Canadian consensus guidelines for the management of pregnancy, labour and delivery and for postpartum care in HIV-positive pregnant women and their offspring (summary of 2002 guidelines)

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

ß See related article page 1683

This article presents a summary of consensus guidelines for the care of HIV-positive pregnant women and their offspring, which have been developed by the Canadian HIV Trials Network Working Group on Vertical HIV Transmission. The 24 recommendations are organized according to the 3 main stages of pregnancy and childbirth: antenatal care, intrapartum care and postpartum care (for the mother and the baby). The full guidelines, including background to the development of the recommendations and the evidence supporting them, as well as descriptions of the levels of recommendations, can be found online at www.cmaj.ca. In addition, 7 short clinical scenarios demonstrating how physicians can use these recommendations in their practices are presented elsewhere in this issue[1] (page 1683).

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.[2–4]

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. 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.[5] 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 resistant 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

An important component of the general care of HIV-positive women is preconception counselling and care. Such counselling must address maternal virologic and immunologic status and the timing and choice of antiretroviral therapy 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, 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

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, opti-

mal 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.[6–11] 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[12–14] must be considered. The following recommendations are consistent with the guidelines of the Society of Obstetricians and Gynecologists of Canada on mode of delivery.[15]

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].
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]
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 in the Practice article[1] 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 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 in the Practice article[1]). [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 of the Practice article.[1] 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, irrespective of antiretroviral therapy, as this practice is contraindicated for

HIV-infected mothers in Canada. [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]

This article has been peer reviewed.

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)

Competing interests: David Burdge, Deborah Money, John Forbes, Sharon Walmsley, Fiona Smaill and Marc Steben have all received speaker fees and/or educational grants from various pharmaceutical companies manufacturing drugs mentioned in this article. David Burdge, John Forbes, Sharon Walmsley, Fiona Smaill and Marc Steben have received travel assistance from various pharmaceutical companies to attend meetings within the past 2 years. Fiona Smaill has had ongoing paid consultancies with 3 pharmaceutical companies within the past 2 years. No competing interests declared for Marc Boucher and Lindy M. Samson.

Contributors: David Burdge was chair of the working group; he wrote the first draft of the guidelines, edited and circulated subsequent drafts, and coordinated input from all other authors. Deborah Money provided extensive input into the guidelines from an obstetrician's perspective, did extensive editing and provided many valuable suggestions. She is a member of the Infectious Diseases Committee of the Society of Obstetricians and Gynecologists of Canada (SOGC) and facilitated that committee's review of the guidelines. John Forbes and Lindy Samson provided extensive input into the guidelines from a pediatric perspective, did extensive editing and provided many valuable suggestions. They are both members of the Canadian Pediatric AIDS Research Group and facilitated review of the guidelines by that group. Lindy Samson also critically reviewed the levels of evidence. Sharon Walmsley provided extensive input into the guidelines from an adult HIV perspective, did extensive editing and provided many valuable suggestions. Fiona Smaill provided extensive input into the guidelines, did extensive editing and provided many valuable suggestions, especially with respect to the levels of evidence. Marc Boucher provided extensive input into the guidelines. He chairs the Infectious Diseases Committee of the SOGC and facilitated the SOGC's review of the guidelines. Marc Steben was a member of the original Working Group and provided extensive editorial suggestions.

Acknowledgments: The guidelines on which this article is based were developed with support from the Canadian HIV Trials Network, which received unrestricted educational grants from Abbott Laboratories Limited, BioChem Pharma Inc., Boehringer Ingelheim (Canada) Ltd., Bristol-Myers Squibb, Glaxo Wellcome Inc., Hoffmann-La Roche Limited, Merck Frosst Canada Inc., and Pharmacia & Upjohn Inc., as well as funding from the National AIDS Strategy of Health Canada.

References

1. Burdge DR, Money DM, Forbes JC, Walmsley SL, Smaill FM, Boucher M, et al. Canadian consensus guidelines for the care of HIV-positive pregnant women: putting recommendations into practice. *CMAJ* 2003;168(13):xxx-xxx.
2. Canadian Charter of Rights and Freedoms, Part I of the Constitution Act, 1982 being Schedule B of the Canada Act 1982 (U.K.), 1982, c. 11.
3. *Winnipeg Child and Family Services (Northwest Area)* v. *D.F.G.* [1997] 3 S.C.R. 925.
4. *Tremblay* v. *Daigle* [1989] 2 S.C.R. 530
5. Brinkman K. Hyperlactatemia and hepatic steatosis as features of mitochondrial toxicity of nucleoside analogue reverse transcriptase inhibitors. *Clin Infect Dis* 2000;31:167-9.
6. International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1. A meta-analysis of 15 prospective cohort studies. *N Engl J Med* 1999;340:977-87.
7. Maguire A, Sanchez E, Fortuny C, Casabona J, and the Working Group on HIV-1 Vertical Transmission in Catalonia. Potential risk factors for vertical HIV-1 transmission in Catalonia, Spain: the protective role of cesarean section. *AIDS* 1997;11:1851-7.
8. Mandelbrot L, Le Chenadec J, Berrebi A, Bongain A, Benifla JL, Delfraissy JF, et al. Perinatal HIV-1 transmission. Interaction between zidovudine prophylaxis and mode of delivery in the French perinatal cohort. *JAMA* 1998;280:55-60.
9. European Collaborative Study. Caesarean section and risk of vertical transmission of HIV-1 infection. *Lancet* 1994;343:1464-7.
10. Kind C, Rudin C, Siegrist CA, Wyler CA, Biedermann K, Lauper J, et al. Prevention of vertical HIV transmission: additive protective effect of elective cesarean section and zidovudine prophylaxis. *AIDS* 1998;12:205-10.
11. European Mode of Delivery Collaboration. Elective caesarean section versus vaginal delivery in preventing vertical HIV-1 transmission: a randomized clinical trial. *Lancet* 1999;353:1035-9.
12. Semprini AE, Castagna C, Ravizza M, Fiore S, Savasi V, Muggiasca ML, et al. The incidence of complications after caesarean section in 156 HIV-positive women. *AIDS* 1995;9:913-7.
13. Read J, Kpamegan E, Tuomala R, Zorrilla C, Brown G, Hammill H, et al. Mode of delivery and postpartum morbidity among HIV-infected women: the Women and Infants Transmission Study (WITS) [abstract 683]. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31 to Feb 4; Chicago.
14. Watts H, Mofenson L, Whistehouse J, Read J, Stiehm R, Lambert J, et al. Complications according to mode of delivery among HIV-positive women with CD4 counts <500 [abstract 684]. 6th Conference on Retroviruses and Opportunistic Infections; 1999 Jan 31 to Feb 4; Chicago.
15. Boucher M. Mode of delivery for pregnant women infected by the human immunodeficiency virus. *J Soc Obstet Gynaecol Can* 2001;23:348-50.

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*