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Guidelines for the Care of Pregnant Women Living With HIV and Interventions to Reduce Perinatal Transmission: Executive Summary

This clinical practice guideline has been prepared by the Infectious Diseases Committee, reviewed by Family Physician Advisory Committee and the Aboriginal Health Initiative Committee and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: This guideline reviews the evidence relating to the care of pregnant women living with HIV and the prevention of perinatal HIV transmission. Prenatal care of pregnancies complicated by HIV infection should include monitoring by a multidisciplinary team with experts in this area.

Outcomes: Outcomes evaluated include the impact of HIV on pregnancy outcome and the efficacy and safety of antiretroviral therapy and other measures to decrease the risk of vertical transmission.

Evidence: Published literature was retrieved through searches of PubMed and The Cochrane Library in 2012 and 2013 using appropriate controlled vocabulary (HIV, anti-retroviral agents, pregnancy, delivery) and key words (HIV, pregnancy, antiretroviral agents, vertical transmission, perinatal transmission). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English or French. There were no date restrictions. Searches were updated on a regular basis and incorporated in the guideline to June 2013. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Key Words: HIV, pregnancy, antiretroviral agents, vertical transmission, perinatal transmission

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Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
	E. There is good evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[69]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[69]

Recommendations

1. All women living with HIV who are planning a pregnancy or who become pregnant should have their individual situations discussed with experts in the area, with referral to both HIV treatment programs and obstetrical care providers, and an overall plan should be made for their pregnancy care. (II-2A)
2. All pregnant women should be offered HIV testing, with appropriate pre- and post-test counselling, as part of their routine prenatal care in each pregnancy. This testing should be repeated in each trimester in women who are recognized to be at high and ongoing risk for HIV infection. (II-2A)
3. Pregnant women living with HIV should be made aware that with the consistent use of combination antiretroviral therapy and abstinence from breastfeeding, the risk of perinatal transmission is < 1%. (I-A)
4. All pregnant women living with HIV should be treated with combination antiretroviral therapy regardless of baseline CD4 and viral load. (II-2A)
5. Antiretroviral therapy should not be discontinued during the first trimester for obstetrical reasons, but if the woman is not on therapy and there is no urgent medical indication for combination antiretroviral therapy, it can be delayed until after 14 weeks' gestation. (III-B)
6. All women living with HIV (both those who still have a detectable viral load after exposure to antiretroviral therapy and those who are antiretroviral-naive) should have their virus genotyped and, if possible, tested for phenotypic resistance to assist in optimizing antiretroviral therapy. It is advisable to discuss the interpretation of the genotype testing and any changes to the antiretroviral therapy with experienced clinicians. Testing for HLA-B*5701, if not done previously, is recommended in case abacavir might be required. (II-2B).
7. A combination antiretroviral therapy regimen including a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one or more NRTIs and a boosted protease inhibitor should be favoured because there is higher confidence in its safety and efficacy in pregnancy. Whenever possible, antiretrovirals known to cross the placenta to the fetal compartment should be used. (II-2B)
8. Whenever possible drugs with no safety data should be avoided during the period of organogenesis. Efavirenz should not be prescribed in the first trimester of pregnancy because of its possible teratogenicity; however, if exposure has occurred and the neural tube has closed, efavirenz can be continued. Nevirapine should not be started in pregnancy, unless indicated by the woman's resistance patterns, because it is associated with a high rate of serious adverse outcomes in this situation; however ongoing, pre-pregnancy treatment with nevirapine can be continued through pregnancy if tolerance and efficacy are established. (II-3D)
9. If antiretroviral therapy is discontinued for any reason during pregnancy, all drugs should be discontinued at once (unless the woman is on non-nucleoside reverse transcriptase inhibitors; in that case a tail of 2 nucleoside reverse transcriptase inhibitors is recommended for 1 week), and all drugs should be resumed simultaneously to minimize the risk of viral resistance developing during therapy. Antiretroviral therapy should be resumed as quickly as possible after discontinuance to minimize the risk of rebound viremia and the potentially increased risk of vertical transmission. (II-1A)
10. If a pregnant woman has significant nausea of pregnancy, do not begin antiretroviral therapy until her nausea is adequately controlled. Most antinauseants used in pregnancy can be co-administered with antiretrovirals. If the woman is already on antiretrovirals and has hyperemesis of pregnancy, discontinue all antiretrovirals at once, and then reinstate all at once, when nausea and vomiting are controlled (unless the woman is on non-nucleoside reverse transcriptase inhibitors [NNRTIs], in which case a tail of 2 nucleoside reverse transcriptase inhibitors is recommended for 1 week to prevent future NNRTI resistance). (II-2B)
11. Therapy should be individualized to maximize adherence to the prescribed antiretroviral regimen. (III-A)

12. Routine dose adjustment of the combination antiretroviral therapy is not recommended in pregnancy. (III-D)
13. The woman's clinical, virological, and immunological statuses should be assessed every 4 to 8 weeks during pregnancy, and again 6 weeks postpartum. Routine criteria should be used to assess the woman's response to, and the possible failure of, antiretroviral therapy. The toxicity of the antiretrovirals should also be monitored at these times. Specific testing should be individualized for the known toxicities of the woman's antiretroviral therapy regimen. (III-B)
14. As for all pregnant women, all those living with HIV, regardless of age, should be offered, through an informed consent process, dating ultrasound and non-invasive prenatal genetic screening for the most common clinically significant fetal aneuploidies. (III-A)
15. A detailed obstetrical ultrasound at 19 to 20 weeks' gestation is recommended. Additional ultrasounds, for fetal growth and amniotic fluid volume, are recommended at least each trimester, or as guided by obstetrical indications. (II-3B)
16. As for all pregnant women, those living with HIV should be screened periodically for substance use, and drug addiction should be addressed as needed in conjunction with HIV management. (III-A)
17. Mode of delivery should be discussed in detail with all women:
    a. Women on optimal antiretroviral therapy with acceptable plasma viral load suppression (less than 1000 c/mL) over the last 4 weeks prior to delivery are recommended to have a vaginal delivery in the absence of other obstetrical indications for Caesarean section. If Caesarian section is recommended for obstetrical indications, it can be conducted at 39 weeks, as usual for those indications. (I-A)
    b. Women not on optimal antiretroviral therapy (i.e., no antiretroviral therapy, monotherapy only, or with an incompletely suppressed viral load) should be offered a scheduled pre-labour Caesarian section at approximately 38 weeks' gestation. (II-2A)
18. Intravenous zidovudine should be initiated as soon as labour onset until delivery, in combination with an oral combination antiretroviral regimen, regardless of mode of delivery, current antiretroviral regimen, or viral load. (III-B)
19. Intrapartum, a single dose of oral nevirapine (200 mg) remains an option in the unusual circumstance of a woman living with HIV who has not received antenatal antiretroviral therapy in pregnancy. (I-B)
20. Plans for ongoing HIV care should be established prenatally, and unless otherwise indicated, maternal antiretroviral therapy should be continued after delivery and reassessed for ongoing therapy by providers of adult HIV care. (II-1A)
21. HIV-exposed newborns should receive antiretroviral therapy for 6 weeks to prevent vertical transmission of HIV. (I-A)
22. Health care practitioners who care for HIV-exposed newborns should provide timely diagnostic HIV testing: HIV polymerase chain reaction at birth, 1 month, and 3 to 4 months and HIV serology at 18 months (II-A), and they should monitor both short- and long-term outcomes, including screening for adverse effects of antiretroviral therapy and for developmental delay. (III-A).
23. Breast-feeding is not recommended regardless of plasma HIV viral load and use of antiretroviral therapy. (I-E)
24. The pregnancy should be registered with surveillance programs to allow the collection of provincial and national data to guide future pregnancy policies. Women undergoing antiretroviral therapy in pregnancy should also be offered inclusion in appropriate studies. (III-B)

The full text of this document is available online at: **http://www.sogc.org** and **http://www.jogc.com**.

ABBREVIATIONS

ALT	alanine aminotransferase
AST	aspartate aminotransferase
cART	combination antiretroviral therapy
EIA	enzyme immunoassay
IV	intravenous
NIH	National Institutes of Health
PCR	polymerase chain reaction
RNA	ribonucleic acid
ZDV	zidovudine

INTRODUCTION

Supportive non-directive counselling regarding reproductive choices, high-risk prenatal care, modified management of labour and delivery, and postpartum and infant care are all important components in the comprehensive care of the woman living with HIV and her infant. The provision of pregnancy and reproductive health care in women living with HIV should involve collaboration with individuals experienced in the management of high-risk pregnancy and HIV care of women and infants.

In Canada, several clinics provide multidisciplinary care and guidance for this population of adults and children living with and exposed to HIV, in coordination with provincial authorities. Longitudinal surveillance on pregnancy outcomes in women living with HIV are tracked by the Canadian Perinatal HIV Surveillance Program through information provided by clinicians who care for pregnant women living with HIV and their infants. This is vital for the continuous quality improvement of antiretroviral prescribing in pregnancy.

BACKGROUND

Scope

The guideline summarized here primarily addresses the management of HIV during pregnancy and does not comprehensively address pre-pregnancy planning issues. Canadian HIV pregnancy planning guidelines are available elsewhere,[1] as are guidelines addressing the HIV care of non-pregnant women,[2] which is not discussed in this document. Management of HIV in pregnant women with co-morbidities is addressed in brief; readers are referred to available guidelines for detailed discussion.[3]

Epidemiology of Perinatal HIV

In 2011, the Joint United Nations Programme on HIV/AIDS and the World Health Organization (WHO) estimated that a total of 34 million people worldwide were living with HIV, approximately half of whom were women.[4] The number of people living with HIV in Canada continues to rise, from an estimated 64 000 in 2008 to 71 300 in 2011.[5] The estimated prevalence in Canada in 2011 was 208.0 per 100 000 (range: 171.0 to 245.1), 23% to 28% of whom were women.[5] Combination antiretroviral therapy has been demonstrated to prolong the lives of people living with HIV,[6] and has also significantly reduced the rate of vertical transmission of HIV from a baseline risk of 25% without intervention to less than 2% in the context of comprehensive pregnancy care and cART administered antenatally, intrapartum, and to the infant in the early neonatal period.[7,8] Overall, the HIV vertical transmission rate in women who received at least 4 weeks of cART before delivery is 0.4% in Canada.[9] As a result of these factors, more women living with HIV are considering their reproductive options and choosing to become pregnant,[1] and the incidence of pregnancies in women living with HIV in Canada has been gradually increasing.[9] However, the vertical transmission of HIV remains a great concern globally as an estimated 26% of women living with HIV remain unaware of their HIV status,[10] and the majority of childhood HIV infections are acquired in this manner.[3]

PRE-CONCEPTION PLANNING

Detailed information and recommendations regarding pre-conception planning for people with HIV is beyond the scope of this document. These issues are addressed in detail in the Canadian HIV pregnancy planning guidelines[1] and in the NIH perinatal guidelines.[3] In brief, the following important clinical issues need to be considered with respect to pregnancy planning and counselling in individuals living with HIV:

1. use of effective methods of birth control for those who do not wish to become pregnant;
2. pre-conceptional health, including the intake of folic acid;
3. transmission between partners during conception; and
4. antiretroviral and other drugs in pregnancy planning.

Recommendation

1. All women living with HIV who are planning a pregnancy or who become pregnant should have their individual situations discussed with experts in the area, with referral to both HIV treatment programs and obstetrical care providers, and an overall plan should be made for their pregnancy care. (II-2A)

NEW DIAGNOSIS OF HIV IN A PREGNANT WOMAN

All pregnant women should be offered HIV testing, with appropriate pre- and post-test counselling as part of their routine prenatal care in each pregnancy.[11] Some provinces have managed this through opt-in testing and others through opt-out testing. Women involved in ongoing high-risk HIV transmission activities who are HIV negative on initial testing should be retested each trimester, and if possible again near term. Testing women for the first time during labour and delivery is not optimal, and HIV issues should be addressed as early as possible in the pregnancy to optimize the health outcomes of both the woman and her infant. Rapid HIV antibody testing (also known as point-of-care HIV testing) in the labour and delivery setting is now available in some facilities and should be used as an important last opportunity to identify women living with HIV before delivery and to provide emergency prophylaxis to decrease the risk of vertical transmission.[11–13]

A clinician who is familiar with HIV management in pregnancy should evaluate every pregnant woman who is newly diagnosed with HIV. Women should be informed about their HIV diagnosis in person and support and counselling should be provided for the woman and her family. Women should be made aware of the improved natural history of HIV, specifically that with adherence to care and therapy, individuals living with HIV now experience an improved quality of life and prolonged life expectancy.[14]

Immediate assessment of risk transmission to others is important, and the woman should be counselled regarding the need for safe sexual practices. All previous children that may have been exposed in the past and all sexual or drug-use partners should be offered testing. Public health consultation should be sought to adhere to provincial regulations on reportable diseases. Disclosure to family and friends not at risk of HIV is not required and should be considered carefully in light of the unfortunate persistence of stigmatization.

Recommendation

2. All pregnant women should be offered HIV testing, with appropriate pre- and post-test counselling, as part of their routine prenatal care in each pregnancy. This testing should be repeated in each trimester in women who are recognized to be at high and ongoing risk for HIV infection. (II-2A)

NEW DIAGNOSIS OF PREGNANCY IN A WOMAN LIVING WITH HIV

A clinician familiar with HIV management should evaluate each HIV positive woman who becomes pregnant. Medical

care recommendations for the pregnant woman living with HIV will depend on the woman's wish to continue or end the pregnancy, her HIV disease status, and her cART medication history.

In the event that the woman does not wish to continue the pregnancy, access to termination of pregnancy services should be facilitated. Health care providers should use this opportunity to continue to engage in and optimize HIV care and to provide reproductive health counselling, including contraception, to reduce the future occurrence of an unintended pregnancy. The HIV status of the exposed sexual or drug use partner should also be verified.

Recommendation

3. Pregnant women living with HIV should be made aware that with the consistent use of combination antiretroviral therapy and abstinence from breastfeeding, the risk of perinatal transmission is < 1%. (I-A)

ANTIRETROVIRAL DRUG THERAPY DURING PREGNANCY

Antiretroviral drug therapy is indicated for all pregnant women living with HIV, regardless of their HIV viral load or CD4-cell count, for the woman's own health, for the prevention of HIV transmission to a partner, and for the prevention of vertical transmission.[3,9,15,16] Antiretroviral agents reduce the risk of vertical transmission through a number of mechanisms, including:

1. lowering maternal viral load using antenatal cART,
2. providing infant pre-exposure prophylaxis using intrapartum antiretroviral therapy that rapidly crosses the placenta in order to achieve adequate systemic drug levels in the infant, and
3. providing infant post-exposure prophylaxis.[3]

It is important to note that cART is effective even in women with low viral loads. Among women with baseline viral loads less than 1000 copies/mL, those who received antenatal antiretroviral therapy demonstrated a lower HIV vertical transmission rate than those who did not (1.0% vs. 9.8%; $P < 0.001$).[16]

The benefit of preventing the vertical transmission of HIV is considered to outweigh the potential risks associated with antiretroviral medications, provided these agents are administered per treatment recommendations and with close monitoring and follow-up by experts in the area of HIV and obstetrics. If a woman is already receiving cART, the current regimen should in most cases be continued if the regimen is effective in suppressing HIV viral load and is tolerated by the woman. There are situations, however, as specified in the recommendations below, when changing antiretroviral medications should be considered. Readers are referred to the comprehensive guideline for discussion of the benefits and potential risks associated with the use of each antiretroviral drug in pregnancy.

If a woman is not already on cART therapy, plans for a cART regimen should be made immediately; the timing of initiation will depend on her HIV disease status (i.e., CD4-cell count and HIV viral load), but cART should generally be initiated before weeks 14 to 20. Selection of a specific antiretroviral drug therapy regimen in an pregnant woman living with HIV must take into account the interrelated issues of:

1. the stage of pregnancy,
2. the current and co-morbid health status of the woman,
3. her HIV-resistance profile,
4. what is currently known about the use of specific drugs in pregnancy and the risk of teratogenicity,
5. unique pharmacokinetic considerations, including altered kinetics in pregnancy and issues of placental passage of medications,
6. the woman's social status and intravenous drug use, and
7. the ability of the woman to cope with the antiretroviral drug therapy pill burden.

All women should be counselled about the importance of adhering to the regimen and should be recommended to continue therapy after delivery.

Recommendations

4. All pregnant women living with HIV should be treated with combination antiretroviral therapy regardless of baseline CD4 and viral load. (II-2A)
5. Antiretroviral therapy should not be discontinued during the first trimester for obstetrical reasons, but if the woman is not on therapy and there is no urgent medical indication for combination antiretroviral therapy, it can be delayed until after 14 weeks' gestation. (III-B)
6. All women living with HIV (both those who still have a detectable viral load after exposure to antiretroviral therapy and those who are antiretroviral-naive) should have their virus genotyped and, if possible, tested for phenotypic resistance to assist in optimizing antiretroviral therapy. It is advisable to discuss the interpretation of the genotype testing and any changes to the antiretroviral therapy with experienced clinicians. Testing for HLA-B*5701, if not done previously, is recommended in case abacavir might be required. (II-2B).

7. A combination antiretroviral therapy regimen including a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one or more NRTIs and a boosted protease inhibitor should be favoured because there is higher confidence in its safety and efficacy in pregnancy. Whenever possible, antiretrovirals known to cross the placenta to the fetal compartment should be used. (II-2B)
8. Whenever possible drugs with no safety data should be avoided during the period of organogenesis. Efavirenz should not be prescribed in the first trimester of pregnancy because of its possible teratogenicity; however, if exposure has occurred and the neural tube has closed, efavirenz can be continued. Nevirapine should not be started in pregnancy, unless indicated by the woman's resistance patterns, because it is associated with a high rate of serious adverse outcomes in this situation; however ongoing, pre-pregnancy treatment with nevirapine can be continued through pregnancy if tolerance and efficacy are established. (II-3D)
9. If antiretroviral therapy is discontinued for any reason during pregnancy, all drugs should be discontinued at once (unless the woman is on non-nucleoside reverse transcriptase inhibitors; in that case a tail of 2 nucleoside reverse transcriptase inhibitors is recommended for 1 week), and all drugs should be resumed simultaneously to minimize the risk of viral resistance developing during therapy. Antiretroviral therapy should be resumed as quickly as possible after discontinuance to minimize the risk of rebound viremia and the potentially increased risk of vertical transmission. (II-1A)
10. If a pregnant woman has significant nausea of pregnancy, do not begin antiretroviral therapy until her nausea is adequately controlled. Most antinauseants used in pregnancy can be co-administered with antiretrovirals. If the woman is already on antiretrovirals and has hyperemesis of pregnancy, discontinue all antiretrovirals at once, and then reinstate all at once, when nausea and vomiting are controlled (unless the woman is on non-nucleoside reverse transcriptase inhibitors [NNRTIs], in which case a tail of 2 nucleoside reverse transcriptase inhibitors is recommended for 1 week to prevent future NNRTI resistance). (II-2B)
11. Therapy should be individualized to maximize adherence to the prescribed antiretroviral regimen. (III-A)
12. Routine dose adjustment of the combination antiretroviral therapy is not recommended in pregnancy. (III-D)

ANTEPARTUM MANAGEMENT

General considerations

It is important to consider the broad context of a woman's life when managing her HIV and prenatal care. Considerations include:

- Providing empathetic, nonjudgemental care to women living with HIV and their children in the spirit of professionalism.[17]
- Addressing early and systematically the need for social support, with at least one interview with a social worker.[9,15] The aim of the comprehensive assessment by a social worker is to determine the woman's needs and to propose culturally relevant support and follow-up if required.
- Maintaining confidentiality, including with relatives.[17]
- Encouraging the testing of partners and previous children if their HIV status is unknown.[18] The medical and psychological needs of the fathers should be addressed, and the men referred to other health care providers if necessary.[19]
- Advising on the use of, and facilitating access to, condoms for the purpose of preventing the transmission of HIV and other sexually transmitted infections.[20] If both members of the couple are living with HIV, they should be informed of the possible risk of superinfection associated with unprotected sex.[21]
- Respecting the wishes of a mother who refuses antenatal cART after being fully informed and counselled. A plan for the care of the newborn should be prepared prior to delivery.[17]

Pregnant women living with HIV should be considered to have high-risk pregnancies. Their medical therapy requires coordination and communication between HIV specialists and obstetrical providers. Virtual or telephone communication between health care providers should be considered if women in remote settings are unable to attend for specialist consultations.

First Trimester (Weeks 0 to 13)

Early pregnancy offers the opportunity for complete HIV and obstetrical laboratory tests and investigations, and permits planning for prenatal genetic screening. Recommended tests and blood work are summarized in Table 2.

All pregnant women living with HIV, regardless of age, should be offered, through an informed consent process, dating ultrasound and prenatal genetic screening for the most common clinically significant fetal aneuploidies. First trimester biochemical screening and nuchal translucency

Table 2. Recommended laboratory tests and investigations for pregnant women living with HIV by visit and gestational age

		Initial visit*	10–13+6 weeks	15–17 weeks	19–20 weeks	24–26 weeks	28–30 weeks	32–36 weeks	Delivery	4–6 weeks
Immunologic assessment	CD4	√	√ opt	√ opt	√	√ opt	√	√	√	√
HIV plasma viral load	HIV viral load	√	√ opt	√ opt	√	√ opt	√	√	√	√
Drug resistance & abacavir hypersensitivity testing	HIV genotypic drug resistance†	√								
	HLA-B*5701‡	√								
Hematologic assessment	CBC with differential	√	√ opt	√ opt	√	√ opt	√	√	√	√
Liver function tests	AST, ALT, LDH, bilirubin	√	√ opt	√ opt	√	√ opt	√	√	√	√
Renal function	Creatinine, BUN	√	√ opt	√ opt	√	√ opt	√	√	√	√
	Phosphatemia§	√	√ opt	√ opt	√	√ opt	√	√	√	√
	Urinalysis & urine culture	√			√ opt			√ opt		
Blood glucose	Fasting glucose		√							
	Gestational diabetes screen‖					√				
Blood type	Blood type	√								
Serology	CMV IgG	√								
	Rubella IgG	√								
	Toxoplasma IgG	√								
	Syphilis (RPR)	√					√ [68]			
	Varicella IgG	√								
	HAV IgG	√								
	HBsAg, anti-HBs, anti-HBc	√								
	HCV IgG¶	√								
Ultrasound & prenatal screening	Ultrasound	√ dating	√ 11–13+6 NT		√ detailed	√ opt growth	√ growth	√ opt growth		
	PAPP-A		√							
	uE3, hCG, AFP, inhibin A			√ 15–20+6						
Sexually transmitted & other infections	Cervix chlamydia & gonorrhea NAAT	√								
	Pap smear	√								√
	HSV history#	√								
	GBS screen anorectal swab**							√		

opt: optional; CBC: complete blood count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; CMV: cytomegalovirus; HAV: hepatitis A virus; HCV: hepatitis C virus; NT: nuchal translucency; PAPP-A: pregnancy associated plasma protein A; uE3: unconjugated estriol; hCG: human chorionic gonadotropin; AFP: alpha-fetoprotein; NAAT: nucleic acid amplification test; HSV: Herpes simplex virus; GBS: group B streptococcus.

*Integrate initial visit laboratory tests and investigations (as indicated) with all others if the visit occurs later than 10 weeks' gestation.

†HIV genotypic drug testing recommended at time of first HIV plasma viral load, at the time of initiation of antiretrovirals, and in the case of treatment failure or incomplete viral load suppression (>250 HIV copies/mL).

‡HLA-B*5701 testing is recommended at baseline, or if not previously performed, before starting therapy with abacavir.

§Phosphatemia should be monitored in women receiving tenofovir-based regimens because it is a potential cause of tubular toxicity.[3,66,67]

‖Screen for gestational diabetes using 50 g glucose challenge test (1 h plasma glucose [PG]) or 75 g oral glucose tolerance test (fasting PG, 1 h PG, 2 h PG).[68] If a woman is receiving a protease inhibitor-based regimen, particularly if initiated before pregnancy, consideration can be given to performing this screening test earlier.

¶Confirm a positive result for HCV antibodies with HCV PCR

#If there is a positive genital herpes history, recommend starting prophylactic treatment (e.g., valacyclovir 500 mg orally twice daily) at 34 to 36 weeks to prevent recurrent HSV at delivery

**Group B streptococcus ano-rectal swab recommended at 35 to 37 weeks, or sooner if delivery within 5 weeks is anticipated.

measurements should be obtained to integrate with second trimester biochemical screening, and these results should be used to inform the need for invasive testing.[22] If integrated prenatal screening is not accessible, then pregnant women living with HIV should be offered the available non-invasive option for screening for aneuploidy in the region based on gestational age.

Nausea and vomiting can be a significant issue for all pregnant women, and in women living with HIV, it may affect their ability to adhere to the prescribed antiretroviral regimen. Evaluation of nausea and vomiting of pregnancy should be conducted and aggressive management of this condition, starting with a prescription for doxylamine-pyridoxine as needed,[23] is necessary to facilitate the initiation and/or continuation of antiretroviral medications. Women should be counselled on all relevant aspects of ensuring a healthy pregnancy, including maintaining a healthy diet and lifestyle. Women should start or ideally continue taking folic acid 1 mg daily for at least the first 3 months of their pregnancy. In cases of food insecurity, resources should be offered to improve nutrition. Within a harm reduction model, women should be encouraged to stop smoking, drinking alcohol, and using recreational drugs, and they should be referred for appropriate counselling support and/or treatment.[1,24,25] Other harm reduction strategies that can be offered if appropriate include nicotine replacement treatment and opiate harm reduction measures such as methadone and/or buprenorphine programs.

Second Trimester (Weeks 14 to 27)

Assessment of the status of the woman's HIV, review of laboratory investigations from the first trimester, and re-evaluation of antiretroviral therapy should be completed during the second trimester. The women's clinical, virological, and immunological status should be assessed every 4 to 8 weeks throughout the pregnancy (see Table 2). Because co-morbidities affect many women living with HIV, more frequent evaluations may be appropriate.

The second part of the integrated prenatal screening tests, including a detailed ultrasound, should be performed in the second trimester.[22] If aneuploidy or any other fetal infection or syndrome that has prenatal diagnostics is a concern, invasive testing should be considered. Invasive testing should only occur if the statistical risk of the condition is higher than the risk of the procedure, taking into consideration the biochemical, serological, and ultrasound results.[22] When amniocentesis is performed, the woman should ideally be on cART, but the timing may not permit full suppression of her HIV viral load prior to the procedure. Non-invasive molecular prenatal testing should be considered as an option to avoid invasive testing.[26]

Third Trimester (Weeks 28 to 40)

The efficacy and toxicity of the cART regimen should be assessed every 4 to 8 weeks (Table 2). Given the risk of placental dysfunction associated with increased rates of intrauterine growth restriction and oligohydramnios in the pregnancies of women living with HIV,[27] follow-up growth ultrasound should preferably be done monthly; if this is not possible, a third trimester scan can assist in determining whether there has been placental or fetal compromise. Considering the higher rate of preterm birth in this population,[28–36] close clinical follow-up is recommended and the schedule of some obstetrical assessments (e.g. group B streptococcus screening) and prophylaxis (e.g. genital herpes prophylaxis) may need to be adjusted.

Adherence to cART regimens should be emphasized at each visit throughout the pregnancy, however, this is critical in the third trimester because virologic suppression (HIV viral load < 50 copies/mL) should be achieved at this time.

Between 30 and 35 weeks it is important that a formula-feeding plan has been arranged for the infant. Women living with HIV are recommended to formula-feed their infants; to avoid the 9.3% (3.8 to 14.8%) increased risk of vertical transmission of HIV through breast milk, breastfeeding is not recommended.[37–39] The risk of disclosure that may arise when a woman does not breastfeed may compromise her confidentiality. Health care providers should assist with a plan before delivery that can help women feel more comfortable when discussing feeding with family and friends.

Plans for ongoing HIV care for the woman should also be established at this time.

Delivery Plans and Mode of Delivery

Planning the hospital location for delivery should take into consideration the woman's gestational history, home location and transportability, the facilities at her regional hospital, and the comfort and experience of the local care providers. The care providers involved and the delivery plan, including location of delivery, can be reviewed during the second trimester, and should be established during the third trimester.

Mode of delivery has been reviewed extensively in cohort studies and a randomized controlled trial of intended mode of delivery. The initial studies that identified elective Caesarean section as a method to reduce vertical transmission were in women who were not receiving any antiretroviral drug therapy or who received monotherapy with ZDV only. Evidence to support elective Caesarean

section in the current cART era, when all women (even with viral loads < 1000 copies/mL)[16] are recommended to initiate cART in pregnancy, is absent.[40,41] Therefore, elective Caesarean section at 38 to 39 weeks' gestation is recommended only in women who have an unknown viral load, have a viral load > 1000 copies/mL, or are not on cART, regardless of their viral load. The benefit of Caesarean delivery shown in early studies appears to have been found exclusively in pre-labour elective Caesarean sections; no benefit was shown for emergency Caesarean sections.[7,42] Women who receive antepartum cART, are adherent to therapy, and have an HIV viral load < 1000 copies/mL within 4 weeks of delivery can be delivered vaginally, reserving Caesarean section deliveries for obstetrical indications only.

Recommendations

13. The woman's clinical, virological, and immunological statuses should be assessed every 4 to 8 weeks during pregnancy, and again 6 weeks postpartum. Routine criteria should be used to assess the woman's response to, and the possible failure of, antiretroviral therapy. The toxicity of the antiretrovirals should also be monitored at these times. Specific testing should be individualized for the known toxicities of the woman's antiretroviral therapy regimen. (III-B)
14. As for all pregnant women, all those living with HIV, regardless of age, should be offered, through an informed consent process, dating ultrasound and non-invasive prenatal genetic screening for the most common clinically significant fetal aneuploidies. (III-A)
15. A detailed obstetrical ultrasound at 19 to 20 weeks' gestation is recommended. Additional ultrasounds, for fetal growth and amniotic fluid volume, are recommended at least each trimester, or as guided by obstetrical indications. (II-3B)
16. As for all pregnant women, those living with HIV should be screened periodically for substance use, and drug addiction should be addressed in conjunction with HIV management as needed (III-A)
17. Mode of delivery should be discussed in detail with all women:
    a. Women on optimal antiretroviral therapy with acceptable plasma viral load suppression (less than 1000 c/mL) over the last 4 weeks prior to delivery are recommended to have a vaginal delivery in the absence of other obstetrical indications for Caesarean section. If Caesarian section is recommended for obstetrical indications, it can be conducted at 39 weeks, as usual for those indications. (I-A)
    b. Women not on optimal antiretroviral therapy (e.g. no antiretroviral therapy, monotherapy only, or with incompletely suppressed viral load) should be offered pre-labour scheduled Caesarean section at approximately 38 weeks' completed gestation. (II-2A)

INTRAPARTUM MANAGEMENT

Intrapartum management for women known to be living with HIV

All women known to be living with HIV should be instructed to attend labour and delivery immediately upon rupture of membranes or regular contractions so that measures can be taken to decrease the risk of vertical HIV transmission. All oral antenatal antiretroviral medications, with the exception of stavudine (d4T), should be continued for as long as possible during labour. Stavudine should not be administered concomitantly with IV ZDV because of an antagonistic drug interaction.[43] There are no randomized controlled trial data on the additional benefit of intrapartum IV ZDV in women who have been receiving antenatal cART. The most recent guidelines published by the NIH in the United States endorse intrapartum IV ZDV for use in pregnant women living with HIV only if they have had antenatal cART and have an HIV viral load > 400 copies/mL (or unknown) near delivery.[3] Canadian data show that 8.7% of women with a previously suppressed viral load have unpredictably elevated viral loads at time of delivery.[44] On the basis of this evidence, intrapartum IV ZDV (2 mg/kg/hour followed by 1 mg/kg/hour until delivery) is recommended for all women in Canada, regardless of mode of delivery, current antiretroviral regimen, or viral load. Intravenous ZDV should be administered as soon as it is determined the woman is in active labour and/or has ruptured membranes, or at least 2 to 3 hours prior to Caesarean section.

Women who did not receive any antiretroviral therapy during pregnancy should also receive a single dose of oral nevirapine (200 mg) as soon as possible at the onset of labour or at least 2 to 3 hours prior to Caesarian section. This recommendation also differs somewhat from that in the NIH perinatal guidelines.[3] In our experience, a number of practicalities must be considered when women present in labour, including the frequent difficulty of obtaining IV access, which makes the administration of IV ZDV difficult or impossible. Because single-dose oral nevirapine has been demonstrated to reduce vertical transmission of HIV,[45] it continues to be recommended for intrapartum administration to women living with HIV who have not received antenatal therapy, in addition to the administration of combination antiretrovirals to their infants.

Data from the pre-cART era indicate that obstetrical interventions that increase the exposure of the infant to maternal blood, such as invasive monitoring or episiotomies, may increase the risk of vertical transmission.[46–49] Extrapolating this data into the present era of cART, it is recommended that interventions that potentially increase fetal exposure, including scalp electrodes, intrauterine catheters,[50] prolonged rupture of membranes, operative vaginal deliveries, and episiotomies should be avoided if possible.

Intrapartum management for women of unknown HIV status and/or ongoing HIV risk

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; have had a recent illness suggestive of seroconversion; have had regular unprotected sex with a partner known to be living with HIV or at significant risk for HIV infection; or have had a diagnosis of a sexually transmitted infection during the pregnancy. Women who have been recently incarcerated or who have emigrated from areas with endemic HIV are also at increased risk if they have not been recently screened.

Women with unknown HIV status or at continued risk of HIV infection since their last negative HIV serology result should be offered (if available in the institution) rapid HIV antibody testing in the labour and delivery setting. If the test result is positive, the woman should be informed of the result, and confirmatory HIV PCR and antibody tests should be performed.[12,13] Maternal intrapartum antiretroviral drug therapy plus post-partum ZDV-lamivudine and infant prophylactic cART should be initiated pending results of the confirmatory test.

If rapid HIV antibody testing is not available within the institution and/or delivery is imminent and HIV seropositivity is a possibility, HIV PCR and HIV antibody tests should be performed. Intrapartum and postpartum antiretroviral drugs therapy should be offered to the woman, and all infants should receive prophylactic cART pending results. If the HIV antibody test is negative and the woman is out of the seroconversion period (i.e., has not engaged in high risk activities in 4 weeks) and/or HIV PCR is negative, infant and maternal antiretroviral therapy may be discontinued.

Recommendations

18. Intravenous zidovudine should be initiated as soon as labour onset until delivery, in combination with an oral combination antiretroviral regimen, regardless of mode of delivery, current antiretroviral regimen, or viral load. (III-B)
19. Intrapartum, a single dose of oral nevirapine (200 mg) remains an option in the unusual circumstance of a woman living with HIV who has not received antenatal antiretroviral therapy in pregnancy. (I-B)

POSTPARTUM MANAGEMENT

Postpartum care involves collaborative efforts between obstetric care providers, HIV specialists, and other multi-disciplinary health care providers to ensure coordinated HIV care for both the mother and her infant. A number of comprehensive issues that must be addressed include contraception, continuation of and adherence to antiretroviral drug therapy regimens, infant feeding and pediatric care, and the woman's needs for mental health services, social services, and/or treatment for substance use.

The use of ergotamine should be avoided because of the risk of exaggerated vasoconstriction in women receiving protease inhibitor therapy.[51] Oxytocin, misoprostol, and prostaglandin F2 alpha are recommended agents for managing postpartum hemorrhage. A number of studies have evaluated the risk of infectious morbidity following delivery in women living with HIV.[52–56] Some studies report higher rates of endometritis and pneumonia following Caesarian section in women living with HIV than in women without,[53] but others do not.[52]

Women who were receiving antenatal antiretroviral therapy should have their complete regimen resumed after delivery as soon as oral intake is tolerated. Women who were not receiving antenatal antiretroviral therapy but who received single-dose nevirapine during labour should receive 7 days of ZDV-lamivudine, 1 tablet orally twice daily, to reduce the risk of developing nevirapine resistance. ZDV-lamivudine therapy can be discontinued before completion of the 7-day treatment period if confirmatory HIV testing results show that the woman is not infected with HIV.

Plans for ongoing HIV care should be established prenatally, and unless otherwise indicated, maternal antiretroviral therapy should be continued after delivery and reassessed for ongoing therapy by providers of adult HIV care. Based on future pregnancy planning and adult HIV status, antiretroviral treatment modifications may be appropriate. Adherence in the postpartum period can be challenging[57,58] and support is important.

Management of the effects of not breastfeeding should include measures such as acetaminophen, ibuprofen, or cold compresses to minimize pain from engorgement. Bromocriptine and cabergoline, the classical therapies used for lactation suppression, are ergot derivatives, whose co-

administration with protease inhibitors is contraindicated. Women who test positive on rapid HIV antibody testing or who are believed to be at high risk of HIV (when rapid HIV antibody testing is not available) are recommended to pump their breast milk, but they should not feed it to the infant unless a confirmatory HIV test result is negative.

An early return to fertility can be expected as a result of not breastfeeding. It is critical to discuss safer sex practices and effective contraception methods with the women. Condom use is recommended to reduce the risk of transmission between partners; however, the contraception failure rate with condoms as commonly used is reported to be as high as 14%.[59] Oral contraceptives may also be used by women living with HIV, particularly with the use of condoms as part of a dual-protection strategy. Drug interactions between antiretroviral drugs and oral contraceptives have been documented, therefore it is important to assess potential interactions between specific antiretroviral agents and oral contraceptive pill.[3,60] Non-oral contraceptive methods including Depo-Provera, contraceptive patches, contraceptive vaginal rings, and intrauterine devices are also options; however, there are less data available on their use in combination with antiretroviral medications.[59,61]

Linkage to care is important for all women with HIV, particularly for women who were newly diagnosed with HIV during labour and delivery. All women should have arrangements for follow-up care with providers experienced in the management of HIV.

Recommendation

20. Plans for ongoing HIV care should be established prenatally, and unless otherwise indicated, maternal antiretroviral therapy should be continued after delivery and reassessed for ongoing therapy by providers of adult HIV care. (II-1A)

INFANT MANAGEMENT

All infants should be offered antiretroviral prophylaxis regardless of maternal antenatal or intrapartum antiretroviral therapy, viral load, or mode of delivery. The prophylaxis should be started as soon as possible, no later than 6 to 12 hours after birth. The recommended regimen will depend on the presumed level of risk.

Infants born to a mother known to be living with HIV infection and with a viral load < 1000 copies/mL should be offered prophylactic therapy with oral ZDV for 6 weeks. Infants born to a mother known to be living with HIV infection and a known or projected viral load > 1000 copies/mL or to a mother known to be living with HIV and who did not receive any antepartum antiretroviral therapy, should receive prophylactic antiretrovirals with a 3-drug regimen including ZDV for 6 weeks combined with 3 doses of nevirapine in the first week of life and oral lamivudine twice daily for 2 weeks. This recommendation is made on the basis of the HPTN040/PACTG 1043 trial in women living with HIV who were not receiving antenatal antiretrovirals, which demonstrated that combination regimens had better efficacy in reducing vertical transmission to infants intrapartum (2.2%) than ZDV alone (4.8%).[62]

In settings where rapid HIV antibody testing is not yet available, the optimal management strategy for infants born to women with unknown HIV status and considered at high risk of HIV infection has not been established in a randomized clinical trial. In this clinical scenario, the potential benefit of preventing vertical transmission of HIV is believed to outweigh the potential risks of the infant's unnecessary exposure to antiretrovirals.

It is important to discuss feeding practices with the mother during antenatal visits, using a sensitive approach and acknowledging the mother's cultural beliefs about infant feeding. Because premastication by caregivers living with HIV has been implicated as a potential route of HIV transmission to young infants, health care practitioners should also inquire specifically about premastication and advise caregivers living with HIV to avoid this practice.

Infants exposed to HIV should be tested for HIV infection by a virological test at birth, at 4 weeks, and at 3 to 4 months of age to determine HIV status. Additional testing for infants at high risk of vertical transmission should be discussed with a pediatric HIV specialist. HIV RNA PCR (or nucleic acid amplification test) is the virological test currently used for diagnostic purposes. HIV infection can be excluded when two HIV virological tests are non-reactive, one collected after 4 weeks of age and the other at least 4 weeks after the end of prophylactic antiretrovirals. Serological EIA tests are not indicative of infant status due to the presence of detectable maternal HIV antibodies in the infant up to 18 to 24 months of age.

A confirmatory HIV EIA test is recommended to document seroreversion after 18 months of age. If an HIV PCR is reactive, a confirmatory RNA PCR test should be requested immediately. When an infant is found to have HIV, antiretroviral prophylaxis should be discontinued and an urgent referral should be made to an HIV specialist;[63] this may prevent the establishment of viral reservoirs in the infant.[64]

All infants born to women living with HIV should be referred for ongoing assessment and care to a pediatrician with expertise in this area. Developmental follow-up is crucial for uninfected HIV-exposed children. Factors such as poverty, food insecurity, low literacy, inexperience in parenting, and parental substance or alcohol use put infants at higher risk for failure-to-thrive, developmental delay, and behavioural disorders. Long-term follow-up of children who were perinatally exposed to HIV and antiretrovirals is recommended into adulthood, because there are unknown and theoretical concerns about the potential carcinogenicity of nucleoside analogue antiretroviral drugs and other long-term effects of antiretroviral medications.[3]

Recommendations

21. HIV-exposed newborns should receive antiretroviral therapy for 6 weeks to prevent vertical transmission of HIV. (I-A)
22. Health care practitioners who care for HIV-exposed newborns should provide timely diagnostic HIV testing: HIV polymerase chain reaction at birth, 1 month, and 3 to 4 months and HIV serology alabort 18 months (II-A), and they should monitor both short- and long-term outcomes, including screening for adverse effects of antiretroviral therapy and for developmental delay. (III-A).
23. Breast-feeding is not recommended regardless of plasma HIV viral load and use of antiretroviral therapy. (I-E)
24. The pregnancy should be registered with surveillance programs to allow the collection of provincial and national data to guide future pregnancy policies. Women undergoing antiretroviral therapy in pregnancy should also be offered inclusion in appropriate studies. (III-B)

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