Canadian consensus guidelines for the management of pregnant HIV-positive women and their offspring

David R. Burdge, Deborah M. Money, John C. Forbes, Sharon L. Walmsley, Fiona M. Smaill, Marc Boucher, Lindy M. Samson, Marc Steben, on behalf of the Canadian HIV Trials Network Working Group on Vertical HIV Transmission

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Abstract

Background: The optimal care of HIV-positive pregnant women and the prevention of mother-to-child transmission of HIV have become important health care issues, in Canada and throughout the world. Patterns of care for HIV-positive pregnant women and their infants have changed dramatically over the past 5 years, with advances in our understanding of HIV-related disease and its treatment and of the pathogenesis of perinatal HIV transmission, as well as advances in our ability to successfully intervene. Combination antiretroviral therapy is now recognized as standard care in pregnancy, despite limited data on safety, tolerability and efficacy, and this therapy is associated with marked reductions in rates of perinatal HIV transmission. Optimal management of labour and delivery is also vital for improving maternal and infant outcomes. Previous guidelines for the care of HIV-positive individuals have focused on nonpregnant adults or were published before the introduction of combination antiretroviral regimens and before changes in management of labour and delivery. For these reasons, new Canadian guidelines were needed.

Objective of guidelines: To assist HIV-positive women and their care teams in making decisions regarding optimal management during pregnancy, delivery and the postpartum period.

Benefits of implementing guidelines: Optimal prenatal, intrapartum and postpartum care of the woman and her infant will result in significant reduction in perinatal HIV transmission (from about 25% to less than 1% with optimal care), improve pregnancy outcomes, minimize the risk of toxic effects to the fetus/neonate, and improve short-term and long-term health outcomes for the mother.

Methods: In October 1998, a representative group of Canadian HIV and infectious disease specialists, obstetricians, family physicians, pediatric HIV specialists, and community members convened to review recently published guidelines and their supporting scientific literature. Common clinical scenarios were discussed, and group consensus was achieved for recommended approaches to management. Information that became available later (either in published form or through presentations at major HIV and infectious disease conferences) was systematically reviewed before the guidelines were finalized. Multiple drafts of the guidelines were reviewed by all workshop participants. In addition, the guidelines were reviewed and endorsed by the Canadian Pediatric AIDS Research Group and the Infectious Diseases Committee of the Society of Obstetricians and Gynaecologists of Canada. The supporting evidence for all recommendations was evaluated, and levels of evidence are indicated.

Recommendations: Recommendations for preconception counselling and HIV testing, antenatal care, intrapartum care and postpartum care of both the mother and the infant were developed. [please set link to "Recommendations for the management …" section later in this document]

Clinical scenarios: Specific recommendations were developed for the management of 7 common clinical scenarios: an HIV-infected pregnant woman who is not receiving antiretroviral therapy when pregnancy is confirmed; an HIV-infected pregnant woman receiving combination antiretroviral therapy when pregnancy is confirmed; a woman diagnosed with HIV infection, who presents or is referred for care within 1 month of term; 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); an infant born to a known HIV-positive mother who received no antiretroviral therapy during pregnancy or intrapartum; a woman who experiences primary HIV infection (seroconversion) during pregnancy; and a pregnant woman presenting at delivery with significant risk factors but unknown HIV status. These scenarios are discussed in a separate *CMAJ* Practice article.

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 a dietitian with HIV expertise is also invaluable. This area of medicine and science is evolving, and it is anticipated that these guidelines will also evolve.

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As of December 2002, an estimated 19.2 million women worldwide were living with HIV infection.[1] Most were of child-bearing age, and it is estimated that 2.5 million HIV-positive women deliver infants each year.[2,3] The perinatal transmission of HIV both in Canada[4–6]

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, and nearly 5.3 million children have been infected since the AIDS epidemic began.[1–3,7] While most cases of mother-to-child transmission currently occur in the developing world, significant changes in the epidemiology of HIV infection in many areas of Canada have resulted in increasing numbers of HIV-infected women of child-bearing age in this country.[8–10] In 2000, 24% of all positive HIV tests in Canadian adults were in women,[8] and an estimated 6800 Canadian women were living with HIV infection at the end of 1999, a 48% increase from 1996.[9] HIV-positive women are living longer and electing to become pregnant. As a result, pregnancy care and issues of mother-to-child transmission have become important health care issues, both in Canada and internationally.

Patterns of care for HIV-positive pregnant women and their infants have changed dramatically in the past 5 years. Combination antiretroviral therapy is now accepted as standard care in pregnancy, despite limited data on safety, tolerability and efficacy.[11,12] There is also increasing information on the importance of appropriate management of labour and delivery in preventing perinatal transmission.[13–22] Coincident with, and presumably as a result of, these changes, marked reductions in perinatal transmission rates are being documented throughout Canada, the United States and Europe.[23–29]

Canadian consensus guidelines for the treatment of HIV infection have been published previously.[30] However, these general antiretroviral therapy guidelines focus on the management of HIV-positive adults and contain minimal information regarding the care of pregnant women, the prevention of mother-to-child transmission or the care of HIV-exposed and HIV-infected children. The Society of Obstetricians and Gynaecologists of Canada published treatment guidelines for obstetric and gynecologic care of women living with HIV in 1994.[31] These guidelines predated the current usual clinical practice of combination antiretroviral therapy in pregnancy, as well as other current information of importance to pregnancy care and optimal management of labour and delivery. For all these reasons, establishment of new Canadian consensus treatment guidelines was imperative.

Methods

In October 1998, a representative group of Canadian 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 convenedto review recently published guidelines and their supporting scientific literature and to make recommendations for the care of pregnant HIV-infected women and their infants. Common clinical scenarios were discussed, and group consensus was achieved for recommended approaches to management. The supporting evidence for all recommendations was evaluated, and levels of evidence (see Appendix 1) were assigned to specific recommendations.[32–34]

Information that became available after the workshop, either in published form or through presentations at infectious disease and HIV conferences (including the 7th and 8th Conferences on Retroviral and Opportunistic Infections, the 8th and 9th Annual Canadian Conferences on HIV/AIDS Research, the 13th International AIDS Conference, and the 39th and 40th Annual Inter-sciences Conferences on Antiretroviral Agents and Chemotherapy) was also considered before the guidelines were finalized. Multiple drafts of the manuscript were widely circulated and reviewed by all the original workshop participants. The guidelines were also reviewed by both the Canadian Pediatric AIDS Research Group and the Infectious Diseases Committee of the Society of Obstetricians and Gynaecologists of Canada. These guidelines therefore represent the current Canadian consensus on the care of HIV-positive pregnant women and their infants.

Background to recommendations

Epidemiology of HIV infection in Canadian women

Rates of acquisition of new HIV infections among Canadian women continue to increase. Between Nov. 1, 1985, and Dec. 31, 2000, 5419 positive test results in adult Canadian women were reported to the Laboratory Centre for Disease Control, Health Canada; of these women, 76.3% were 15 to 39 years of age.[8,9] Overall, women represent 13.8% of the total number of positive tests reported, where sex is known.[8] Of greater concern is the fact that between 1995 and 2000 the proportion of all positive results accounted for by women increased from 19% to 24%.[8,9] Using data from HIV serodiagnostic databases, epidemiologic studies and behavioural surveys, the Bureau of HIV/AIDS, STD and TB estimated that by the end of 1999 there were 6800 Canadian women living with HIV infection.[9]

HIV prevalence studies in pregnant women suggest that the rate in Canada is about 3 or 4 cases per 10 000 pregnant women, although data for most provinces have not been updated for more than 5 years.[8–10] Given the increasing rates of HIV infection among women, most of whom are of child-bearing age, increasing numbers of HIV-positive women will become pregnant. Data from the Canadian Women's HIV Study Group suggest that, of women who are aware of being HIV-positive, fewer are terminating their pregnancies,[35,36] presumably because of improved survival with highly active antiretroviral therapy and markedly decreased rates of perinatal transmission. The experience in all Canadian centres specializing in the care of HIV-positive women is that many women are now planning to have children and becoming pregnant, often while they are receiving combination antiretroviral therapy. All this information suggests that the number of pregnancies involving HIV-positive women in Canada will increase over the foreseeable future.

HIV testing in pregnancy

The first step in managing HIV-infected pregnant women is diagnosis of the infection. Any sexually active

woman is at risk of HIV infection, but not all women will be aware of, or openly acknowledge to their health care providers, their potential risk factors for acquiring HIV infection. Ideally, women should be offered testing routinely, so that HIV infection can be diagnosed before conception. Studies have shown that selective testing of only "high-risk" women results in many missed diagnoses.[37,38] Therefore, all women should be offered HIV testing as part of routine pregnancy care, preferably as early in the pregnancy as possible. Testing must be accompanied by appropriate counselling, before and after the test. Even in settings of relatively low seroprevalence, uniform offering of testing allows diagnosis of HIV infection in women not perceived as being in high-risk groups.[39] Canadian studies have clearly demonstrated the cost-effectiveness and potential benefits of this approach.[40] Diagnosis allows optimal therapy and care to be offered to women both for their own long-term well-being and for optimal health outcomes for their infants.

HIV testing is currently recommended as part of routine pregnancy care in all Canadian provinces. Rates of testing have been increasing in Quebec, Manitoba and British Columbia,[10,41–43] and in Alberta about 98% of pregnant women presenting for care are tested.[44] However, in many parts of Canada, rates of testing in pregnancy should be improved. Remis and associates[45] have reported on the variability of testing rates within Ontario and the opportunities for intervention that have been lost. Health Canada recently estimated that if 90% of pregnant women in Canada were tested during pregnancy, there would be a 65% reduction in the number of HIV-infected newborns (compared with no prenatal testing and assuming that 25% of untreated pregnancies and 6% of treated pregnancies result in transmission of HIV infection to the infant).[10,46] Recent data from Montreal, Toronto and British Columbia suggest that even lower rates of perinatal transmission (less than 2%) can be achieved in women receiving combination antiretroviral therapy along with appropriate pregnancy, labour and delivery care.[10,26–29]

Given that interventions, including antiretroviral therapy and altered labour and delivery management, can have a beneficial impact, even if initiated toward term,[47–53] women who test negative early in pregnancy but who continue to engage in high-risk behaviours throughout the pregnancy should be offered repeat testing each trimester and at term. Point-of-care testing, which allows for rapid antibody diagnosis, may prove of particular benefit in testing women at term.

Factors associated with perinatal HIV transmission

Our understanding of the pathophysiology, timing and factors that increase the risk of perinatal HIV-1 transmission have improved substantially over the past few years.[54] Early studies showed that women with more advanced HIV disease, lower CD4 counts and a diagnosis of AIDS had higher risk of transmission.[15] More recently, a general, but not absolute, association has been demonstrated between measurable maternal plasma viral load and vertical transmission.[54–62] In general, the higher the plasma viral load at term, the greater the risk of transmission. However, transmission can occur in women with undetectable plasma viral loads, and, conversely, transmission does not necessarily occur in all women with high viral loads.[63] There does not appear to be a definite "threshold" of viral load below which a woman has absolutely no risk of transmission.[11] However, recent data suggest that transmission occurs only rarely among women with a plasma viral load of less than 1000 copies/mL.[64] Other less well defined virologic characteristics, including the level of virus in the genital tract, may also play a role, and differences have been reported between plasma and genital secretions.[65–67] Twin studies, which suggest that the first-born twin may be at higher risk of transmission than the second-born twin, also support the potential importance of the presence of virus in the genital tract in vertical transmission.[68] In a trial of short-course zidovudine for perinatal prophylaxis in Thailand, plasma and cervicovaginal HIV-1 RNA levels were both reduced by the therapy, and each was independently correlated with perinatal transmission.[69]

In studies predating combination antiretroviral therapy, a variety of obstetric factors were associated with increased risk of perinatal transmission, including duration of rupture of membranes,[17] presence of chorioamnionitis and invasive monitoring (e.g., use of scalp electrodes and fetal scalp venous sampling).[15,16] Other invasive interventions such as use of forceps, episiotomy and possibly external cephalic version may also increase the risk of vertical transmission. Amniocentesis and chorionic villus sampling have been implicated, but there are no data on the risk associated with these prenatal diagnostic procedures. It is generally recommended that HIV-positive pregnant women not undergo any of these procedures unless the benefits outweigh the risks.

The potential role that mode of delivery plays in perinatal HIV transmission has received a great deal of attention.[14,18–22] A meta-analysis of 15 prospective cohort studies suggested that the rate of transmission is reduced by approximately 50% with elective cesarean section, compared with normal vaginal delivery.[14] However, these studies included very few women who were receiving any antiretroviral therapy. Furthermore, among women who were receiving therapy, almost all were receiving zidovudine monotherapy. No well-designed and well-executed prospective study of women receiving combination antiretroviral therapy has yet been published that demonstrates lower transmission rates with cesarean section than with vaginal delivery. Indeed, given the low rates of transmission now being reported among women receiving combination antiretroviral therapy, a very large sample size would be required to demonstrate such a difference.

Breast-feeding is responsible for a significant amount of perinatal transmission. A meta-analysis of prospective stud-

ies showed that for women who breast-fed, the risk of transmission was 7% to 22% greater than that for women who did not breast-feed.[70] The European Collaborative Study[20] and the French Perinatal Study[19] also demonstrated a doubling in the risk of transmission with breast-feeding. As a result, wherever possible, it is recommended that HIV-infected women not breast-feed. There is no low level of plasma viral load that is associated with absence of virus in all other body compartments. In addition, there is no proven method to safely eliminate HIV from breast milk and allow safe banking of breast milk. Therefore, at least in Canada, breast-feeding remains contraindicated, even among women receiving highly active antiretroviral therapy with suppressed plasma viral loads. Some Canadian authorities also recommend that seronegative women who engage in high-risk behaviour that could result in HIV acquisition during the postpartum period should also be advised about the potential dangers of breast-feeding during seroconversion.

The major factor now associated with higher risk of perinatal transmission in Canada is lack of antiretroviral therapy. Over the past few years, in all major Canadian centres, virtually all perinatal transmission has been observed in cases where the mother's infection was not diagnosed in pregnancy, she did not receive optimal pregnancy care, or she did not receive antiretroviral therapy.[26–29] In the absence of antiretroviral therapy, approximately 25% of infants born to HIV-positive women in Canada acquire infection,[10] whereas with antiretroviral therapy, major centres have been reporting transmission rates of less than 2%.[26–29]

Our understanding of optimal antiretroviral therapy in pregnancy is still evolving. The first important study examining antiretroviral therapy in pregnancy was the AIDS Clinical Trial Study Group study protocol 076.[71] This placebo-controlled study demonstrated that zidovudine therapy, administered orally antepartum (started between 14 and 34 weeks' gestation), intravenously intrapartum and orally to the neonate for 6 weeks after delivery, resulted in dramatic and statistically significant reduction in mother-to-child transmission (25% in the placebo group, 8% in the treatment group). The final results of the study, reported in 1996, were similar.[57] Continued follow-up of the infants (to 5 years of age) has not revealed any significant toxic effects, other than transient anemia.[72] Subsequently, work in several nonstudy settings, including in Canada, has shown that the 076 protocol can be successfully implemented in clinical practice and is effective in reducing rates of perinatal transmission.[40,73–77]

Since 1994, when the initial results of the 076 protocol were published, there have been major advances in our understanding of HIV infection and in our ability to monitor and treat HIV-related disease. Current recommendations for the treatment of HIV-infected adults call for combination antiretroviral regimens designed to maximally suppress viral replication, reduce the development of resistance, preserve immune function and prolong survival with good quality of life.[78,79] These combinations usually consist of at least 3 different agents, usually from 2 different drug classes. The main classes of antiretroviral agents include nucleoside analogues (e.g., zidovudine, lamivudine, didanosine, stavudine and abacavir), non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine, delavirdine and efavirenz) and protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, saquinavir, amprenavir and lopinavir). Although both zidovudine and nevirapine reduce perinatal transmission when used alone as chemoprophylactic agents,[50,71] any antiretroviral monotherapy is now considered suboptimal for the treatment of HIV infection.[78,79] Furthermore, even more impressive reductions in rates of perinatal transmission with combination antiretroviral regimens are now being reported from throughout the developed world.

The optimal selection of antiretroviral drugs in pregnancy is not yet known, and the published information regarding the safety of these drugs in pregnancy is still minimal.[11,80] Recently, fatal lactic acidosis has been reported in 3 pregnant women being treated with stavudine (d4T) and didanosine (ddI).[81] There has also been heightened awareness of the potential for severe hepatotoxicity with nevirapine therapy outside the setting of pregnancy.[82–84] Despite these reports and concerns and the lack of long-term safety data, most experts (and the US Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women[11]) suggest a combination of 2 nucleoside analogues and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor in pregnancy. Box 1 summarizes the known information about each of the currently available antiretroviral agents in pregnancy.

Lessons learned from the developing world

Shorter, more cost effective courses of zidovudine than were used in the 076 study protocol[71] have been studied in Africa and Asia, with demonstrated benefit in terms of perinatal transmission.[50–53,69,88,89] The results achieved in all these studies were less optimal than those of the 076 study and far less optimal than are now being reported with combination therapy. One recently reported trial, the HIVNET 012 study, is of particular note.[50] In this large trial, performed in Uganda, women were randomly assigned to receive either a single dose of nevirapine (200 mg) during labour (with the infants receiving one dose of nevirapine within 72 hours of birth) or oral zidovudine during labour (with the infants receiving the same drug for 1 week after delivery). At 14 to 16 weeks after delivery, the rate of infant infection was 13% in the nevirapine-treated group and 25% in the zidovudine-treated group, and at 1 year the rates were 16% and 24% respectively. It should be noted that 99% of the women in the study breast-fed their children, and none received antiretroviral therapy before the onset of labour.

Of possible concern is that mutations associated with resistance to nevirapine were detected in samples from 17

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
- Embryotoxic in mice; vaginal carcinoma develops in adult mice exposed in utero
- 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 characteristics[85]
- Very good placental transfer (newborn:maternal drug ratio 0.85)

Lamivudine (3TC)

- FDA pregnancy category C
- Limited pregnancy-related information available
- Lethal to early rabbit embryos when given in high doses
- No documented toxic effects in humans; third-trimester pharmacokinetic studies show no significant difference from nonpregnant patients[86]
- Excellent placental transfer (newborn:maternal drug ratio 1.0)

Didanosine (ddI)

- FDA pregnancy category B
- Limited pregnancy-related information available
- No evidence of teratogenicity or toxic effects in rodents or rabbits
- Peripheral neuropathy and pancreatitis may develop
- Cases of fatal lactic acidosis have been reported in pregnant women receiving didanosine and stavudine;[81] physicians should use caution in prescribing this combination in pregnancy
- 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
- Minimal pregnancy-related information available
- Teratogenic (causing hydrocephalus) in rats at doses 1000 times greater than typical human dose
- Development toxicity (indicated by lower fetal weight and by skeletal defects) in rodents at moderate to high doses
- No studies in pregnant women or neonates
- Poor placental transfer (newborn:maternal drug ratio 0.3–0.5)

[Box continued]

Stavudine (d4T)

- FDA pregnancy category C
- Limited pregnancy-related information available
- No birth defects in rats or rabbits at 400 times and 183 times usual human dose respectively
- Cases of fatal lactic acidosis have been reported in pregnant women receiving stavudine and didanosine;[81] physicians should use caution in prescribing this combination in pregnancy
- 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
- Limited pregnancy-related information available
- Development toxicity (indicated by lower fetal weight and by skeletal defects) in rats at 35 times usual human dose
- Embryotoxic in rodents at 500 mg/kg per day
- No developmental toxic effects or malformation in rabbits at 8.5 times usual human dose
- No studies in pregnant women or neonates
- Placental transfer unknown

Nucleotide analogue reverse transcriptase inhibitor

Tenofovir

- FDA pregnancy category B
- Long-term carcinogenicity studies in animals not yet complete
- No adverse effects on embryo or fetal development of rats or rabbits
- Long-term administration to immature animals of various species resulted in bone abnormalities
- No studies in pregnant women or neonates
- Placental transfer unknown

Non-nucleoside reverse transcriptase inhibitors

Nevirapine

- FDA pregnancy category C
- Minimal embryotoxicity data (lower fetal weight in rats)
- Severe, sometimes fatal, hepatotoxicity[84] 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
- Virtually no pregnancy-related information available
- Teratogenic (ventricular septal defects, embryotoxicity, developmental delay) in rats at 5 times usual human dose
- Toxic effects to embryo and mother, as well as abortions, in rabbits at 6 times usual human dose
- No studies in pregnant women or neonates
- Placental transfer unknown

Efavirenz

- FDA pregnancy category C
- High rates of midline neurologic defects (anencephaly, anophthalmia) in primates exposed in utero during first trimester at doses comparable to therapeutic human doses
- 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
- Limited pregnancy-related information available
- 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 studies in pregnancy under way
- Placental transfer minimal in humans

Ritonavir

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

Saquinavir

- FDA pregnancy category B
- Limited pregnancy-related information available
- Pharmacokinetic studies suggest that, during pregnancy, regular dosing does not achieve therapeutic levels

[Box continued]

- Placental transfer minimal

Nelfinavir

- FDA pregnancy category B
- Limited pregnancy-related information available
- No embryonic or developmental toxic effects in rats or rabbits
- 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 evidence of teratogenicity with either drug in rats or rabbits
- No studies of lopinavir in pregnant women
- Placental transfer unknown for lopinavir, minimal for ritonavir

Amprenavir

- FDA pregnancy category C
- In pregnant rabbits, exposure at 5% of typical human exposure was associated with abortions and greater incidence of minor skeletal variations
- 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
- Potent teratogenic effects observed in all animal species tested; defects reported in multiple organ systems
- Should be avoided during pregnancy

(18%) of 95 women assessed 6 weeks postpartum and also in 9 (45%) of 20 infected infants.[90] However, samples from 5 of the 17 women obtained 12 to 18 months after delivery all lacked these mutations. Women with nevirapine resistance mutations had higher baseline plasma viral loads and lower CD4 cell counts than those who did not develop resistance. The nevirapine resistance mutations were different in the women (K 103 mutation most common) and infants (Y 181 mutation most common). These mutations were not present in pretreatment isolates. Development of these mutations is surprising, given that none of the women had received prior or concurrent zidovudine therapy, and none had previously received nevirapine. The significance of these findings remains unclear.

Another study of interest from Africa is the PETRA trial,[89] in which breast-feeding HIV-infected women received a combination regimen of zidovudine and lamivudine, which was given orally starting at 36 weeks' gestation and orally intrapartum, and was also given to both mother and infant for 1 week postpartum. This therapy reduced transmission by approximately 50% compared with placebo (9% v. 17%) at age 6 weeks. An intrapartum–postpartum regimen, started during labor and continued for 1 week postpartum in the woman and infant, reduced transmission at age 6 weeks from 17% in the placebo group to 11% with the 2-part zidovudine–lamivudine regimen, a reduction of 35%.

The women in studies of short-course antiretroviral prophylaxis in Africa and Asia are different from women receiving care in Canada, which affects the generalizability of these results to this country. Nonetheless, these studies do provide the basis for revising the recommendations for HIV-positive Canadian women who present at term having had little or no pregnancy care. We have used these studies, combined with the results of protocol 076[71] and other published data, to develop guidelines for the care of women (and their infants) who have not been tested in pregnancy and who present toward term.

Recommendations for the management of pregnancy, labour and delivery and for postpartum care

General principles

Several important and unique issues are associated with the use of antiretroviral drugs in pregnancy. Treatment decisions must take into account the interrelated issues of the current and future health of the woman; the stage of the pregnancy; the woman's wishes regarding the outcome of the pregnancy; the prevention of maternal-to-infant transmission; the well-being of the fetus and neonate; pharmacokinetic considerations, including altered kinetics in pregnancy and issues related to the placental passage of medications; and the potential for side effects and toxic effects that may be unique to pregnancy.

Maternal-fetal medicine involves balancing maternal risks and benefits with fetal risks and benefits. This process can result in potentially conflicting priorities, and the risks and benefits of any potential intervention must be carefully weighed. In general, however, the accepted basic principle is that the pregnant woman should receive appropriate treatment for any medical or surgical problems, despite her pregnancy. Treatments must be undertaken only if the woman is in full agreement and understands the potential risks to both her and the fetus. However, until the fetus is born and becomes an independent neonate, the woman's legal right to make a therapeutic decision always has priority under Canadian law.[91–93]

Recommendations for antiretroviral treatment for an HIV-infected pregnant woman are based on the principle that therapies of known benefit to the woman should be offered and not withheld during pregnancy. Women should ideally receive optimal antiretroviral therapy regardless of pregnancy status. While optimizing maternal care and health is of prime importance, it is also clear that we must, whenever possible, minimize the exposure of the developing fetus to potentially toxic medications (Box 1). The data currently available on the pharmacokinetics and safety of antiretroviral drugs in pregnancy are minimal, and therefore all treatment decisions during pregnancy require full discussion between the patient and her physician with regard to the known and potential benefits and risks. It is not clear at present whether pregnancy increases the risk of toxic effects such as the lactic acidosis – hepatic steatosis syndrome that has been associated with nucleoside analogue therapy.[94] However, the recent enhanced appreciation of the risk of serious side effects and toxic effects associated with these drugs, as well as their potential for mitochondrial toxicity, simply strengthens the argument that the management of antiretrovirals in pregnancy requires specialized expertise. Physicians caring for HIV-infected pregnant women need to be alert to complications such as lactic acidosis. Careful monitoring of hepatic enzymes and electrolytes and assessment of any new symptoms are imperative. Optimal care should involve the woman herself, an HIV specialist, an HIV-experienced obstetrician and a pediatric HIV specialist. The assistance of pharmacists and dietitians with HIV expertise is also invaluable.

For patients who are not pregnant, debate continues regarding the optimal CD4 and viral load at which antiretroviral therapy should be initiated. In pregnancy, however, it is recommended that women be offered combination antiretroviral therapy regardless of their viral load and CD4 count. If the woman's immunologic and virologic characteristics are such that no intervention would be deemed necessary outside the setting of pregnancy, then treatment can be discontinued after delivery. By ensuring maximal viral suppression during the pregnancy, the risk of resistance mutations developing because of the therapy should be minimized, and the woman's long-term treatment options should be maintained. [Level III A recommendation]

Preconception counselling and HIV testing

An important component of the general care of HIV-positive women is preconception counselling and care. Preconception counselling is appropriate for all known HIV-positive women of child-bearing age. Such counselling must address maternal virologic and immunologic status and the timing and choice of antiretroviral therapy (which must take into account the potential for pregnancy) and should encompass education regarding risk of perinatal transmission and intervention strategies. Effective contraception to minimize the risk of unwanted pregnancy is clearly important. In women of child-bearing age, antiretroviral choices should be made such that agents with potential toxic effects in pregnancy or for the developing fetus (e.g., efavirenz, delavirdine and hydroxyurea) are avoided [level II-3 E recommendation], and agents known to be effective in reducing perinatal transmission are used whenever possible. In women with favourable immunologic and virologic characteristics, antiretroviral therapy can be delayed until after the first trimester. In women who would benefit from antiretroviral intervention before becoming pregnant, the objective is to achieve stable, maximal suppression of the viral load before conception. Therapy decisions must also take into account the potential for side effects that might adversely affect maternal and fetal health, including hyperglycemia, anemia and hepatic toxicity. [Level III A recommendation]

Other components of preconception counselling include optimization of maternal nutritional status, assessment of reproductive and familial genetic history, screening for infectious diseases and sexually transmitted diseases, and screening for maternal psychological and substance abuse disorders. The initiation of folic acid supplementation should also be included. [Level III A recommendation]

Antenatal care

All women should be offered HIV testing as part of their routine pregnancy care, preferably as early in the pregnancy as possible. Interventions instituted late in pregnancy, including during labour and delivery and the immediate postpartum period, can alter the risk of perinatal HIV transmission. Therefore, women who test negative early in pregnancy but who continue high-risk behaviours should be offered repeat testing each trimester and at term. Women not tested earlier in pregnancy should be offered testing as soon as they present for care. [Level III A recommendation]

Therapy should be individualized to minimize the risk of toxic effects and to maximize adherence. Therapy with 2 nucleoside analogues (e.g., zidovudine and lamivudine) and either a protease inhibitor (e.g., nelfinavir) or a non-nucleoside reverse transcriptase inhibitor (nevirapine) is recommended for women who have not previously received antiretroviral therapy. [Level II-2 A recommendation]

Unless early therapy is judged important for maternal health, combination antiretroviral therapy should be delayed until after 14 weeks' gestation and, whenever possible, until after detailed ultrasonography at 18 weeks' gestation. For women who are receiving combination antiretroviral therapy at the time pregnancy is diagnosed, the drug regimen should be reviewed; if the regimen is deemed safe and efficacious, this therapy should be continued through the entire pregnancy. [Level III B recommendation]

In addition to the management of antiretroviral therapy and the prophylaxis and treatment of any opportunistic infections, there are other unique aspects to prenatal care in HIV-infected women. Although no specific HIV-related adverse obstetric outcomes have been reported, care is complex, and referral to an obstetrician with expertise in this area is recommended. There are many potential complications related to antiretroviral therapy, and close communication between the woman's HIV specialist and the obstetrician is imperative. Other care issues may include drug and substance exposure, methadone therapy and maintenance, and, if appropriate, controlled narcotic and other substance withdrawal. Harm reduction strategies should be reinforced repeatedly. It may be necessary to address language or cultural barriers in order to deliver optimal care.

Recommendations

1. In addition to usual pregnancy management, monitor CD4 cell count and viral load at diagnosis, during each trimester and toward term. The optimal interval is every 4 to 6 weeks. [Level III A recommendation]
2. It is particularly important to monitor for toxic effects related to the particular antiretroviral therapy being used (e.g., hematologic, hepatic, renal, pancreatic or metabolic effects). Such monitoring should be performed 2 weeks after initiation of antiretroviral therapy and monthly thereafter. [Level III A recommendation]
3. After appropriate discussion about the potential benefits, limitations and safety of ultrasonography, offer the woman a detailed obstetric ultrasound examination at 18 to 19 weeks' gestation. [Level III A recommendation] Serial follow-up is suggested for women receiving antiretroviral therapy with concomitant substance exposure or with other obstetric complications. [Level III B recommendation]
4. For women who are immunocompromised, with CD4 counts of 0.20×10^9 /L (200/μL) or below, offer prophylaxis against *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* complex infection and other prophylactic therapies, according to usual adult guidelines, with input from an expert in the field. Trimethoprim-sulfamethoxazole is relatively safe for use in pregnancy and is the first choice for PCP prophylaxis. The increased risk of neonatal hyperbilirubinemia related to use of this drug in the third trimester is acceptable and is outweighed by the serious potential impact of PCP on the mother and

infant. [Level III A recommendation]
5. Screen all women appropriately for other sexually transmitted infections and for cervical cytologic abnormalities. [Level III A recommendation]
6. Advise women antenatally of the recommendation that they not breast-feed (this is particularly important for women who come from countries where breast-feeding is expected), and devise strategies regarding formula feeding. [Level II-2 E recommendation]
7. Manage any complications, including opportunistic infections, with assistance from experts in the field. [Level III A recommendation]

Intrapartum care

Debate continues regarding the optimal intrapartum management of HIV-infected women. For example, optimal intrapartum antiretroviral therapy in different clinical scenarios remains to be defined. There is also potential for disagreement regarding recommendations for mode of delivery, with some authorities recommending elective term cesarean section for all women, regardless of their antepartum antiretroviral therapy or their viral status toward term. The following recommendations represent the current consensus of Canadian experts.

Early in the course of pregnancy care, discussions regarding mode of delivery should be initiated with the woman. All HIV-infected women should be made aware of the published evidence suggesting that cesarean section decreases the likelihood of perinatal transmission in women who are not taking antiretroviral therapy and those receiving zidovudine monotherapy.[14,18–22] However, if a woman is receiving optimal antiretroviral therapy and has achieved complete suppression of the plasma viral load, then vertical transmission is considered extremely unlikely. In this situation, there is no documented advantage to cesarean section, and the added morbidity associated with cesarean birth relative to vaginal birth[95–97] must be considered. The following recommendations are consistent with the guidelines of the Society of Obstetricians and Gynaecologists of Canada on mode of delivery.[98]

Recommendations

8. Women receiving optimal antiretroviral therapy with complete suppression of the plasma viral load (less than 50 copies/mL) may deliver vaginally (in the absence of other obstetric indications for cesarean section) [level II-2 A recommendation], but elective cesarean section may be performed at the patient's request [level III A recommendation]. After appropriate discussion with the patient, vaginal delivery may still be considered appropriate for some women with incompletely suppressed viral load (less than 1000 copies/mL). [Level II-2 B recommendation]
9. At approximately 38 completed weeks of gestation, offer elective cesarean section to any woman who is not receiving optimal antiretroviral therapy (e.g., no antiretroviral therapy or incomplete suppression of viral load with existing antiretroviral therapy) [level II-2 A recommendation]. Women in active labour do not benefit from cesarean section for HIV indications [level II-2 E recommendation].
10. Continue antenatally prescribed combination oral antiretroviral therapy for as long as possible during labour. [Level III B recommendation]
11. In the event of a planned cesarean section, initiate intravenous zidovudine therapy at least 2 hours preoperatively and discontinue once the infant is delivered (see Box 2 for dosing details). [Level II-2 A recommendation]
12. If the woman presents for a vaginal delivery and is at term, initiate intravenous zidovudine therapy immediately at the onset of regular contractions or at the time the membranes rupture. Women who did not receive antiretroviral therapy antenatally and those who likely do not have full suppression of the viral load should also be given a single dose of oral nevirapine as soon as possible after presentation. The zidovudine infusion should be maintained until delivery of the infant(s) (see Box 2). [Level I A recommendation]
13. Take routine precautions for blood and body fluid infection control. [Level III A recommendation]
14. Epidural analgesia is not contraindicated and may be given to these women. [Level III B recommendation]
15. Avoid unnecessary rupture of the membranes. In addition, avoid use of fetal scalp electrodes and fetal scalp sampling. Carefully evaluate the need to use forceps or vacuum, taking into account the entire clinical situation. [Level II D recommendation]

Postpartum care of the woman

Recommendations

16. Carefully monitor the woman for signs of endometritis or wound infection. [Level III B recommendation]
17. A longer-than-average postpartum hospital stay may be required to ensure satisfactory recovery and also to establish that the infant is tolerating zidovudine therapy, is feeding and is gaining weight. [Level III B recommendation]
18. Provide supportive management of breast engorgement, as breast-feeding is contraindicated in HIV-infected women in Canada, regardless of the woman's antiretroviral therapy and plasma viral load. [Level II-2 E recommendation]
19. If the woman plans on continuing antiretroviral therapy for her own health, encourage her to resume the therapeutic regimen as soon as she can tolerate oral intake, and organize postpartum follow-up for ongoing HIV care. [Level III A recommendation]
20. Contraception counselling and planning should occur before hospital discharge. Care must be taken to avoid drug interactions associated with oral contraceptive medications. [Level III A recommendation]

Postpartum care of the neonate

Recommendations

21. Regardless of what antiretroviral therapy the woman received antenatally and intrapartum, offer antiretroviral treatment to the infant according to the protocol for perinatal prophylaxis outlined in Box 2. If the mother did not receive any antiretroviral therapy antenatally or intrapartum, initiate zidovudine and nevirapine therapy for the infant as soon as possible after birth. The interval for which benefit may be gained from postexposure prophylaxis is undefined. If the mother received intrapartum prophylaxis, zidovudine is usually started in the infant within 6 to 12 hours after delivery and is continued for 6 weeks (if tolerated). [Level I A recommendation]
22. Breast-feeding should be avoided, as this practice is contraindicated for HIV-infected mothers in Canada, irre-

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 likely 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 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.[99]
- 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.

spective of antiretroviral therapy. [Level II-2 E recommendation]

23. If possible, wash the infant with soap and water to remove maternal blood or amniotic fluid before intramuscular injections or venipuncture. [Level III A recommendation]
24. Refer all infants born to HIV-positive women to a centre with expertise in this area for ongoing assessment and care. Infants who are not infected but who have been exposed to antiretrovirals require careful long-term follow-up of their neurodevelopmental and general clinical status. [Level III A recommendation]

Management of common clinical scenarios

Specific recommendations were developed for the management of 7 common clinical scenarios: an HIV-infected pregnant woman who is not receiving antiretroviral therapy when pregnancy is confirmed; an HIV-infected pregnant woman receiving combination antiretroviral therapy when pregnancy is confirmed; a woman diagnosed with HIV infection, who presents or is referred for care within 1 month of term; 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); an infant born to a known HIV-positive mother who received no antiretroviral therapy during pregnancy or intrapartum; a woman who experiences primary HIV infection (seroconversion) during pregnancy; and a pregnant woman presenting at delivery with significant risk factors but unknown HIV status. These scenarios are discussed in a separate *CMAJ* Practice article.[100]

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From the Oak Tree Clinic, Children's and Women's Health Centre of British Columbia and University of British Columbia, Vancouver, BC (Burdge, Money, Forbes); Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of British Columbia, Vancouver, BC (Money); Division of Infectious Diseases, Department of Medicine, Toronto Hospital, University Health Network, Toronto, Ont. (Walmsley); Department of Microbiology, McMaster Health Science Centre, Hamilton, Ont. (Smaill); Department of Gynecology, Hôpital Sainte-Justine, Montreal, Que. (Boucher); Division of Infectious Diseases, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ont. (Samson); and Clinique Médicale de l'Ouest, Verdun, Que. (Steben)

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Correspondence to: *Dr. David R. Burdge, Oak Tree Clinic, B4 West Old Shaughnessy Building, Children's and Women's Health Centre of British Columbia, 4500 Oak St., Vancouver BC V6H 3N1; fax 604 875-3063; dburdge@cw.bc.ca*

Members of the Canadian HIV Trials Network Working Group on Vertical HIV Transmission (in addition to the authors of this paper): *Upton Allen, Toronto, Ont.; François Boucher, Centre hospitalier de l'Université Laval, Sainte-Foy, Que.; Glen Hillson, BC Persons with AIDS Society, Vancouver, BC; Susan King, Hospital for Sick Children, Toronto, Ont.; Normand Lapointe, Hôpital Sainte-Justine, Montreal, Que.; Maude Loignon, Verdun, Que.; Stanley Read, Hospital for Sick Children, Toronto, Ont.; Kurt E. Williams, Royal University Hospital, Saskatoon, Sask.; Don Zarowny, Canadian HIV Trials Network, Vancouver, BC.*

Appendix 1: Designations for quality of evidence and strength of recommendations[32-34]

Category	Description
Levels of evidence	
I	Evidence from at least one well-designed randomized, controlled trial
II-1	Evidence from well-designed controlled trials without randomization
II-2	Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one investigational centre
II-3	Evidence from observational cross-sectional studies or from dramatic results in uncontrolled experiments
III	Opinions of respected clinical experts or evidence from descriptive studies and case reports
Strength of recommendations	
A	Good evidence to support a recommendation for use of a diagnostic test, treatment or intervention
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use