy in 2003 focus on treatment to be given to optimize therapy for the mother's disease and prevent transmission to the infant. This should not compromise the mother's future ability to take antiretroviral agents. The choice and timing of drug therapy also must be selected to minimize toxicity on the infant. Antiretroviral management in pregnancy has been discussed in other papers, with an excellent up-to-date review that lays out the US approach to this disease [64]. Antiretroviral management is only one component of HIV care in pregnancy. This care must incorporate careful obstetric management, management of any comorbid conditions (eg, anemia, poor nutrition, substance or alcohol use), coexistent medical problems (eg, hepatitis C, diabetes), and proper evaluation of the fetal status. The general management of HIV in pregnancy has been well described in recent reviews [66,67].

To counsel women best as to what medications to take in pregnancy, one must try to understand the most up-to-date toxicology information on all of the available antiretroviral medications. This information changes rapidly, and published articles are insufficient for the most recent embryotoxicity or fetal toxicity data. Before prescribing these medications in pregnancy, the data should be reviewed with experts in the area who are keeping up to date with new, rapidly emerging data.

Nucleoside analog reverse transcriptase inhibitors

The first clinically successful antiretroviral agent introduced was zidovudine (AZT, ZDV, Retrovir). Drugs from this class of agents terminate the action of the

reverse transcriptase enzyme that is required to convert the viral RNA to DNA for integration into the host genome. Since the introduction of zidovudine, many nucleoside analogs have been developed, including didanosine (ddI, Videx), zalcitabine (ddC, Hivid), stavudine (d4T, Zerit), lamivudine (3TC, Epivir), and abacavir [68]. These medications were used as single agents and in dual combination regimens but have been found to be insufficient alone to suppress viral replication for prolonged periods as resistance develops rapidly [59]. For example, 3TC is an agent to which resistance develops quickly. Although these agents can be used in combination, D4T and AZT should not be used together because they have competing intracellular mechanisms of activation. All combinations must be considered carefully because of the potential for side effects.

Currently, there is no known human teratogenic syndrome associated with the use of nucleoside analog reverse transcriptase inhibitors. Use of zidovudine monotherapy is the most extensively studied regimen in pregnancy and in short- and long-term follow-up studies (up to 5 years of age after in utero exposure), transient anemia in the neonate is the only significant adverse effect reported. It should be noted, however, that no prospective study has been conducted on the use of any of these agents in humans in the first trimester. A multicenter study of experience with dual nucleoside antiretroviral therapy revealed no evidence of teratogenicity or worrisome fetal toxicity [69].

Mitochondrial toxicity

Mitochondrial toxicity is believed to be related primarily to exposure to nucleoside reverse transcriptase inhibitors. These drugs are able to bind to the mitochondrial gamma DNA polymerase found in different organ systems, which results in mitochondrial dysfunction [70,71]. The phenomenon of mitochondrial toxicity varies based on individuals, the particular antiretroviral combination, and the duration of therapy. These clinical effects in adults can include myopathy, myelosuppression, pancreatitis, peripheral neuropathy, and hepatic steatosis. Until reliable mitochondrial DNA assays are developed, serum lactate is used as a marker of mitochondrial toxicity. When mitochondrial function is significantly affected, there is a downstream accumulation of lactic acid. Some clinicians and investigators have raised the concern that mitochondrial toxicity may be even more common in pregnant women than in adults on these medications [72]. Some limited data suggest that there may be adverse effects in the neonate because of mitochondrial effects from in utero or neonatal treatment. Lactic academia has been observed in some studies [73–76], and case reports of fatal lactic acidosis have been made in nucleoside exposed neonates [74].

Zidovudine

The recommended dose of zidovudine is 200 mg every 8 hours or 300 mg twice daily. The original study in pregnancy (ACTG 076) used 100 mg 5 times per day [77]. One of the main concerns is bone marrow toxicity. In the ACTG 076

study no significant toxicities were noted in the women on zidovudine monotherapy. Macrocytosis usually occurs, and mild anemia is often noted. Nausea, headache, and malaise are common. Zidovudine has favorable pharmacokinetics in pregnancy and was found to be safe in early phase I and II studies [78–80]. It is actively transported across the placenta and is in an equivalent concentration in the fetus as in the maternal circulation. No congenital anomalies were attributable to zidovudine in the ACTG 076 study or in prior safety studies [81–84]. Animal studies do show embryo and fetal toxicity. Macaques treated with up to 2.5 times the maximal human dose had increased fetal and neonatal death, with hematologic alterations in the offspring. Pregnant mice given zidovudine showed increased rates of embryonic death but no specific malformation pattern [85]. There have been reports of possible carcinogenicity in zidovudine in animal studies. A National Cancer Institute study showed an increase in liver, lung, and genitourinary tract tumors in offspring of mice given high doses of AZT in the last trimester. A Glaxo-Wellcome study with lower doses (to simulate treatment doses) did not show an increase in tumors. No tumors have been identified in more than 1000 children exposed to AZT in pregnancy who were followed for more than 3 years [86]. Monitoring of maternal and subsequent neonatal blood count is advised.

Mitochondrial dysfunction has been a concern and was observed in 8 of 1754 children treated with zidovudine in pregnancy. Four of these children, who were on combination zidovudine and lamivudine, developed severe neurologic complications; 2 died [76]. There have been isolated reports of cardiomyopathy, but in a study in which echocardiograms were performed on 107 infants whose mothers were treated with zidovudine during pregnancy, no abnormalities were seen [87]. In a large survey, there were no associated mitochondrial dysfunction mortalities among exposed children [88].

Lamivudine (3TC)

The recommended dosage of lamivudine is 150 mg orally twice daily. There is a favorable side effect profile, with mild diarrhea, headache, and nausea being the major concerns. The pharmacokinetics do not seem to be affected by pregnancy [89], and placental transfer is excellent [90]. Pregnant rats and rabbits given 130 to 160 times the human dose did not reveal adverse effects. Embryo studies in rabbits but not in rats revealed embryo lethality at high doses. There are no documented human malformations in studies with combination therapy. Phase I and II studies in the third trimester have shown favorable pharmacokinetics and safety. Dual therapy with nucleosides, primarily zidovudine and lamivudine, shows minimal toxicities [69].

Didanosine (ddI)

The recommended dosage of didanosine is 200 mg twice daily if the patient weighs more than 60 kg or 125 mg twice daily if the patient weighs less than 60 kg.

Side effects of note include pancreatitis and peripheral neuropathy, which should be monitored regardless of pregnancy status. Currently there are no special concerns regarding embryo or fetal toxicity [85].

Zalcitabine (ddC)

The recommended dosage of zalcitabine is 0.75 mg orally every 8 hours. The major side effect is peripheral neuropathy. Teratology testing conducted in mice reveals decreased fetal weight and skeletal defects when given at high doses (2000 mg/kg/d). Lower doses (400 mg/kg/d) do not seem to produce this effect [38,39]. Placental transfer seems to occur by simple diffusion and is present in the fetus in approximately 0.6 of the concentration in maternal circulation [91].

Stavudine (d4T)

The recommended dosage of stavudine is 40 mg orally twice daily if the patient weighs more than 60 kg and 30 mg orally twice daily if the patient weighs less than 60 kg. The major side effect is peripheral neuropathy. Transfer of stavudine across the placenta is passive and results in a concentration in the fetus of 0.77 to 1.0 of maternal circulation. Exposure of early embryos to stavudine inhibited progression to the blastocyst stage. Studies in pregnant rats and rabbits that were administered 183 to 400 times the human serum concentrations did not show an increase in birth defects [92,93].

Abacavir

The recommended dosage of abacavir is 300 mg twice daily. It seems to be well tolerated, except for the 2% to 5% risk of potentially serious hypersensitivity reactions. Rechallenging after hypersensitivity has occurred, should never be done. Cross-resistance with other nucleoside analog reverse transcriptase inhibitors may be a problem. Human placental transport studies suggest that this drug can be transported from mother to fetus. Until better data are available, use in pregnancy should be reserved for times when maternal/fetal benefit outweighs risk.

Protease inhibitors

The protease inhibitors in use are indinavir sulfate (Crixivan), saquinavir (Fortavase or Invirase), ritonavir (Norvir), and nelfinavir mesylate (Viracept), amprenavir, lopinavir, and tenofovir [53]. These classes of medications have a unique mode of action. They inhibit HIV-1 protease activity. The HIV-1 protease enzyme is critical for the terminal maturation of infectious virions. Once viral RNA is converted to DNA and integrated into the host genome, it is transcribed and translated by cellular proteins to produce large, nonfunctional polypeptide chains, referred to as polyproteins. These polyproteins must be cleaved to small functional proteins for mature virions to be produced. The enzyme that performs this cleavage

is the protease. Each of the drugs in this class has a different side effect profile and great drug interaction potential. They can all interact with inhibitors or inducers of cytochrome P-450 system.

Many concerns have been raised about the effect of protease inhibitor therapy and a higher risk of gestational diabetes [94] and concern regarding an association with low birth weight [95,96]. One specific concern was raised with evidence of ergotamine toxicity in protease inhibitor–treated individuals. Ergot derivatives can be used for management of hemorrhage in pregnancy, which may be a concern, but this does not seem to have been repeated in other studies [52].

Indinavir

The recommended dosage of indinavir is 800 mg orally every 8 hours, although twice daily regimens are also being used and dose modifications are required with certain drug combinations. The most significant adverse effect is nephrolithiasis, which should be monitored carefully in pregnancy. There is one report of its occurrence in pregnancy [97]. It is not known if nephrolithiasis can occur in the fetus in utero. Given the potential nephrotoxicity, this raises concerns with the concurrent use of indomethacin, which also can cause oligohydramnios. Any other medication with cytochrome P-450 effects may result in significant drug interactions and should be reviewed before use. Studies performed in rats and rabbit using dosages at or slightly higher than human dosages revealed no evidence of teratogenicity. Overall indinavir seems to be well tolerated in pregnancy.

Saquinavir

The recommended dose of saquinavir as fortavase is 1200 mg orally three times daily. Poor bioavailability is a problem. The most significant side effects are diarrhea, abdominal discomfort, and nausea. In rats given five times the human dose and rabbits given four times the human dose, no embryo toxicities were reported. Small series human reports have revealed no specific problems [97,98]. Of note, there seems to be little transfer of saquinavir across the placenta [99].

Ritonavir

The recommended dose of ritonavir is 600 mg (six 100-mg capsules) twice daily with a gradual dose escalation. Side effects include gastrointestinal disturbance and circumoral paresthesias. There are many potential drug interactions, so a careful review of an individual's concurrent medications should be undertaken. Developmental toxicity studies in rats (0.3 times the human dose) revealed decreased fetal body weight. In rabbits exposed to 1.8 times the human dose there was a decrease in litter sizes and decreased fetal weights. Placental transfer has been described in rats. In the pregnancy registry data, one case of a congenital malformation was noted in 38 first-trimester exposures and no specific problems were noted in 54 second- and third-trimester exposures [100].

Nelfinavir

Nelfinavir has become a commonly used protease inhibitor because of its generally benign side-effect profile, with self-limited diarrhea being the most commonly reported problem [100]. The usual dose of nelfinavir is 1250 mg twice daily. Animal data from preclinical trials did not include embryo problems in rats at comparable human serum concentrations. First-trimester exposure reports have noted 9 of 301 congenital defects in the pregnancy registry [100]. Limited reports on safety in pregnancy have indicated individual reports of low birth weight and prematurity [98,101], which have not been confirmed in larger studies [102].

Amprenavir

Dosing of amprenavir is twice daily at 1200 mg per dose, but this is given in eight tablets, which results in a high pill burden. There are limited safety data regarding nonpregnant individuals, but nausea, diarrhea, and headache all have been reported. Of note, rash is uncommon but can be severe, with one case of Stevens-Johnson syndrome being reported. This drug seems to cross the placenta in in vitro studies [103]. Preclinical reports showed an increase in abortion in rabbits and deficient skeletal ossification in the offspring of pregnant rabbits. Limited data are available from the pregnancy registry, with one child born with defects in only 11 first-trimester exposures [100].

Lopinavir

Lopinavir is marketed in combination with ritonavir as Kaletra. The dosage is usually 400/100 mg (3 capsules) orally twice daily. This lopinavir/ritonavir combination showed no increase in congenital malformation in pregnant rats. Neither of these agents seems to cross the placenta [99]. No published data on humans are currently available, so use in pregnancy should be avoided.

Tenofovir

Tenofovir is a recently approved protease inhibitor with limited pregnancy data available. The usual dose is 300 mg once daily. Limited data show that it seems to cross the placenta in monkeys without evidence of congenital anomalies [104]. There is concern of changes in fetal bone porosity in these maternal monkey studies, which are also seen in administration to juvenile monkeys. There are no published human studies.

Non-nucleoside reverse transcriptase inhibitors

These drugs are noncompetitive inhibitors of the reverse transcriptase enzyme required for conversion of viral RNA to DNA. Neveripine (Viramune), delaverdine

(Rescriptor), and efavirenz (Sustiva) are the three drugs currently in common use. As with all of the current antiretroviral drugs, these medications have been shown to effect successful suppression of viral replication alone or in dual combinations with nucleoside analog reverse transcriptase inhibitors.

Nevirapine

Usual adult dosing of nevirapine is 200 mg once daily for 2 weeks, then 200 mg twice daily. Side effects include gastrointestinal symptoms and rash (22%). Animal studies in preclinical trials did not suggest embryotoxicity or teratogenicity. Registry data suggest that there is no evidence of an increase in birth defects in first-trimester–exposed human pregnancies, with a prevalence of birth defects in first-trimester exposures of 2% [100]. Safety and toxicity have been evaluated in limited third-trimester exposures. The findings suggest that serum levels were similar to nonpregnant adults [105]. HIVNET 012 has studied the use of single-dose nevirapine for the mother before delivery and the infant at birth. This study did not reveal any adverse effects [106]. A concern with the use of nevirapine in pregnancy is the risk of serious, life-threatening hepatic toxicity [107], which has been reported in nonpregnant individuals and must be evaluated further in pregnancy. Unpublished reports of serious life threatening complications in pregnancy warrant careful monitoring in pregnancy.

Delaverdine

The recommended dose of delaverdine is 400 mg three times daily. Rodents given high doses were observed to develop ventricular septal defects. Currently, no data are available regarding human pregnancies, other than early reports from premarketing studies, in which seven unplanned pregnancies are reported to have resulted in three ectopic pregnancies, three live births, and one infant with a small ventricular septal defect.

Efavirenz

DuPont Merck has conducted teratology studies on efavirenz in pregnant animals. In studies of rats and rabbits given doses of efavirenz that approximated blood levels achieved in humans who were given 600 mg/d, no fetal malformations were observed. A study was conducted on 60 pregnant monkeys. In 3 of 13 fetuses delivered by cesarean section, significant malformations were observed: 1 had a cleft palate, 1 had microphthalmia, and 1 had anencephaly and anophthalmia [108]. Few data are available in humans, but there is a case report of a myelomeningocele in a human infant born to a woman who received efavirenz in the first trimester [109]. It is important that this drug be avoided in the first trimester of pregnancy, which particularly requires careful consideration of use in reproductive-age women.

T20 Inhibitors

Enfuritide

This new drug is in a novel class of antiretroviral agents that are fusion inhibitors. They act to inhibit the binding of HIV to the host's CD4 cell wall. The agent requires subcutaneous administration. Animal data reveal no early evidence of embryotoxicity or teratogenicity, but there is no primate or human data are available. It is not known if this agent crosses the placenta.

The effects of these antiretroviral agents in combinations are difficult to sort out, and studies that examined the effects of combination data show variable results. Some studies report serious maternal toxicities, including hepatotoxicity [72,101, 110,111], or higher rates of neonatal malformations [84,112], prematurity and low birth weight [94,98,102,113,114], or serious neonatal complications, including mitochondrial toxicity [73–76,115–117]. Many studies have been conducted, however, including a meta-analysis that suggested that there are generally few serious effects for the mother or infant [69,77,83,98,102,118–122]. There is an interesting observation of a decreased risk of pre-eclampsia in HIV-infected women with restoration to a usual rate in HAART-treated women. This finding requires further exploration [123,124].

In summary, there is greater need for an understanding of the effects of antiviral and antiretroviral therapy on pregnant women and their fetuses as more of these therapies are developed and are entering medical practice.

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