Motherisk Update

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Antiretroviral treatment of maternal HIV infection

ABSTRACT

QUESTION One of my pregnant patients tested positive for human immunodeficiency virus. Will HIV therapy put her pregnancy outcome at risk?

ANSWER The biggest risk is vertical transmission of HIV to her baby. She should be treated with combination therapy; triple therapy is required to reduce vertical transmission. Zidovudine is not teratogenic in humans, but information on other antiretroviral drugs is incomplete.

RÉSUMÉ

QUESTION L'une de mes patientes qui est enceinte a reçu des résultats positifs confirmant qu'elle est porteuse du virus de l'immunodéficience humaine. Une thérapie contre le VIH met-elle sa grossesse en péril?

RÉPONSE Le plus grand risque est la transmission verticale du VIH à son enfant. Elle devrait être traitée avec une thérapie combinée; une trithérapie est nécessaire pour réduire la transmission verticale. La zidovudine n'est pas tératogène chez l'humain, mais les renseignements sur les autres médicaments antirétroviraux sont incomplets.

Mother-to-child transmission of HIV can be reduced from 25% to less than 2% by appropriate antiretroviral therapy (ARV) and avoiding breastfeeding.[1] Use of ARV drugs during pregnancy might require dose adjustments because of the physiologic changes associated with pregnancy. The current consensus is that therapy should be initiated with three drugs, either a combination of two nucleoside analogue reverse transcriptase inhibitors (NARTI) and a protease inhibitor (PI) or a combination of two NARTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI).[1]

In a 10-year longitudinal epidemiologic study, vertical transmission of HIV was observed in 20% of women with HIV-1 infection who received no ARV treatment during pregnancy, in 10.4% who received zidovudine (AZT) alone, in 3.8% who received combination therapy without PIs, and in 1.2% who received combination therapy with PIs.[2] These results are similar to results in other studies. These studies also found no increase in rates of preterm labour, low birth weight, low Apgar scores, or stillbirth in suboptimally treated women.[3,4]

Four clinical situations

In discussing HIV during pregnancy, four clinical situations should be considered.[3]

Women who have not received ARV therapy. Regardless of antenatal virus load, an AZT chemoprophylaxis regimen, initiated after the first trimester, should be recommended to all pregnant women with HIV-1 infection.[2-5] A combination of AZT with an additional ARV drug is recommended for

Motherisk Update

infected women whose HIV-1 RNA is more than 1000 copies/mL regardless of clinical or immunologic status.[6] Women in the first trimester can consider delaying initiation of therapy until after 10 to 12 weeks' gestation because the risks associated with various agents during organogenesis (the first 10 weeks of gestation) are largely unknown.[3,7] We know the extent to which AZT passes through the placenta, but we do not know if this transfer is similar for other ARV drugs.[1,8] If a woman does not receive AZT as a component of her antenatal ARV regimen, she should receive AZT therapy during the intrapartum period and her newborn should receive it also.[9-11]

Women who have received ARV therapy during the current pregnancy. These patients should continue therapy; AZT should be included as a component of the antenatal ARV regimen after the first trimester whenever possible, although this might not always be feasible.[12] Women receiving ARV therapy in whom pregnancy is recognized during the first trimester should be counseled regarding the benefits and risks of such therapy during this period. Continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid development of drug resistance.[13] Regardless of antepartum ARV regimen, AZT is recommended during the intrapartum period and for newborns.[2,11]

Women who are in labour and have had no prior therapy. Two effective regimens have been documented. Intrapartum AZT intravenously followed by 6 weeks of AZT for the newborn, or oral AZT and lamivudine (3TC) during labour followed by 1 week of oral AZT or 3TC for the newborn[1,3,5,8,9,11,14-17] have been recommended. A single dose of nevirapine at onset of labour followed by a single dose of nevirapine for the newborn at 48 hours old has also been recommended.[7,12,13,18-21] The second regimen involves two doses of nevirapine combined with intrapartum AZT intravenously and 6 weeks of oral AZT for the newborn.[19-22] In the immediate postpartum period, women should have appropriate assessment ($CD4^+$ count and HIV-1 RNA copy number) in order to plan continuation of therapy.

Infants born to mothers who have received no ARV therapy during pregnancy or the intrapartum period. Between 7% and 40% of infants born to HIV-positive mothers become infected. The prognosis of these infants is poor; most develop early and rapidly progressive disease.[23] At 6 weeks, neonatal AZT should be offered to newborns. Zidovudine therapy should be initiated as soon as possible after delivery, preferably within 6 to 12 hours of birth. Some clinicians use AZT in combination with other ARV drugs, particularly if a mother is suspected of having an AZT-resistant virus.[4,5,23] Efficacy for infants is currently unknown. In the immediate postpartum period, mother and infant should undergo diagnostic testing to tailor appropriate therapy.

Types of ARV drugs

There are four different types of ARV drugs and only partial information on their fetal safety.

Nucleoside analogue reverse transcriptase inhibitors. Zidovudine and 3TC are well tolerated during pregnancy.[16,24] Infants exposed in utero to AZT and followed up for approximately 6 years appeared similar to healthy controls.[25,26] No evidence indicates an increased rate of congenital abnormalities among infants born to women with antepartum exposure to AZT.[2,25,27]

The pharmacokinetics of 3TC are similar in pregnant women and nonpregnant women; no pharmacokinetic interactions with AZT have been reported.[14,16,17,24] Similarly, the pharmacokinetics of didanosine and stavudine are not affected by pregnancy.[24,27,28] Abacavir exhibits developmental toxicity and increased incidence of fetal anasarca and skeletal malformations in animals. Zalcitabine (ddC) appeared to be teratogenic (hydrocephalus) in rats.[27,29]

The NARTI drugs might induce mitochondrial dysfunction characterized by neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis (the two latter might have a female preponderance).[30-32] These drugs occasionally produce a life-threatening syndrome of acute fatty liver of pregnancy and hemolysis, elevated liver enzymes, and low platelet count (the HELLp syndrome) during the third trimester of pregnancy.[32] Whether mitochondrial dysfunction affects fetuses is still debated; case reports suggest a positive association, but population-based studies refute that. Hepatic enzymes and electrolytes should be assessed more frequently during the last trimester, and any new symptoms should be evaluated thoroughly.

Non-nucleoside analogue reverse transcriptase inhibitors. Delavirdine is teratogenic in rats, but has not been evaluated in HIV-infected pregnant women. Efavirenz exhibits teratogenic effects in primates and should be avoided in pregnant women until more information is available. Severe, life-threatening and, in some cases, fatal hepatotoxicity, including cholestatic and fulminant hepatitis, hepatic necrosis, and hepatic failure, have been reported in HIV–infected patients receiving nevirapine in combination with other drugs for prophylaxis against nosocomial or sexual HIV exposure.[22,27,32]

Protease inhibitors. Hyperglycemia and diabetes mellitus have been reported among patients taking PIs.[33,34] Limited data show almost 80% of women taking PIs developed one or more typical adverse effects, such as anemia, nausea, vomiting, aminotransferase elevation, or hyperglycemia.[27,31-34] Clinical trials on indinavir, ritonavir, nelfinavir, and saquinavir are ongoing. No evidence of teratogenicity with these drugs appeared in animal studies. Amprenavir and lopinavir have not yet been studied in pregnant women or neonates, although lopinavir is relatively well tolerated and provides potent ARV activity in heavily pretreated patients.[35]

Miscellaneous agents. Hydroxyurea used for myeloproliferative disorders and sickle cell anemia has potent teratogenic effects in animals. It should be avoided.[36]

Conclusion

Use of ARV prophylaxis with combination therapy is recommended for all pregnant women with HIV-1 infection regardless of antenatal HIV-1 RNA level. These women should be treated throughout pregnancy. They should be followed by a multidisciplinary team with careful, regular monitoring of the pregnancy and potential toxicities. No clinical evidence of adverse neurodevelopmental effects of ARV drugs is currently available.

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Motherisk Update

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. Drs Talaie and Nava-Ocampo are fellows and Dr Koren is Director of the Motherisk Program. Dr Koren is a Senior Scientist at the Canadian Institutes for Health Research.

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