

Canadian consensus guidelines for the care of HIV-positive pregnant women: putting recommendations into practice

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§ See related article page 1671

As of December 2002, an estimated 19.2 million women worldwide were living with HIV infection.¹ It is clear that HIV-positive women are living longer and are choosing to become pregnant, and a substantial proportion of infected women give birth each year.^{2,3} The perinatal transmission of HIV both in Canada⁴⁻⁶ and around the world^{1-3,7} is a source of concern. In fact, the vast majority of all HIV infections in children are acquired perinatally.^{1-3,7} Thus, care of the mother and her offspring in the setting of HIV infection has become an important health care issue.

Canadian consensus guidelines for the treatment of HIV infection in adults have been published previously,⁸⁻¹⁰ but they contained only minimal information about the complexities of caring for HIV-positive pregnant women. In October 1998 a representative group of HIV and infectious disease specialists, obstetricians with interest and expertise in the care of HIV-positive pregnant women, family physicians, pediatric HIV specialists and community members convened to review recently published guidelines and their supporting scientific literature and to make recommendations. Information that became available after the 1998 workshop, either in published form or through presentation at conferences, was also considered before the guidelines were finalized. The guidelines therefore represent the current Canadian consensus on the care of HIV-positive pregnant women and their infants.

These consensus recommendations are summarized as a commentary on page 1671 of this issue.¹¹ The full-length guidelines and the evidence supporting them can be accessed online at www.cmaj.ca. In this article we present 7 scenarios demonstrating how the recommendations are intended to be applied in practice.

Scenario 1

An HIV-infected pregnant woman who is not receiving antiretroviral therapy when pregnancy is confirmed

The woman's clinical, virologic and immunologic status should be assessed. Antiretroviral therapy should be offered, the regimen being carefully chosen on the basis of the principles outlined in the consensus guidelines.¹¹ If the

woman has never received antiretroviral therapy, then the regimen selected should include a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor; trials comparing these 2 types of regimens are currently being planned and initiated. Most experts still recommend including zidovudine whenever possible, as it remains the best-studied perinatal prophylactic agent.¹² If the woman has previously received antiretroviral therapy, resistance testing should be performed on viral isolates obtained during the prior antiretroviral therapy, if possible, and the results used to aid in the choice of regimen. Experts should be consulted in determining the best regimen. The available information regarding potential toxicities of individual antiretroviral agents in pregnancy is outlined in Box 1.

In most circumstances, initiation of antiretroviral therapy should be delayed until after the first trimester (and consideration should be given to awaiting the results of a detailed ultrasound assessment at 18 weeks' gestation), unless early initiation of therapy is judged important for maternal health. Delaying the initiation of antiretroviral therapy until after the first trimester minimizes the risk of drug-related teratogenicity and usually results in better adherence, as the nausea associated with pregnancy has usually diminished by this time. Adherence to antiretroviral therapy during pregnancy may be difficult, even in the second and third trimesters, and close monitoring for and management of side effects is important to maximize adherence.

The woman should be encouraged to continue oral antiretroviral therapy until as close to delivery as possible, and intravenous administration of zidovudine should be offered during labour, as outlined in the perinatal prophylaxis protocol (Box 2). In the postpartum period, the physician or another health care provider should discuss with the woman her need for ongoing antiretroviral therapy. If her immunologic characteristics are favourable, complete discontinuation of the therapy in the postpartum period and ongoing monitoring is a reasonable option. However, if it is considered appropriate for the woman's health, then antiretroviral therapy should be continued postpartum, and the woman should be followed and monitored according to usual adult HIV treatment guidelines.⁸⁻¹⁰

Any woman who declines combination antiretroviral ther-

Box 1: Summary of pregnancy-related information for currently available antiretroviral agents*†‡**Nucleoside reverse transcriptase inhibitors***Zidovudine (AZT)*

- Approved by FDA and HPB for use in pregnancy
- FDA pregnancy category C
- No documented toxic effects in humans, aside from reversible anemia in neonates
- Infants exposed in utero have been followed for almost 6 years with no significant differences from placebo in growth, immunologic or neurologic characteristics¹³
- Very good placental transfer (newborn:maternal drug ratio 0.85)

Lamivudine (3TC)

- FDA pregnancy category C
- No documented toxic effects in humans; third-trimester pharmacokinetic studies show no significant difference from nonpregnant patients¹⁴
- Excellent placental transfer (newborn:maternal drug ratio 1.0)

Didanosine (ddI)

- FDA pregnancy category B
- Peripheral neuropathy and pancreatitis may develop
- Cases of fatal lactic acidosis have been reported in pregnant women receiving didanosine and stavudine; physicians should use caution in prescribing this combination in pregnancy¹⁵
- Phase I study in third trimester showed pharmacokinetics not significantly altered by pregnancy
- Fair placental transfer (newborn:maternal drug ratio 0.5)

Zalcitabine (ddC)

- FDA pregnancy category C
- No studies in pregnant women or neonates
- Poor placental transfer (newborn:maternal drug ratio 0.3–0.5)

Stavudine (d4T)

- FDA pregnancy category C
- Cases of fatal lactic acidosis have been reported in pregnant women receiving stavudine and didanosine; physicians should use caution in prescribing this combination in pregnancy¹⁵
- Phase I and II safety and pharmacokinetic studies in pregnant women are under way
- Good placental transfer (newborn:maternal drug ratio 0.76)

Abacavir

- FDA pregnancy category C
- No studies in pregnant women or neonates
- Placental transfer unknown

Nucleotide analogue reverse transcriptase inhibitor*Tenofovir*

- FDA pregnancy category B
- No studies in pregnant women or neonates
- Placental transfer unknown

Non-nucleoside reverse transcriptase inhibitors*Nevirapine*

- FDA pregnancy category C
- Severe, sometimes fatal, hepatotoxicity¹⁶ and life-threatening hypersensitivity have been reported
- Most studies to date have been toward term; pharmacokinetics in pregnancy similar to those in nonpregnant women
- Elimination is prolonged in neonates
- Excellent placental transfer (newborn:maternal drug ratio 0.9)

[Box continued]

Delavirdine

- FDA pregnancy category C
- No studies in pregnant women or neonates
- Placental transfer unknown

Efavirenz

- FDA pregnancy category C
- Contraindicated in first trimester because of the potential for teratogenicity; safety profile later in pregnancy unknown
- Placental transfer good in rats, rabbits and primates

Protease inhibitors*Indinavir*

- FDA pregnancy category C
- Risk of nephrolithiasis in mother and, theoretically, in fetus and neonate
- Regular ultrasound examination of fetal renal system and quantification of amniotic fluid are recommended
- May exacerbate hyperbilirubinemia in neonates
- Phase I and II safety and pharmacokinetic study in pregnancy under way
- Placental transfer minimal

Ritonavir

- FDA pregnancy category B
- Side effects may be particularly problematic in pregnancy
- No documented toxic effects in humans
- Placental transfer minimal

Saquinavir

- FDA pregnancy category B
- Pharmacokinetic studies suggest that, during pregnancy, regular dosing does not achieve therapeutic levels
- Placental transfer minimal

Nelfinavir

- FDA pregnancy category B
- No documented toxic effects in humans
- Pharmacokinetic studies suggest that, during pregnancy, regular dosing may not achieve therapeutic levels
- Placental transfer minimal

Lopinavir–ritonavir

- FDA pregnancy category C
- No studies of lopinavir in pregnant women
- Placental transfer unknown for lopinavir, minimal for ritonavir

Amprenavir

- FDA pregnancy category C
- Amprenavir solution (but not the capsule formulation) contains high levels of propylene glycol; the capsular form may be used in pregnancy, but the oral solution is contraindicated for pregnant women and neonates
- No studies in pregnant women or neonates
- Placental transfer unknown

Miscellaneous agent*Hydroxyurea*

- FDA pregnancy category D
- Should be avoided during pregnancy

Note: FDA = US Food and Drug Administration, HPB = Health Protection Branch of Health Canada.

*See complete guidelines at www.cmaj.ca for a more detailed version of this table, including the results of animal studies.

†See also "Safety and toxicity of individual antiretroviral drugs in pregnancy."¹⁷

‡FDA pregnancy categories: B = animal reproduction studies failed to demonstrate a risk to the fetus; adequate, well-controlled studies of pregnant women have not been conducted. C = safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted; drug should not be used unless the potential benefit outweighs the potential risk to the fetus. D = evidence of human fetal risk from adverse reaction data obtained in investigational or marketing experiences, but potential benefits from use of the drug in pregnant women may be acceptable.

apy after appropriate counselling and education should be offered modified antiretroviral treatment for perinatal prophylaxis (see Box 2). A woman who chooses to take only prophylactic therapy to minimize exposure of her fetus to these drugs should be informed of the potential risk of resistance developing in the course of suboptimal antiretroviral therapy (e.g., zidovudine monotherapy), and she should be reassessed postpartum to determine the need for combination antiretroviral therapy. Discussion of treatment options and recommendations must be noncoercive, and the final decision regarding the use of these drugs is the woman's responsibility.

Scenario 2

An HIV-infected pregnant woman receiving combination antiretroviral therapy when pregnancy is confirmed

The woman's antiretroviral regimen should be reviewed in light of the pregnancy, both from the perspective of safety and toxicity and from the perspective of efficacy. Dosages should be reviewed to account for the increased volume of distribution in pregnancy. The potential need for antiemetics should be addressed, and doxylamine-pyridoxine with or without dimenhydrinate should be prescribed as required. If nausea and vomiting are significant problems, consideration should be given to discontinuing all antiretrovirals until the symptoms are controlled. If the existing combination therapy regimen is judged to be safe in pregnancy and is providing adequate viral suppression, the regimen should be continued. Antiretroviral combinations should be discontinued or changed if the regimen is thought to be potentially teratogenic or fetotoxic (e.g., if it contains efavirenz, delavirdine or hydroxyurea).

If the current regimen is not controlling viral replication, the physician should review the history of antiretroviral use and, if possible, perform resistance testing to aid in the choice of a new regimen. Drugs should be chosen on the basis of the principles outlined in the recommendations.¹¹ Experts in the field should be consulted.

If the woman chooses to discontinue antiretroviral therapy during the first trimester, all drugs should be discontinued at the same time and then resumed at the same time, at 14 weeks' gestation (or as soon as possible after the detailed ultrasound examination at 18 weeks' gestation) to minimize the risk of viral resistance developing. Any woman who chooses to discontinue her combination antiretroviral therapy should be warned about the possibility of viral load rebound and the theoretical increased risk of perinatal transmission.

The woman should be encouraged to continue her combination antiretroviral regimen until as close to delivery as possible; in addition, she should be offered intrapartum zidovudine, administered intravenously, according to the perinatal prophylaxis protocol (Box 2). After the birth, the infant should be referred to a specialized centre for ongoing assessment and care.

The woman should be assessed in the postpartum period to determine the need for continuing antiretroviral therapy, contraceptive therapy, and other health care needs and issues, according to adult HIV care guidelines.⁸⁻¹⁰

Scenario 3

A woman diagnosed with HIV infection, who presents or is referred for care within 1 month of term

In this situation, it may not be possible to reliably suppress the plasma viral load before delivery (because of time constraints), and the following steps are recommended:

- The woman should be treated with combination antiretroviral therapy according to the principles outlined in the recommendations.¹¹
- Elective cesarean section should be offered at 38 completed weeks of gestation.
- Oral antiretroviral therapy should be continued until 2 hours before the cesarean section (in consultation with anesthesia colleagues).
- Zidovudine should be administered intravenously starting 2 hours before the cesarean section, as outlined in the perinatal prophylaxis protocol (see Box 2). In addition, if the antepartum regimen did not contain nevirapine, a single oral dose of this drug should be considered.
- The infant should be given zidovudine (see Box 2).

Scenario 4

A woman who probably has detectable plasma viral load at term (because of suboptimal antiretroviral therapy during the pregnancy, problems with adherence or other drug-related issues, or lack of pregnancy care)

If labour has not commenced, the woman should be offered a cesarean section.

Several antiretroviral options are available, including intrapartum intravenous administration of zidovudine, followed by 6 weeks of zidovudine for the infant, combined with a single oral dose of nevirapine for the woman and a single oral dose of nevirapine for the infant. Although this approach has not been formally studied in a controlled clinical trial, it is currently favoured by the majority of Canadian experts.

Scenario 5

An infant born to a known HIV-positive mother who received no antiretroviral therapy during pregnancy or intrapartum

Oral administration of zidovudine and a single oral dose of nevirapine for the infant should be discussed with the mother; such therapy should start as soon as possible,

preferably within 6 hours of birth, as efficacy after 96 hours is considered low.¹² Details of antiretroviral prophylaxis for the infant are given in Box 2. The infant should be referred to a centre with specialized expertise for ongoing assessment and care.

The woman should be assessed postpartum (for viral load, CD4 count and other HIV markers), referred for ongoing HIV care and offered combination antiretroviral therapy according to the guidelines for adult HIV care.⁸⁻¹⁰

Scenario 6

A woman who experiences primary HIV infection (seroconversion) during pregnancy

Documented primary infection during pregnancy is an indication for combination antiretroviral therapy. Initiating such therapy is important not only for long-term maternal well-being but also for the prevention of perinatal transmis-

Box 2: Protocol for perinatal antiretroviral chemoprophylaxis

Intrapartum

- Initiate antiretroviral therapy at onset of active labour, at rupture of membranes, 2 hours before cesarean section or in any other situation where delivery is anticipated.
- Give zidovudine intravenously to the woman. If she received no antiretroviral therapy antenatally or does not have full virologic suppression, give a single dose of oral nevirapine, in addition to intravenous zidovudine, as soon as possible after presentation.
- If the woman was receiving combination antiretroviral drugs during her pregnancy, continue these medications for as long as possible through labour.

Zidovudine dosage

- Give a loading dose of 2 mg/kg intravenously in 100 mL D5W over 1 hour, then 1 mg/kg each hour by continuous infusion during labour until the umbilical cord has been clamped. If the patient has not delivered and labour has stopped, then resume the previously prescribed oral antiretroviral regimen. If the zidovudine infusion is discontinued for more than 6 hours, readminister the loading dose and resume the continuous infusion when labour recommences.

Nevirapine dosage

- For any woman who received no antenatal antiretroviral therapy or who has inadequate suppression of viral load, give a single 200-mg dose orally as soon as possible after presentation.

Postpartum neonate

Term infant

- Give zidovudine syrup 2 mg/kg orally every 6 hours for 6 weeks. If the infant is unable to tolerate oral feeding, zidovudine 1.5 mg/kg may be given intravenously every 6 hours.
- Initiate zidovudine immediately if the mother was not given this drug intravenously intrapartum; however, if the mother received a full course of intravenous zidovudine, then initiate the drug at 8 to 12 hours after birth.
- If the mother received nevirapine intrapartum, then give the infant a single dose of oral nevirapine (2 mg/kg) within 48 to 72 hours after birth. If the mother did not receive nevirapine intrapartum, then give the infant a single dose of oral nevirapine (2 mg/kg) as soon as possible after birth.*
- Refer the infant to an appropriate HIV care centre for ongoing assessment and care.

Preterm infant (34 weeks' gestation or less)

- Reduce the dose of zidovudine to 2.0 mg/kg orally or 1.5 mg/kg intravenously every 12 hours (give orally if possible, intravenously if the infant cannot tolerate oral feeding) from birth to 2 weeks of age, and then 2 mg/kg every 8 hours from 2 to 6 weeks of age. If the infant was born at less than 30 weeks' gestation, continue 12-hourly dosing for 4 weeks, then every 8 hours for the final 2 weeks of the 6-week period.¹⁸
- Refer the infant to an appropriate HIV care centre for ongoing assessment and care.

Postpartum mother

- Resume combination antiretroviral therapy with as short an interruption as possible. If the woman is not receiving optimal antiretroviral therapy, review her immunologic and virologic status, and offer optimal therapy according to guidelines for nonpregnant adults. Breast-feeding is strongly discouraged, regardless of the woman's antiretroviral, virologic and immunologic status postpartum.
- Refer any HIV-positive woman to an appropriate HIV care centre for ongoing assessment and care.

Note: D5W = 5% dextrose in water.

*At present, no intravenous preparation of nevirapine is available.

sion, since the risk of maternal-infant transmission in this situation is probably higher than among women who experience seroconversion before pregnancy. In the setting of documented seroconversion during pregnancy, the woman should be carefully counselled, in a noncoercive manner, regarding her reproductive choices, and she should be supported in her decisions. If the woman chooses to initiate combination antiretroviral therapy, it should be started as soon as possible, regardless of gestational age. If a woman with primary infection chooses to continue the pregnancy and refuses combination therapy, perinatal antiretroviral chemoprophylaxis should be offered, as outlined in Box 2.

Scenario 7

Use of perinatal prophylactic antiretroviral therapy in pregnant women presenting at delivery with significant risk factors but unknown HIV status

Many women who are at risk for HIV infection do not receive antenatal care and present late in their pregnancy or in early labour with unknown HIV status. Women at particular risk of HIV infection include those who use injection drugs and have shared needles, those who have had a recent illness suggestive of a seroconversion illness, and those who have had regular unprotected sex with a known HIV-infected partner or a partner with significant risk factors for HIV infection.

HIV testing should be offered to any woman who has not been tested during her pregnancy, and particularly to those recognized to be at risk for HIV infection. The test should be performed as rapidly as possible; with point-of-care test kits, the screening result should be available within 1 hour. Positive results must be verified by formal serologic testing, including HIV enzyme-linked immunosorbent assay and Western blot test. Rational decisions can then be made regarding the need for ongoing chemoprophylaxis for the infant, and appropriate care can be offered to the woman. Testing should always be done with the woman's knowledge and consent, and the woman must give her consent for any antiretroviral therapy.

A woman at high risk may be offered perinatal prophylaxis as outlined in scenario 4. The infant's zidovudine therapy should be continued until the HIV status of the mother is known. If the woman proves to be HIV negative and seroconversion is unlikely, the chemoprophylaxis for the infant can be discontinued. If the woman proves to be HIV positive, then a full course of zidovudine chemoprophylaxis should be offered to the infant, as outlined in Box 2. Both the infant and the woman should be referred to the nearest appropriate HIV care centre for ongoing assessment and care.

Conclusions

The care of HIV-positive pregnant women and their infants is complex. Ideally, such care should involve the

woman herself, her HIV specialist, an HIV-experienced obstetrician and a pediatric HIV specialist. The assistance of a pharmacist and dietitian with HIV expertise is also invaluable. A wide variety of issues must be addressed, and close monitoring of the patient is essential. This area of medicine and science is evolving, and we anticipate that these guidelines will also evolve. Further clinical research is needed to ensure that the health outcomes of HIV-positive women and their infants will improve in the future.

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