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Guideline No. 450: Care of Pregnant Women Living with HIV and Interventions to Reduce Perinatal Transmission

The English document is the original version; translation may introduce small differences in the French version.

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This document reflects emerging clinical and scientific advances as of the publication date and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure. Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

Informed consent: Patients have the right and responsibility to make informed decisions about their care, in partnership with their health care provider. To facilitate informed choice, patients should be provided with information and support that is evidence-based, culturally appropriate, and personalized. The values, beliefs, and individual needs of each patient in the context of their personal circumstances should be considered and the final decision about care and treatment options chosen by the patient should be respected.

Language and inclusivity: The SOGC recognizes the importance to be fully inclusive and when context is appropriate, gender-neutral language will be used. In other circumstances, we continue to use gendered language because of our mission to advance women's health. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

Weeks Gestation Notation: The authors follow the World Health Organization's notation on gestational age: the first day of the last menstrual period is day 0 (of week 0); therefore, days 0 to 6 correspond to completed week 0, days 7 to 13 correspond to completed week 1, etc.

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Subject Categories: Infectious disease, Maternal Fetal Medicine, Obstetrics

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RECOMMENDED CHANGES IN PRACTICE

1. Pregnant women should be assessed for risk of acquisition of HIV during pregnancy and lactation and offered pre-exposure prophylaxis when indicated for use throughout pregnancy and lactation.
2. Women living with HIV should generally continue to follow established antiretroviral regimens in pregnancy. There are uncommon situations where antiretroviral switching is indicated following specialist review.
3. Women living with HIV who become pregnant should have their past serology results and medical history reviewed for pregnancy-relevant co-infections including syphilis, cytomegalovirus, herpes simplex virus 1 and 2, hepatitis B and C, toxoplasmosis, varicella-zoster virus, and tuberculosis and be screened in the absence of prior testing.
4. Evaluation and treatment of nausea during pregnancy is critical to maintaining antiretroviral adherence.
5. Pregnancy care providers for women living with HIV should be aware of potential drug–drug interactions with antiretrovirals and commonly prescribed medications in pregnancy including iron, magnesium, calcium, and acid suppression agents.
6. The antiretroviral nevirapine should not be prescribed for the first time in pregnancy but can be continued if it is part of an established regimen and well tolerated.
7. A single dose of oral nevirapine is no longer recommended for intrapartum prophylaxis. In unique situations where intravenous access for zidovudine is not possible, expert guidance is recommended.
8. Categorization of risk of perinatal transmission should be based on adherence to the antiretroviral regimen and viral load near delivery, with those with viral loads $<$50 copies/mL considered low risk and those with viral loads $\geq$400 copies/mL or an unknown viral load considered high risk.
9. Antiretroviral therapy should be continued during labour and delivery. In women with consistently undetectable viral loads throughout their antenatal care, intravenous zidovudine before and during delivery can be withheld as part of the multidisciplinary plan.

KEY MESSAGES

1. With consistent use of antiretrovirals in pregnancy, newborn prophylaxis, and avoidance of breastfeeding, the rates of HIV transmission to the newborn is $<$1%.
2. Management of HIV in pregnancy is greatly enhanced by multidisciplinary input and benefits from review by obstetric specialists with expertise in this area.
3. The development of new treatments and new information on established antiretrovirals will require real-time assessment of safety and efficacy in pregnant women and is beyond the scope of this guideline.

ABSTRACT

Objective: This guideline provides an update on the care of pregnant women living with HIV and the prevention of perinatal HIV transmission. This guideline is a revision of the previous guideline, No. 310 Guidelines for the Care of Pregnant Women Living With HIV and Interventions to Reduce Perinatal Transmission, and includes an updated review of the literature with contemporary recommendations.

Target Population: Pregnant women newly diagnosed with HIV during antenatal screening and women living with HIV who become pregnant. This guideline does not include specific guidance for girls/women of reproductive age living with HIV who are not pregnant.

Outcomes: Prevention of perinatal HIV transmission is a key indicator of the success of a health care system and requires multidisciplinary care of pregnant women living with HIV. Intended outcomes include guidance on best practice in perinatal management for Canadian health care providers for pregnant women living with HIV; reduction of perinatal transmission of HIV toward a target of eradication of perinatal transmission; provision of optimal antenatal care for pregnant women to ensure the best maternal health outcomes and HIV suppression; and evidence-based support and recommendations for pregnant women living with HIV, maintaining awareness and consideration of the complex psychosocial impacts of living with HIV.

Benefits, Harms, and Costs: The perinatal transmission of HIV has significant morbidity and mortality implications for the child, with associated lifelong health care costs. Pregnancy presents an emotionally and physically vulnerable time for pregnant women as well as an opportunity to engage them in health promotion. This guidance does not include recommendations with additional costs to health care facilities compared with the previous guideline. Application of the recommendations is aimed at health benefits to both mother and child by optimizing maternal health and preventing perinatal HIV transmission.

Evidence: Published and unpublished literature was reviewed with a focus on publications post-2013. OVID-Medline, Embase, PubMed and the Cochrane Library databases were searched for relevant publications available in English or French for each section of this guideline. Results included systematic reviews, randomized controlled trials, and observational studies published from 2012 to 2022. Searches were updated on a regular basis and incorporated in the guideline until May 2023. Unpublished literature, protocols, and international guidelines were identified by accessing the websites of health-related agencies, clinical practice guideline collections, and national and international medical specialty societies.

Validation Methods: The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. See Appendix A (Tables A1 for definitions and A2 for interpretations of strong and conditional recommendations).

Intended Audience: The intended users of this guideline include obstetric care providers and infectious disease clinicians who provide care for pregnant women living with HIV.

Social Media Summary: Updated Canadian HIV in pregnancy guideline informed by global research and tailored to Canadian healthcare needs and goals for pregnant women living with HIV and their families.

SUMMARY STATEMENTS:

1. With the consistent use of effective antiretroviral therapy and abstinence from breastfeeding, the risk of perinatal transmission of HIV is less than 1% (*high*).
2. Antiretroviral therapy is indicated for all pregnant women living with HIV, regardless of HIV viral load or CD4 cell count, for the woman's own health, the prevention of HIV transmission to a partner, and the prevention of perinatal transmission (*high*).
3. Individualization of antiretroviral therapy will maximize adherence to the prescribed regimen in pregnancy (*moderate*).
4. Inclusion of data on pregnancies affected by HIV in surveillance programs allows for the collection of provincial and national data to guide future pregnancy policies (*high*).

RECOMMENDATIONS:

1. All pregnant women living with HIV should be treated with antiretroviral therapy regardless of baseline CD4 cell count and viral load (*strong, moderate*).
2. All women living with HIV who are planning a pregnancy or who become pregnant should have their individual circumstances discussed with experts in the area. Referral to both HIV treatment programs and obstetrical care providers should be made with the goal of a multidisciplinary plan for pregnancy care (*strong, moderate*).
3. Routine dosage adjustment of combination antiretroviral therapy is not currently recommended in pregnancy (*strong, high*).
4. Choice of pre-pregnancy antiretroviral therapy should consider whether sufficient data on safety and effectiveness is available for the regimen in pregnancy (*strong, moderate*).
5. Antiretroviral therapy should not be discontinued during the first trimester because of theoretical concerns regarding teratogenicity in women currently taking antiretroviral therapy (*strong, moderate*).
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 viral genotyping and testing for phenotypic resistance, where possible, to assist in optimizing antiretroviral therapy. Experienced clinicians in referral centres can aid in facilitating this testing and interpretation of the genotype testing to guide any necessary changes to the antiretroviral therapy. Testing for HLA B*5701, if not done previously, is recommended in the event abacavir is considered (*strong*, *high*).
7. Women living with HIV should generally continue established antiretroviral regimens (including those containing efavirenz, nevirapine, or dolutegravir) following the diagnosis of pregnancy. There are uncommon situations where antiretroviral switching is indicated following specialist review (*conditional, moderate*).
8. Whenever possible, antiretrovirals with no safety data should be avoided in pregnancy and particularly during the period of organogenesis (*conditional, moderate*).
9. If a pregnant woman has significant hyperemesis of pregnancy, antiretroviral therapy should not be initiated until nausea is adequately controlled. Most anti-nauseants used in pregnancy can be co-administered with antiretrovirals. If the woman is already on antiretroviral therapy and has severe hyperemesis of pregnancy, first maximize anti-nauseant regimens, and only discontinue antiretrovirals if unable to prevent emesis of the antiretroviral medication. If discontinued, stop all drugs at once, then reinstate all at once when nausea and vomiting are controlled (*strong, moderate*).
10. The woman's clinical, virological, and immunological status should be assessed every 4–12 weeks, including at 36 weeks gestation, at delivery, and again 4–8 weeks postpartum. Specific testing should be individualized for the known toxicities of the antiretroviral regimen (*conditional, moderate*).
11. As for all pregnant women, those living with HIV, regardless of age, should be offered, through an informed consent process, first-trimester ultrasound (ideally at 11–14 weeks) and a prenatal screening test for the most common fetal aneuploidies (*strong, moderate*).
12. A detailed obstetrical ultrasound at 19–20 weeks gestation is routinely recommended for quality pregnancy care (*strong, high*). Additional ultrasounds, for fetal growth and amniotic fluid volume, should be considered with at least one additional ultrasound in the third trimester and further ultrasound assessments as guided by obstetrical/medical indications (*conditional, moderate*).
13. Mode of delivery should be discussed throughout pregnancy with plans made in the third trimester according to viral load and obstetric factors. Women on optimal antiretroviral therapy with undetectable viral loads ($<$50 copies/mL) measured in the 4 weeks prior to delivery are recommended to have a vaginal delivery in the absence of other obstetrical indications for cesarean delivery. If cesarean delivery is recommended for obstetrical indications, it can be conducted at the gestation required for those indications (*strong, high*).
14. Women not on optimal antiretroviral therapy (i.e., no antiretroviral therapy, unknown viral load, or viral load $\geq$400 copies/mL) should be offered scheduled pre-labour cesarean delivery at approximately 38 weeks gestation (*strong, moderate).*
15. Plans for delivery should include the recognition that there are higher rates of preterm delivery for women living with HIV (*conditional, moderate*).
16. For patients with detectable viral loads or suboptimal antiretroviral therapy adherence, intravenous zidovudine should be initiated as soon as possible after labour onset, rupture of membranes, or precesarean (2 hours pre-op) until delivery, with continuation of the woman's oral antiretroviral regimen, regardless of mode of delivery, current antiretroviral regimen, or viral load (*conditional, low*). This recommendation could be individualized, and intravenous zidovudine may not be necessary for extremely stable patients with undetectable viral loads ($<$50 copies/mL) under specialist advice (*conditional, moderate*).
17. For women without an existing HIV provider, a referral should be made as soon as possible. Plans for ongoing HIV care should be established antenatally, and maternal oral antiretroviral therapy should be continued through labour and postpartum. Later reassessment of the antiretroviral regimen can be made by the providers of adult HIV care (*strong, high*).
18. Infant feeding should be discussed with the woman and her care team. At present, in Canada, formula feeding remains the preferred method of infant feeding regardless of plasma HIV viral load and use of maternal antiretroviral therapy (*strong*, *moderate*). Should the woman choose to breastfeed, she should be supported during her pregnancy care, and consultation with pediatric HIV experts should be sought to plan for enhanced surveillance and/or prophylactic treatment for the infant *(strong, moderate*).

INTRODUCTION

In 2020, the Joint United Nations Programme on HIV/AIDS estimated that 37.7 million people were living with HIV globally, with more than half being women over the age of 15 years.[1] Globally, new infections have decreased since their peak in 1997, and since 2021 new infections in children have decreased by 53%, owing mainly to the prevention of perinatal transmission.[1] Since 1994, when the use of antiretroviral therapy in pregnancy was shown to significantly reduce the risk of perinatal transmission, from approximately 20% in the pre-antiretroviral therapy era, there has been increasing access to antiretroviral therapy for pregnant women with a corresponding reduction in perinatal transmission.[2] Despite this, in Canada, optimal access and adherence to antiretroviral therapy in pregnancy has not been universally achieved, leading to persistent cases of perinatal transmission every year, with increasing rates in recent years.[3,4] Much of this rise has been attributed to pandemic-related lack of engagement in care and highlights the importance of regular contact with health care providers throughout the perinatal period for people at risk of HIV acquisition or with barriers to accessing medical therapy.[5,6]

Over the last decade in Canada there have been an average of 250 (range 217−268) perinatal exposures (mother−infant pairs) per year with an average of 5.5 (range 1−12) confirmed infections.[4] Despite decreases in other rates, the rate of new infections in women has increased with a diagnosis rate of 3.4 per 100 000 in 2019 compared with 2.6 per 100 000 in 2015,[4] with heterosexual transmission in the 30−39-year-old age group and injection drug use being the highest risk factors for females.[4] A Canadian perinatal HIV transmission surveillance study from 1997 to 2016 demonstrated an overall perinatal transmission rate of 3.4%, with the rate for the 2011−2016 period being 1%.[5] The majority of perinatal transmission cases for the 2011−2016 period (12 out of 14 cases) occurred in pregnant women living with HIV who had not received adequate antenatal antiretroviral therapy.[5] A recent review of the data from 2015 to 2020 showed an increase in perinatal transmission in 2020 of 3.2%. It is presumed that the impact of the COVID-19 pandemic played a role, but these data serve to demonstrate that alterations in access to care and other factors can rapidly adversely impact perinatal transmission.[6]

ABBREVIATIONS

NAT	nucleic acid amplification testing
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
PEP	post-exposure prophylaxis
PCR	polymerase chain reaction
PrEP	pre-exposure prophylaxis

SCOPE

This updated guideline summarizes the management of HIV infection first diagnosed in pregnancy and pregnancy management for women living with HIV in Canada. Related guidelines that address areas not covered in this guideline include SOGC Clinical Practice Guideline No 354: Canadian HIV Pregnancy Planning Guidelines,[7] SOGC Clinical Practice Guideline No 185: HIV Screening in Pregnancy,[8] the Canadian Guideline on HIV Pre-exposure Prophylaxis and Nonoccupational Post-exposure Prophylaxis,[9] and the Canadian Pediatric and Perinatal HIV/AIDS Research Group Consensus Recommendations for Infant Feeding in the HIV Context.[10]

In summary, it is recommended that all women living with HIV who plan a pregnancy have a preconception counselling visit to address issues such as preconception health, including folic acid supplementation and horizontal transmission between partners during conception, and to review antiretrovirals and other medications in pregnancy planning.[7] Exclusive formula feeding remains the recommended mode of feeding for babies born to women living with HIV in Canada at this time, but there is an emphasis on providing support for mothers who choose to breastfeed to ensure their ongoing engagement in care.

All pregnant women should be screened for HIV in the first trimester or at the first antenatal visit, and if they are involved in ongoing high-risk HIV transmission activities or in discordant partnerships, should be retested each trimester, again near term, and in the postpartum period, particularly if breastfeeding.[8] In addition, clinicians should assess exposure and offer pre-exposure prophylaxis (PrEP) when indicated for use throughout pregnancy or breastfeeding.[9]

The purpose of this guideline is to provide evidence-based recommendations for obstetric care providers for pregnant women living with HIV. Its aim is to minimize the chance of perinatal transmission and ensure the pregnancy does not have detrimental effects on maternal health.

NEW DIAGNOSIS OF HIV INFECTION IN PREGNANCY

In a review of perinatal transmission cases in Canada from 2011 to 2016, 9 out of the 14 cases where perinatal

transmission occurred had not had a pre-labour diagnosis of HIV.[5] In line with early identification of HIV in the antenatal period, each province has included this screening in the regular schedule of antenatal investigations in either an opt-in or opt-out form.

When informing a pregnant woman of the diagnosis following antenatal screening, it is important to consider several aspects:

- Informing the woman in a supportive environment, keeping in mind the importance of confidentiality
- Emphasizing the improved outcomes and life expectancy for people living with HIV, as a result of modern antiretroviral therapy[11]
- Assessing the risk of transmission to (a) current sexual partners or people with whom the woman may share injecting equipment and (b) previous children
- Referring for assessment to a provider experienced in managing HIV in pregnancy
- Discussing with public health authorities required reporting of HIV
- Disclosing to other contacts or family members is not required if they are not at risk of infection but can be supported after full discussion of the impact of disclosure on the pregnant woman.

Of note, confidentiality requires additional care in light of the unfortunate persistence of stigmatization and potential safety issues for pregnant women.

Rapid HIV antibody testing (or point-of-care HIV testing) in the labour and delivery setting is now available in many 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 perinatal transmission.[12] This is recommended by both the SOGC and the Public Health Agency of Canada as part of the action plan in reducing HIV transmission.[8,13]

FIRST TRIMESTER AND FIRST ANTENATAL VISITS

Following the first detection of pregnancy, it is recommended that all pregnant women living with HIV be considered to have medically complex pregnancies and offered multidisciplinary care including consultations with obstetrics or maternal–fetal medicine and HIV specialists. While awaiting these referrals several interventions can be initiated by the primary care or emergency medicine provider making the diagnosis (Table 1).

Table 1. Diagnosis of pregnancy in a woman living with HIV: First steps for primary care

Steps for primary care
1) Refer immediately for dating ultrasound to determine intrauterine location, viability, and estimated gestational age.
2) Commence 1 mg daily folic acid supplementation (ideally pre-conception) for at least the first 3 months of pregnancy.[a]
3) Discuss the woman's antiretroviral regimen with an HIV pregnancy care provider to categorize the urgency of review but continue current antiretroviral regimen.
4) Address nausea and vomiting that may impact adherence to antiretroviral therapy with a low threshold for pre-emptive use of doxylamine/pyridoxine and use of second- and third-line agents if required.[b]
5) Discuss and promote healthy behaviours including harm reduction involving cessation of smoking, drinking alcohol, and use of recreational drugs.[c,d]
a. Harm reduction strategies that can be offered if appropriate include nicotine replacement and methadone and/or buprenorphine programs.

References:

[a]Wilson RD, Genetics Committee, Wilson RD, et al. Pre-conception folic acid and multivitamin supplementation for the primary and secondary prevention of neural tube defects and other folic acid-sensitive congenital anomalies. J Obstet Gynaecol Can 2015;37:534–52.

[b]Campbell K, Rowe H, Azzam H, et al. Prise en charge des nausées et vomissements de la grossesse. J Obstet Gynaecol Can 2016;38:1138–49.

[c]Carson G, Cox LV, Crane J, et al. N° 245-Directive clinique de consensus sur la consommation d'alcool et la grossesse. J Obstet Gynaecol Can 2017;39:e255–92.

[d]Ordean A, Wong S, Graves L. N° 349– consommation de substances psychoactives pendant la grossesse. J Obstet Gynaecol Can 2017;39:938–56.e3.

Routine antenatal serology investigations (hepatitis B and syphilis) should be organized, and additional tests including tuberculosis testing and serology for hepatitis C, varicella-zoster virus, toxoplasmosis, and cytomegalovirus should be requested, as per baseline serologic testing recommendations for all women newly diagnosed with HIV and pregnancy-specific guidelines.[14] In addition, pregnancy care providers should screen early in pregnancy for sickle cell disease or thalassemia, given immigration patterns, with 42.1% of females living with HIV in Canada reported as Black and 2.5% as Asian or South Asian.[4] Practically, hemoglobinopathy screening should be considered for all pregnant women other than those who are Japanese, Korean, White of Northern European ancestry, First Nations, or Inuit.[15]

Pregnant women living with HIV should be offered, through an informed consent process, the best available non-invasive option for screening for aneuploidy in their region based on gestational age as well as first-trimester prenatal ultrasound with nuchal translucency measurement, ideally performed at 11–14 weeks gestation.[16,17] If amniocentesis is required, the woman should ideally be taking antiretroviral therapy with an undetectable HIV viral load.[18]

ANTIRETROVIRAL THERAPY DURING PREGNANCY

General Principles and Antiretroviral Selection

The health benefits of appropriate, critical HIV treatment for the woman and the prevention of perinatal transmission of HIV outweigh any potential risks associated with antiretroviral medication use in pregnancy.

Antiretroviral therapy is indicated for all pregnant women living with HIV, regardless of 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 perinatal transmission.[19] A surveillance study from 1997 to 2016 demonstrated an overall perinatal transmission rate of 28.9% in the absence of combined antiretroviral therapy. The rates were 4.3% when there was <4 weeks of therapy and 0.2% with >4 weeks of combined antiretroviral therapy.[5] In 2019−2020 in Canada, the proportion of pregnant women living with HIV who did not receive at least 4 weeks of continuous combined antiretroviral therapy was 2.8%.[6]

Antiretrovirals reduce the risk of perinatal transmission through a number of mechanisms, including (a) lowering maternal viral load; (b) 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 (c) providing infant post-exposure prophylaxis.

With the substantive rise in the mean maternal age in Canada,[20] the likelihood of comorbid health conditions has greatly increased, and careful attention to optimizing care and medications for these conditions, in addition to HIV care, is essential.

Antiretroviral Considerations for a New Diagnosis of HIV in Pregnancy

If a woman is not already on treatment, plans for an appropriate regimen should be made immediately in consultation with experts in HIV care and, ideally, experts in HIV care in pregnancy. Initiating antiretroviral therapy early increases the likelihood that the woman will achieve early and sustained viral suppression by delivery and is associated with a lower risk of perinatal HIV transmission.[21]

Early initiation is particularly important for women with high baseline HIV viral loads[22]; however, timing of initiation will depend on the woman's ability to tolerate oral medications, particularly if experiencing severe nausea and vomiting associated with pregnancy.

Selection of a specific antiretroviral regimen for a pregnant woman living with HIV must consider the inter-related issues of:

- the stage of pregnancy;
- the current and comorbid health status of the woman, including other medications she may be taking;
- the woman's HIV-resistance profile and HLA B*5701 status;
- what is currently known about the use of specific drugs in pregnancy;
- unique pharmacokinetic considerations, including altered kinetics in pregnancy and issues of placental passage of medications as well as drug−drug interactions;
- the ability of the woman to manage an antiretroviral therapy pill burden; and
- affordable drug access in the province or territory.

Antiretroviral drug-resistance testing should be performed before starting an antiretroviral therapy. All women should be counselled about the importance of adhering to the regimen and should be recommended to continue therapy after delivery.

In general, a potent antiretroviral regimen, typically including a dual nucleoside (-tide) reverse transcriptase inhibitor (NRTI) backbone and a boosted protease inhibitor or integrase strand transfer inhibitor (INSTI) can be used, preferably with selection of drugs with safety and efficacy data in pregnancy. Regimens other than combination three-drug regimens (i.e., two-drug) are not recommended. There are still minimal data on the pharmacokinetics and safety in pregnancy of many antiretroviral medications, particularly the newer agents. Details regarding specific drugs can be found in Appendix B and are summarized in Table 2.

NEW DIAGNOSIS OF PREGNANCY IN A WOMAN LIVING WITH HIV

Primary care providers and infectious disease specialists looking after women of reproductive age living with HIV should regularly review their patient's family planning and take this into consideration when planning antiretroviral regimens, while remaining aware that over 50% of pregnancies are unplanned.[23]

On diagnosis of pregnancy in a woman living with HIV, referral should be made to a clinician with experience in

Table 2. Summary of commonly prescribed antiretroviral medications and considerations in pregnancy

Drug class	Drugs with limited data	Drugs with PKPD changes in pregnancy affecting practice use	Drugs with other associations of adverse pregnancy outcomes	Suggested drugs with established use in pregnancy
NNRTI	• Doravirine • Etravirine	• Rilpivirine	• Efavirenz[a] • Nevirapine[b]	
NRTI	• Tenofovir alafenamide			• Abacavir[c] • Emtricitabine[d] • Lamivudine[d] • Tenofovir disoproxil fumarate[e] • Zidovudine
Protease inhibitor		• Atazanavir[f] • Darunavir[g,h] • Lopinavir/r[g,k]	• Atazanavir[h] • Lopinavir/r[i]	
INSTI	• Bictegravir • Elvitegravir • Cabotegravir	• Elvitegravir • Raltegravir HD		• Raltegravir[j] • Dolutegravir[k]
Entry inhibitors	• Fostemsavir • Maraviroc			
Boosters		Cobicistat		Ritonavir

[a]Use limited by side effect profile and potential exacerbation of mental health disorders. Should be continued for women on established treatment (antiretroviral switch not recommended).

[b]Use limited by risk of life-threatening hepatotoxicity when initiated with CD4 >250/mm^3. Should be continued for women on established treatment (antiretroviral switch not recommended).

[c]For patients with confirmed HLA B*5701 negativity only.

[d]Can result in flare of disease upon cessation in Hepatitis B co-infected patients.

[e]Inclusion indicated in women with hepatitis B co-infection. Note limitation of use in women with abnormal renal function; avoid use if eGFR below normal range.

[f]Requires ritonavir boosting in pregnancy. Combination with cobicistat not recommended in pregnancy.

[g]Requires twice daily dosing.

[h]Use limited by non-pathologic hyperbilirubinemia in mother and neonate observed.

[i]Association with preterm birth most concerning for this protease inhibitor.

[j]Requires twice daily dosing.

[k]See Appendix B for further discussion. Small increased risk of neural tube defects with exposure during first 90 days of pregnancy initially reported, no longer considered statistically significant.

INSTI: integrase strand transfer inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PKPD: pharmacokinetic–pharmacodynamic.

HIV management in pregnancy, and recommendations will depend on the woman's wish to continue or end the pregnancy, her HIV disease status, and her antiretroviral medication history.

The woman's current antiretroviral regimen should be continued until reviewed by a specialist, regardless of the regimen, as long as it is well-tolerated and achieves adequate viral suppression.[24]

As for any pregnant woman regardless of HIV infection, access to safe termination of pregnancy services should be facilitated if the woman with HIV does not wish to continue the pregnancy. Health care providers should use this engagement in health care opportunity to optimize HIV care and to provide reproductive health counselling, including contraception, to reduce a future unintended pregnancy. The HIV status of a potentially exposed sexual or drug use partner should also be verified.

Antiretroviral Therapy Considerations for Continuation of Therapy in Pregnancy

It is important for patients and care providers to be aware of several aspects relating to continuation of antiretrovirals in pregnancy:

1. Antiretroviral therapy is required to reduce HIV viral load at delivery and is needed even in women with low or undetectable baseline viral loads because maternal viremia is not the only factor associated with perinatal transmission.[25,26]

2. Ongoing surveillance of the commonly used antiretrovirals in pregnancy does not associate any specific antiretroviral with a statistically significant risk of teratogenicity or congenital anomaly.[27] Data on the risk of birth defects for many antiretroviral drugs, particularly the newer agents, are limited and evolving. Overall, there are inconsistent quality data on the safety of conception exposure for any specific antiretroviral drug (see Appendix B).
3. The majority of antiretroviral recommendations in pregnancy relate to concerns regarding adverse effect profiles and the pharmacokinetic and pharmacodynamic changes of pregnancy.
4. Modifications of regimens to severe nausea and vomiting of pregnancy may be required.

Drug–Drug Interactions with Antiretrovirals to Consider in Pregnancy

There are a number of drug interactions to consider in regard to pregnancy and antiretrovirals. In general, many interactions between medications and antiretrovirals are related to involvement of hepatic CYP enzyme inhibition or induction by protease inhibitors or NNRTIs respectively, but there are also some special considerations for other possible important interactions between medications commonly taken in pregnancy or postpartum and antiretrovirals. Clinicians are encouraged to consult with clinical pharmacists and the online HIV drug interaction websites from the University of Liverpool (https://www.hiv-druginteractions.org/checker) and the Toronto General Hospital Immunodeficiency Clinic (https://www.uhn.ca/Medicine/Clinics/HIV_Clinic).

Prenatal multivitamin/iron supplements. Pregnant women will routinely be receiving prenatal multivitamins that contain positively charged cations including iron (Fe^{2+}), magnesium (Mg^{2+}), and calcium (Ca^{2+}). These cations can interact by causing chelation with INSTI-containing antiretroviral regimens. These interactions can usually be managed by dose spacing.

Acid suppression agents. The potential for drug interactions between antacids and INSTI-containing antiretroviral regimens is similar to that described for prenatal multivitamins above. Histamine type 2 (H2) receptor antagonists and proton pump inhibitors also have the potential to interact with antiretrovirals that require acidic pH for absorption, including the protease inhibitor atazanavir and the NNRTI rilpivirine.

It is important that all new medications are evaluated for their drug interaction potential with a current antiretroviral regimen.

Summary Statements 1, 2, 3 and Recommendations 1, 2, 3, 4, 5, 6, 7, 8, 9

SECOND TRIMESTER AND MONITORING

Providing pregnancy care for pregnant women living with HIV requires recognition of the broader social challenges women may be experiencing and careful navigation to provide confidential, non-judgmental, trauma-informed care.[28,29] This includes:

- Maintaining confidentiality (including with relatives), which is crucial to building and maintaining a trusting therapeutic relationship
- Addressing early and systematically the need for social support with involvement of social workers
- Emphasizing adherence to antiretroviral regimens with each visit and advising patients on undetectable = untransmissible (U = U; i.e., that an undetectable viral load represents the inability to transmit the virus), to promote confidence with the goals of treatment in the context of stable relationships with known risks[30,31]

The woman's clinical, virological, and immunological status should be assessed every 4 weeks until stable, then every 4–12 weeks throughout the pregnancy, including a last viral load measurement at 36 weeks gestation.[32] Monitoring of potential toxicity related to the antiretrovirals should be performed based on the specific medication the woman is taking.

In addition to the routine anatomic ultrasound between 18 and 20 weeks, more regular monitoring of growth throughout the pregnancy is recommended. The exact frequency of ultrasound monitoring can be individualized, but at a minimum a third-trimester ultrasound should be performed to assess fetal growth and well-being.[33] Additional ultrasounds should be arranged based on findings and clinical context.

Management of Pregnant Women with Advanced HIV and Detectable Viral Loads

Stable HIV without evidence of significant CD4 depletion is termed stage 1, with progressive declines in CD4 count termed stage 2 when the CD4 count reaches 14%–25% and stage 3 with a CD4 count <200 cells/mm^3 or <14%

or an AIDS-defining illness.[34] Advanced HIV and AIDS is associated with significant maternal and neonatal mortality and adverse pregnancy outcomes including stillbirth and preterm birth.[35,36] Management of these patients requires specialized input from infectious disease specialists. See Table 3 for a summary of major considerations.[37-42]

Recommendations 10, 11, 12

THIRD TRIMESTER AND DELIVERY PLANNING

Considering the higher rate of preterm birth in women living with HIV, 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.[43]

Table 3. Opportunistic infections considerations in pregnancy for patients with advanced HIV/AIDS

Infection considerations[a]
1) *Pneumocystis jirovecii* pneumonia prophylaxis: This is initiated at a CD4 count of <200 cells/mm^3 or <14% and requires initiation of sulfamethoxazole/trimethoprim prophylaxis (or alternatives if allergies are concerning) and is necessary to reduce mortality in pregnant women at risk of opportunistic infections. It has also been shown to reduce preterm delivery and neonatal mortality. Safety has been demonstrated in systematic review with benefits outweighing risks and concern relating to folate metabolism. Patients requiring prophylaxis with sulfamethoxazole/trimethoprim should be advised to take folic acid supplementation at a dose of at least 1 mg daily.[b]
2) Mycobacterium avium complex disease: Prevention of this infection focuses on viral suppression with prophylaxis generally not recommended unless a suppressive regimen is not achievable but is considered when CD4 <50 cells/mm^3.[c]
3) Reactivation of cytomegalovirus and toxoplasmosis infections: Requires careful observation for signs and symptoms of these infections informed by prior serology determining prior exposure to these infections.
4) Antiretroviral changes: Regimens to obtain rapid viral suppression may require inclusion or addition of an integrase inhibitor and specialist input to achieve this as rapidly as possible.[d]
5) Disseminated candidiasis infection: Treatment with anti-fungal agents other than fluconazole is recommended, given possible adverse pregnancy outcomes with high-dose, prolonged fluconazole treatment.[e]

[a]Adapted from Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Jan 2023. Available from URL: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new?view=full

[b]References 37–39

[c]Reference 40

[d]Reference 41

[e]Reference 42

Discussions regarding mode of delivery should begin early in pregnancy and revisited in the mid–third trimester, with a final decision made based on viral load levels and obstetrical factors by 36 weeks gestation. The late pregnancy HIV viral load information will separate patients into low- and high-risk categories for perinatal transmission, which influences intrapartum and neonatal prophylaxis.

Mode of delivery has been reviewed extensively in cohort studies and a randomized controlled trial of intended mode of delivery.[44,45] The initial studies that identified elective cesarean delivery as a method to reduce perinatal transmission were in women who were not receiving any antiretroviral drug therapy or who received monotherapy with zidovudine. Evidence to support elective cesarean delivery in the current antiretroviral therapy era, when all women are recommended to receive antiretrovirals in pregnancy, is absent.[46,47] Therefore, elective cesarean delivery at 38–39 weeks gestation is recommended only in women who have an unknown viral load, have a viral load ≥400 copies/mL, or, are not on antiretroviral treatment, regardless of their viral load, given the higher rates of perinatal transmission in these groups. This is a pragmatic approach to employ all possible interventions to reduce transmission given the paucity of guiding evidence.[25,48-50] The benefit of cesarean delivery shown in early studies appears to have been found exclusively in pre-labour elective cesarean delivery; no benefit was shown for emergency cesarean delivery when there is active labour or rupture of membranes for more than 4 hours.[44,51]

Review by a pediatrician with experience in caring for neonates born to women living with HIV should occur in the third trimester to reinforce and prepare parents for the recommended neonatal prophylaxis regimen, review newborn feeding recommendations, and plan long-term follow-up of the child.

INTRAPARTUM MANAGEMENT

Intrapartum Management: Low Risk of Perinatal Transmission

This category includes pregnant women living with HIV on antiretroviral therapy with undetectable viral loads measured at 36 weeks or within 4 weeks of delivery. General recommendations include:

- Vaginal delivery, if not contraindicated; cesarean delivery is reserved for obstetric indications only[24,26,52-54]
- Attending the delivery hospital immediately at rupture of membranes or onset of contractions

  - Management of pre-labour rupture of membranes should consider the HIV infection as a co-factor. In a virally undetectable cohort, recent data suggest that there is no statistically significant association with increased transmission related to duration of rupture of membranes,[52,53] but there are limited data for rupture of membranes exceeding >24 hours, and therefore these patients should be prioritized for induction or augmentation of labour[54]
- Continuing all oral antiretroviral medications throughout labour or induction of labour until delivery
- Avoiding fetal scalp blood sampling and monitoring with fetal scalp electrodes to prevent direct contact with maternal blood or secretions
- Initiating intravenous zidovudine at onset of labour, rupture of membranes, or 2 hours prior to cesarean delivery
  - This recommendation could be individualized for extremely stable, HIV undetectable patients under specialist advice[55,56]
  - Intravenous zidovudine is given as an initial 2 mg/kg loading dose followed by 1 mg/kg/h continuous infusion until delivery

Intrapartum Management: High Risk of Perinatal Transmission

The risk of perinatal transmission is higher for those with viral loads ≥400 copies/mL at the time of delivery.[25,26,48,49,56] With detectable viral loads at or near term, interventions known to reduce transmission in isolation need to be implemented as a package of care, with the aim that, in combination, this risk might be reduced. Patients for whom the low-risk criteria are not met, including those with detectable viral loads, not taking antiretrovirals, or with concerns regarding adherence,[5,49] as well as those who have not had a viral load tested within the preceding 4 weeks,[5] the following high risk of perinatal transmission approach is suggested:

- Elective cesarean delivery at 38−39 weeks (prior to the onset of labour) if viral load ≥400 copies/mL or not on optimal antiretroviral therapy[44,49]
  - These viral load thresholds are derived from recent, large, cohort analyses that evaluate modern groups of pregnant women in an era where antiretrovirals are recommended throughout pregnancy.[48,49] These studies have helped to better delineate increased risk thresholds which align with other guidelines from high-resource settings.[54]
- For women with detectable viral loads >50 copies/mL but <400 copies/mL and taking antiretroviral therapy: a multidisciplinary approach regarding choice of mode of delivery, as there are limited data regarding transmission rates for vaginal versus cesarean delivery in this scenario
- Intravenous zidovudine as described above in the low-risk protocol[55]
- For women known to be living with HIV and not taking antiretrovirals: specialist input regarding a rapid start of oral antiretroviral therapy at the time of presentation in early labour
  - In such cases consideration can be given to a potent antiretroviral regimen including an INSTI, such as raltegravir, which has been shown to rapidly reduce viral load.[57,58] This drug could be given in combination with tenofovir and emtricitabine, usually given in PEP, as one possible combination; however, specialist input is recommended
- Avoidance of fetal scalp electrodes and blood sampling, intrauterine catheters, prolonged rupture of membranes, and operative deliveries where possible[59]

In contrast to prior guidelines, we no longer recommend oral nevirapine for patients already taking antiretrovirals but who are not virally undetectable. In high-risk situations for perinatal transmission, guidance is sought from findings in low-resource settings, where a Cochrane review determined that combination therapy was more effective in preventing perinatal transmission with the addition of nevirapine, but this was in a cohort that subsequently breastfed and was therefore at an increased risk of transmission.[60] The efficacy of nevirapine as an oral intrapartum prophylactic measure is drawn from the findings of the HIVNET 012 trial,[61] which assessed its use to reduce transmission in conjunction with zidovudine in a breastfeeding population, with good long-term safety data at 5-year follow-up and reviews of the trial indicating its reliability.[62,63] This finding was not replicated in pregnant women who were already taking combined antiretroviral therapy prior to delivery, and therefore it is not recommended in this group.[64] In pregnant women known to be living with HIV but not taking antiretrovirals, given the availability of newer, better-tolerated agents, nevirapine is no longer recommended. Instead, a combination of a dual-NRTI, such as tenofovir and emtricitabine (widely available as used in PEP regimens), with an INSTI, such as raltegravir, has demonstrated rapid viral suppression and could be considered in women presenting in early labour.[57,58]

Intrapartum Management: Women with Unknown HIV Status or Ongoing HIV Risk

Many women who are at risk for HIV infection do not receive antenatal care and present late in pregnancy or in early labour with unknown HIV status. In this instance, a rapid HIV test should be performed.[8]

Risk factors for pregnant women at particular risk of HIV infection include:

- injection drug use and needle sharing;
- another sexually transmitted infection during pregnancy, in the absence of HIV screening;
- recent illness suggestive of seroconversion;
- regular condomless sex with a partner known to be living with HIV or at significant risk for HIV infection themselves;
- recent incarceration; and
- emigration from an area with endemic HIV in the absence of recent HIV screening.

The seroconversion period is approximately 4 weeks since exposure or infection.[65]

If a rapid antibody test is positive, the woman should be informed of the result. Management should include:

- Immediate confirmatory antibody test *and* polymerase chain reaction (PCR)/ nucleic acid amplification testing (NAT)
- Immediate initiation of intravenous zidovudine
  - Oral antiretrovirals are not recommended given the potential for false positives and the lack of research into preventive measures for perinatal transmission in this scenario[66]
- Expedited delivery with induction or augmentation of labour, as indicated
  - Cesarean delivery should be offered only if the patient is not in established labour and membranes are intact
- Immediate discussion with paediatricians and planning for prophylactic antiretroviral therapy for the neonate pending results of the confirmatory tests
  - The mother may pump and store breast milk, but this should not be given to the newborn until results of the confirmatory tests are available
- Early discussion with and referral to an adult HIV care provider

If the rapid antibody test is negative or unavailable, management should be individualized based on the level of risk for recent HIV acquisition. An antibody test and a PCR/NAT should be performed. In cases deemed to be at significant risk for HIV infection, the provider can offer intrapartum intravenous zidovudine and consultation with paediatricians regarding prophylactic antiretroviral therapy for the newborn. The mother may pump and store breast milk, but this should not be given to the newborn until results of the confirmatory tests are available.

POSTPARTUM CARE

Planning for the postpartum period should begin in the third trimester, as multiple aspects need to be considered including:

- infant feeding choice and lactation suppression;
- infant PEP;
- antiretroviral continuation;
- contraception; and
- psychosocial support for the parent(s) (beyond the scope of this guideline).

Infant Feeding

Infant feeding can be a sensitive aspect when counselling a new mother. Hence, this topic should be discussed during pregnancy and a plan established prior to delivery.

Women living with HIV, even when reliably taking antiretrovirals, should be advised that formula feeding remains the recommended form of infant feeding.[10] Despite optimal virologic suppression, there remains a risk of perinatal transmission of HIV with breastfeeding of between <1% and 5%.[48,67-71] In the absence of antiretroviral therapy, perinatal transmission rates of HIV for breastfed infants are 12% and 22% at 1 and 24 months, respectively.[72,73]

Some women will choose to breastfeed following appropriate counselling. In these cases, she should be supported to ensure adherence to antiretroviral therapy and support exclusive breastfeeding. Close and coordinated clinical and biological monitoring of the mother's viral load and the infant's HIV test results should be planned by a multidisciplinary team, including an adult HIV specialist, paediatrician, and obstetrician.

Barriers to formula feeding need to be considered, and these can include:

- the cost of formula;

- cultural pressure to breastfeed, leading to a concern regarding unintended HIV status disclosures[74,75];
- the health benefits of breastfeeding for mother and child[76]; and
- pain from breast engorgement.

Practical aspects can be addressed by establishing local or provincial free formula programs and administration of oral cabergoline as a single 1-mg dose to be given within 24 hours of delivery for lactation suppression (when not contraindicated by uncontrolled maternal hypertension).[77]

For women at continuing risk of HIV acquisition, ongoing assessment of HIV transmission in the postpartum period is required. If there is ongoing risk regarding new infection, consideration of PrEP/PEP or avoidance of breastfeeding should be discussed and organized prior to discharge from hospital.

Infant Post-Exposure Prophylaxis

Ideally pregnant women living with HIV should have been counselled regarding the recommendation for neonatal antiretroviral prophylaxis prior to delivery and a plan made for the neonate. The neonatal prophylactic treatment and its duration is decided based on the risk of perinatal transmission. In low-risk neonates (those born to pregnant women with optimal adherence to antiretrovirals and viral suppression) a 4-week course of zidovudine, as single-agent prophylaxis, is usually recommended.[54,78,79] Dual-agent antiretroviral prophylaxis or presumptive HIV therapy are recommended for infants born to women living with HIV with a detectable viral load prior to delivery or those who are untreated.[54,79,80] In both circumstances, safety and tolerability of these regimens has been generally well established.

Guidelines agree that PEP should commence as early as possible following delivery in the neonate and ideally within 6 hours of delivery.

All infants born to women living with HIV should be referred to a pediatrician with expertise in this area for ongoing assessment and care. Developmental follow-up is crucial for HIV-exposed, uninfected children, given increased rates of developmental impairment, infections (particularly lower respiratory tract infections), and higher infant mortality in some settings.[81]

Maternal Antiretroviral Continuation and Postpartum Contraception

All women living with HIV should continue antiretroviral therapy postpartum. However, the postpartum period may present several barriers to sustained adherence to antiretroviral therapy and retention in care.[82] These include a potential shift from obstetric care to routine adult care, stigma, and financial barriers.[83-85] These barriers are exacerbated in situations where the infant is cared for by other family members or placed in care by social services. Risk factors for poor adherence include:

- late engagement in HIV care antenatally[86-89];
- lack of viral suppression at time of delivery[87];
- injection drug use[90,91]; and
- postnatal depression, with higher rates being reported in women living with HIV.[92]

Contraception

It is very important to discuss safe sex practices and effective postpartum contraception methods with women not wishing to become pregnant immediately. Of note, with women who are not breastfeeding, ovulation can resume shortly after pregnancy, making conception more likely if effective contraception is not used. Condom use is recommended to reduce the risk of transmission between partners if either partner has a detectable viral load[30]; however, the contraception failure rate with condoms is higher than with hormonal contraceptive options. All effective contraception options available should be discussed, including long-acting reversible contraceptive methods, as they are the most effective method of reversible contraception.[93] Permanent contraception, which can include bilateral tubal ligation or salpingectomy can be performed at the time of a cesarean delivery, but care needs to be taken to ensure this is a well thought out plan and is the fully informed choice of the woman.

HIV does not preclude the use of any contraceptive method[79]; however, the potential for drug–drug interactions between hormonal contraceptives and antiretroviral therapy, with the potential of contraceptive failure resulting in unintended pregnancy should be considered.[94-96] The potential for interactions vary by contraceptive method, with the greatest interaction potential reported with combined hormonal contraceptives (i.e., pills, patch, ring) and fewest interactions reported for depot medroxyprogesterone acetate (DMPA), intrauterine devices, and subdermal long-acting contraception. Similarly, the lowest potential for interaction exists when using NRTI- and INSTI-containing antiretroviral regimens, while the highest exists with the use of protease inhibitors (darunavir/ritonavir) and NNRTIs (efavirinz, nevirapine). Selecting a non-interacting method of contraception,

encouraging the use of additional contraception, or changing the woman's antiretroviral regimen to optimize a contraceptive choice may be necessary depending on the situation.

Summary Statement 4 and Recommendations 13, 14, 15, 16, 17, and 18

CONCLUSION

The risk of perinatal transmission of HIV can be greatly reduced through coordinated, regular, and comprehensive perinatal care for women living with HIV and their children. It is recommended that care for each pregnancy be individualized and involve a multidisciplinary team. Key messages for all health care providers regarding the importance of continuation of antiretrovirals in pregnancy is essential, as is remaining vigilant to a woman's ongoing risk of HIV transmission during pregnancy and lactation. A supportive, non-judgemental approach to a woman's decisions regarding her pregnancy and infant feeding is necessary to maintain their engagement in care. Ongoing review of the literature to inform advice regarding antiretroviral regimens is necessary and requires specialist input, given the rapidly evolving research in this area.

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APPENDIX A

Table A1. Key to Grading of Recommendations, Assessment, Development and Evaluation Quality of Evidence

Grade	Definition
Strength of recommendation	
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional (weak)[a]	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of evidence	
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Adapted from GRADE Handbook (2013), Table 5.1.
[a]Do not interpret conditional (weak) recommendations to mean weak evidence or uncertainty of the recommendation.

Table A2. Implications of Strong and Conditional (Weak) recommendations, by guideline user

Perspective	Strong Recommendation • "We recommend that…" • "We recommend to not…"	Conditional (Weak) Recommendation • "We suggest…" • "We suggest to not…"
Authors	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy.
Patients	Most individuals in the situation would want the recommended course of action, while only a small proportion would not.	The majority of individuals in the situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences.
Policy makers	The recommendation can be adapted as policy in most settings.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.

Adapted from GRADE Handbook (2013), Table 6.1.

APPENDIX B: SUMMARY INFORMATION ON ANTIRETROVIRAL MEDICATIONS IN PREGNANCY

Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs)

- Function as competitive substrate inhibitors that are intracellularly phosphorylated to form the active triphosphate nucleoside moiety and are incorporated into HIV DNA, which terminates the action of the reverse transcriptase enzyme and prevents the conversion of viral RNA into DNA.[1]
- NRTIs are recommended for use as part of combination regimens, which usually include two NRTIs (i.e., backbone therapy) with the addition of either a boosted protease inhibitor, an integrase strand transfer inhibitor (INSTI), or a non-nucleoside reverse transcriptase inhibitor (NNRTI).
- **Preferred backbones in pregnancy:**
  - Abacavir* plus lamivudine (3TC) ***or*** tenofovir disoproxil fumarate† (TDF) plus emtricitabine; which are available as fixed-dose combination tablets.

* *Abacavir should not be used in patients who test positive for HLA B*5701 because of the risk of developing a hypersensitivity reaction.*

† *Tenofovir disoproxil fumarate would be a preferred NRTI in combination with lamivudine or emtricitabine for pregnant women with chronic hepatitis B infection.*

- **Alternative preferred backbones:**
  - Tenofovir alafenamide plus emtricitabine which are available as fixed-dose combination tablets. There are limited data on the safety of tenofovir alafenamide exposure at conception and during the first trimester.
- NRTI pharmacokinetics are similar in pregnant and non-pregnant women and dosing adjustments are not required in pregnancy.[2]
- All NRTIs readily cross the placenta and have cord-to-maternal blood ratios greater than 0.60.[2]
- There are some data regarding an association between maternal tenofovir disoproxil fumarate use and transient, small growth delays and bone abnormalities in the first year of life. The clinical significance of these findings for in utero use are not certain.[3]

Protease Inhibitors

- Function as competitive inhibitors that bind to the HIV protease enzyme and prevent the conversion of HIV viral particles into mature infectious forms.[4]
- Protease inhibitors are recommended in pregnancy in combination with a dual-NRTI backbone.
- In pregnancy, protease inhibitors should be used with a boosting agent, usually low-dose ritonavir, which functions as a pharmacokinetic booster to increase serum drug levels of the first protease inhibitor.
- In pregnancy, protease inhibitors should not be co-administered with the boosting agent cobicistat because of its association with substantial reductions in protease inhibitor concentrations in pregnancy.[5-7]
- **Preferred protease inhibitors:**
  Among this class, the preferred ritonavir-boosted protease inhibitors include darunavir/ritonavir ***or*** atazanavir*/ritonavir.
  **Atazanavir requires an acidic pH for absorption and its use is limited in women who require acid suppression therapy with histamine type 2 receptor antagonists or proton pump inhibitors.*[8]
- **Protease inhibitors not recommended in pregnancy:**
  - Darunavir/cobicistat ***or*** atazanavir/cobicistat are not recommended because of their association with substantial reductions in drug concentrations in pregnancy.[5,6]
  - The pharmacokinetics of protease inhibitors are variable in pregnancy, particularly in the second and third trimesters. Current data suggest that exposure to atazanavir[8–10] and darunavir[11–15] is decreased during the second and third trimesters. The clinical significance of reduced exposure during pregnancy, however, is not clear. Although some experts will recommend an increased dose of atazanavir and twice daily dosing of darunavir/ritonavir for all women during the second and third trimesters, it is currently recommended that the need for a dose increase in pregnancy depend on the antiretroviral treatment experience of the specific woman, the use of concomitant interacting medications, and virologic response to the prescribed dose throughout pregnancy. HIV viral load should be closely monitored, particularly in the second and third trimesters to detect virology failures due to increased plasma volumes, which can result in reduced protease inhibitor concentrations. In this situation, increasing the protease inhibitor dosage (e.g., oral darunavir/ritonavir dosed 600 mg/100 mg twice daily, oral atazanavir/ritonavir increased to 400 mg/100 mg once daily) should be considered. There is currently no standard recommendation for monitoring drug levels in pregnancy; however, if available, therapeutic

drug monitoring may also be considered to guide the need for protease inhibitors dosage adjustments. Consideration for protease inhibitor dosage increases should be made in the context of multiple gestations (i.e., twins or triplets), where an even greater volume of distribution and clearance may adversely affect drug levels.[16-18]

- All protease inhibitors have minimal to low placental transfer to the fetus with cord-to-maternal blood ratios <0.3.[2]
- Protease inhibitors have not demonstrated evidence of human teratogenicity.[2]

- **Additional considerations in pregnancy:**
  - *Preterm delivery*: Pregnant women living with HIV have an approximate three-fold higher risk of preterm delivery than the general population(15.5% vs. 5.3% in British Columbia, Canada).[19] There is conflicting evidence as to whether combination antiretroviral drug therapy increases this risk further.[20,21] There are also mixed data to suggest a potential association between ritonavir-boosted protease inhibitor regimens[22,23]; however, a causal relationship has not been established.
  - At present there are insufficient data to avoid particular antiretroviral treatments to reduce the known risk of preterm birth in women living with HIV.[19,24]
  - *Hyperbilirubinemia*: Inhibition of hepatic UGT enzymes by atazanavir frequently results in an elevation of indirect (unconjugated) bilirubin. Elevations in neonatal bilirubin in infants exposed to atazanavir in utero have been observed in some clinical trials[25-27]; however, these results were not considered clinically significant.
  - *Drug interactions*: Drug—drug interactions are a concern with boosting agent combination. Therefore, reference to tools for assessing this risk or involvement of a clinical pharmacist is recommended.

Integrase Strand Transfer Inhibitors (INSTI)

- Function as competitive inhibitors of the HIV integrase enzyme, preventing the insertion or integration of HIV genetic DNA into the host cell DNA (i.e., strand transfer inhibition).[28—33]
- **Preferred integrase strand transfer inhibitors:**
  - Among this class, the preferred INSTIs in pregnancy include dolutegravir ***or*** raltegravir* with a preferred dual-NRTI backbone.

* *Raltegravir should be dosed twice daily in pregnancy; there is no pharmacokinetic data to support the use of the raltegravir HD formulation in pregnancy.*[34]

- There are currently *insufficient data* to recommend initiation of bictegravir in pregnancy; however, ongoing use can be considered in individual cases.[35]
- Cobicistat-boosted elvitegravir—containing regimens are *not recommended* in pregnancy because of their association with significant reductions in drug exposures during pregnancy, with evidence of detectable viral loads in the third trimester.[36,37]
- Long-acting injectable cabotegravir plus rilpivirine is *not recommended* owing to limited data in pregnancy.[30,38] Because of the long half-life of injectable cabotegravir (and rilpivirine), drug levels may persist up to 12 months after the last dose.[38]
- The INSTIs raltegravir, dolutegravir, and elvitegravir readily cross the placenta and have cord-to-maternal blood ratios greater than 0.60.[2] There are insufficient data to determine placental transfer of bictegravir and cabotegravir.[2]

Teratogenicity

Early data suggested a possible safety signal for neural tube defects with dolutegravir[39,40]; however, this risk has been adjusted as additional exposure data have become available. Overall, the reported prevalence of neural tube defects did not differ between dolutegravir and non-dolutegravir antiretroviral drug use at conception.[41] Therefore, dolutegravir-containing regimens can be used in the peri-conception period and first trimester along with folic acid supplementation. There is no increased birth defect risk reported with the use of elvitegravir and insufficient data to determine the safety of either bictegravir or cabotegravir in pregnancy.[2]

- **Additional considerations in pregnancy:**
  - *Drug interactions with common pregnancy medications*: INSTIs interact with polyvalent cation supplements, including multivitamins with minerals and antacids. These interactions may be managed by appropriate dose spacing; however, raltegravir should not be used when taking calcium or magnesium supplements/antacids and only used if spaced at least 3 hours apart from iron supplements.[42,43]

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Function as non-competitive inhibitors of reverse transcriptase by binding and inducing a conformational change in the enzyme, which alters its active site and prevents its ability to convert viral RNA to DNA.[44] NNTRIs may be used in pregnancy in combination with a dual-NRTI backbone, primarily reserved for cases where a preferred boosted protease inhibitor or INSTI cannot be used.
- Alternative agents in pregnancy include efavirenz[45] and rilpivirine, both of which are available as fixed-dose combination medications.
- Initiation of nevirapine is *not recommended* in pregnancy because of the risk of a potentially fatal rash and hepatotoxicity; however, women who are tolerating nevirapine and become pregnant may continue taking it.[46]
- There is currently *insufficient safety and pharmacokinetic data* to support the use of etravirine or doravirine in pregnancy.
- NNTRI pharmacokinetic considerations: Plasma rilpivirine concentrations are highly variable in pregnancy and may be reduced 20%–50% during the second and third trimesters of pregnancy.[47] There is, however, no evidence for empiric increase of the rilpivirine dosage; instead, it is recommended to monitor HIV viral load, ensure adherence, and advise the patient to always take the medication with food.
- The following NNRTIs have variable placental transfer to the fetus: nevirapine (high), rilpivirine and etravirine (moderate-high), efavirenz (moderate), and doravirine (unknown).[2]
- Compared with NRTI data, teratogenicity data for NNRTIs use are more limited and variable. There is no evidence of animal or human teratogenicity with nevirapine, and no evidence of teratogenicity in animals with etravirine or rilpivirine; however, there is limited data on these agents in human pregnancy. Meta-analysis of 23 studies reporting on 2026 first trimester exposures to antiretroviral drugs reported no statistically significant increased risk of birth defects for infants born to women receiving efavirenz during the first trimester versus other antiretroviral drugs (RR 0.78; 95% CI 0.56–1.08). The rate of total major abnormalities with efavirenz use at conception was 0.68% versus 0.59% for women without HIV.[45]
- **Additional considerations in pregnancy:**
  - *Drug interactions with common pregnancy medications*: Concomitant use with acid suppression agents including histamine type 2 receptor antagonists and proton pump inhibitors is not recommended, as rilpivirine requires an acidic environment for absorption.[42,43]

Other Agents: Entry (Fusion), Attachment, HIV Capsid Inhibitors

- Work by various methods to block viral binding or fusion of HIV to host cells or interfere with the HIV capsid.
- Agents within these classes include marviroc, enfuvirtide (T-20), fostemsavir, and lenacapavir; any newer agents that become available in this category are not currently recommended because of insufficient pharmacokinetic and safety data in pregnancy. [48–51]

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