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

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 Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline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
Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

<table>
<thead>
<tr>
<th>Quality of evidence assessment*</th>
<th>Classification of recommendations†</th>
</tr>
</thead>
<tbody>
<tr>
<td>I:</td>
<td>A. There is good evidence to recommend the clinical preventive action</td>
</tr>
<tr>
<td>II-1:</td>
<td>B. There is fair evidence to recommend the clinical preventive action</td>
</tr>
<tr>
<td>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group</td>
<td>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</td>
</tr>
<tr>
<td>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</td>
<td>D. There is fair evidence to recommend against the clinical preventive action</td>
</tr>
<tr>
<td>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</td>
<td>E. There is good evidence to recommend against the clinical preventive action</td>
</tr>
<tr>
<td></td>
<td>F. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making</td>
</tr>
</tbody>
</table>

*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.*

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

**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-2D)

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 Caesarean 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 Caesarean 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. (II-2B)

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)
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 to 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 or exposed to HIV, in coordination with provincial authorities. Longitudinal surveillance on pregnancy outcomes in women living with HIV is tracked by the CPHSP 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
This guideline primarily addresses the management of HIV during pregnancy and does not comprehensively address pre-pregnancy planning issues. Canadian HIV pregnancy planning guidelines are available.1 Similarly, HIV care of non-pregnant women is addressed in guidelines available elsewhere2 and is not discussed in this document. Management of HIV in pregnant women with comorbidities is addressed in brief; readers are referred to available guidelines for detailed discussion of this and other aspects of caring for people living with HIV (Table 2).

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.3 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 rate in Canada in 2011 was 208.0 per 100 000 population (range: 171.0 to 245.1 per 100 000 population), 23% to 28% of whom were women.5 According to 2009 statistics, women account for approximately 26% of the new HIV diagnoses in Canada.6 Cumulative surveillance data report that two thirds of positive test results for HIV occurred in women of reproductive age, with 37.6% in women aged 30 to 39 years and 32.5% in women aged 20 to 29 years.6 Combination antiretroviral therapy has been demonstrated to prolong the lives of people living with HIV,7 and has also significantly reduced the rate of vertical transmission of HIV from a baseline risk of 25% without intervention to < 2% in the context of comprehensive pregnancy care and cART administered antenatally, intrapartum, and to the infant in the early neonatal period.8,9 As a result of these factors more women living with HIV are considering their reproductive options and choosing to become pregnant.1 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,6 and the majority of childhood HIV infections are acquired in this manner.3

The CPHSP identified a total of 2692 women known by care providers to be living with HIV who delivered infants between 1990 and 2010.10 Based on rates of spontaneous and therapeutic abortions in Canada, it is estimated that an equal number of women have been pregnant but have not delivered a living infant.10 The incidence of pregnancies in women living with HIV in Canada has been gradually increasing at different rates from province to province.10 With the implementation of cART for pregnant women in the late 1990s, the CPHSP documented a substantial reduction in HIV transmission rates from 20.2% (1990–1996) to 2.9% (1997–2010). Overall, the HIV perinatal transmission rate in women who have accessed care is 0.4% in Canada.10 However, despite the availability of routine HIV testing in pregnancy and effective interventions to reduce vertical transmission, there were a total of 93 infants perinatally infected with HIV in Canada between 2000 and 2010.11

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 Guidelines1 and in the National Institutes of Health 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 if not desiring pregnancy;
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.
Table 2. Guidelines related to the care of people living with HIV

<table>
<thead>
<tr>
<th>Topic</th>
<th>Website</th>
<th>Issuing agency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult HIV infection therapeutic guidelines</td>
<td><a href="http://www.cfenet.ubc.ca/therapeutic-guidelines/adult">http://www.cfenet.ubc.ca/therapeutic-guidelines/adult</a></td>
<td>BC Centre for Excellence in HIV/AIDS</td>
</tr>
<tr>
<td>Opportunistic infections therapeutic guidelines</td>
<td><a href="http://www.cfenet.ubc.ca/therapeutic-guidelines/opportunistic-infection">http://www.cfenet.ubc.ca/therapeutic-guidelines/opportunistic-infection</a></td>
<td>BC Centre for Excellence in HIV/AIDS</td>
</tr>
<tr>
<td>Primary care guidelines</td>
<td><a href="http://cfenet.ubc.ca/therapeutic-guidelines/primary-care">http://cfenet.ubc.ca/therapeutic-guidelines/primary-care</a></td>
<td>BC Centre for Excellence in HIV/AIDS</td>
</tr>
<tr>
<td>Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents</td>
<td><a href="http://www.aidsinfo.nih.gov/guidelines">http://www.aidsinfo.nih.gov/guidelines</a></td>
<td>Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America</td>
</tr>
<tr>
<td>Guidelines for prevention and treatment of opportunistic infections in adults and adolescents</td>
<td></td>
<td>Society of Obstetricians and Gynaecologists of Canada</td>
</tr>
<tr>
<td>Recommendations for the use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States</td>
<td></td>
<td>Society of Obstetricians and Gynaecologists of Canada</td>
</tr>
<tr>
<td>Alcohol use and pregnancy consensus clinical guidelines</td>
<td><a href="http://www.sogc.org/guidelines/documents/gui245CPG1008E.pdf">http://www.sogc.org/guidelines/documents/gui245CPG1008E.pdf</a></td>
<td>Society of Obstetricians and Gynaecologists of Canada</td>
</tr>
</tbody>
</table>
**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. Some provinces have managed this through opt-in testing and others through opt-out testing. Women involved in ongoing high-risk HIV transmission activities (see Appendix 1) 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 whenever possible early in the pregnancy in order 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 perinatal transmission.12-14 (see Appendix 1)

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.15 Women should also be made aware that with the use of cART and abstinence from breastfeeding the risk of vertical transmission is < 1%.10

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. Non-judgemental counselling regarding continuation of the pregnancy based on a complete understanding of the woman’s medical and social circumstances is important.

**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 woman living with HIV who becomes pregnant. Medical care recommendations for the pregnant woman living with HIV will depend on the woman’s wish to continue or discontinue the pregnancy, her HIV disease status, and her cART medication history. Pregnancy dating should be done through taking a careful history and conducting a dating ultrasound.

Women should be made aware that with the use of cART and abstinence from breastfeeding the risk of vertical transmission is < 1% in Canada. 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 queried, and if the partner is not known to be living with HIV, testing is recommended.

If the woman desires to continue the pregnancy, immediate review of HIV status including recent CD4-cell count, HIV viral load, and antiretroviral medication use is warranted. Specific recommendations regarding antiretroviral drug therapy management and trimester-specific information are discussed in more depth below. Overall, it is important to consider that all pregnant women living with HIV present high-risk pregnancies. Their medical therapy requires coordination and communication between HIV specialists and obstetrical providers. If, for geographic reasons, a woman is unable to attend for specialist consultations, these can be provided virtually through effective communications between care providers in remote settings and urban sub-specialists.

**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

Background

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 HIV vertical transmission. In general, the recommendations for the use of antiretroviral therapy for the benefit of maternal health during pregnancy are similar for all women regardless of pregnancy status. However there are a number of important considerations based on limited experience and/or specific concerns with some antiretroviral drugs in pregnancy. While optimizing maternal care and health is of prime importance, it is important whenever possible to limit exposure of the developing fetus to potentially toxic medications. There are still minimal data available on the pharmacokinetics and safety of many antiretroviral drugs, particularly the newer agents, in pregnancy (see Table 3 and Appendix 2); therefore all treatment decisions during pregnancy require full discussion between the patient and her physician with regard to known and unknown benefits and risks.

Antiretroviral agents administered in pregnancy have demonstrated a reduction in the risk of vertical transmission of HIV. Both published literature and analysis of Canadian data inform treatment in pregnancy. Literature from resource-rich countries provides information on optimizing antiretroviral therapy for both maternal health and the prevention of vertical transmission, while literature from resource-poor countries provides insight on recommendations for the care of pregnant women living with HIV with absent or delayed prenatal care. A detailed table describing results of major studies on antiretroviral prophylaxis to prevent perinatal transmission of HIV is available in the NIH perinatal guidelines.

The Pediatric AIDS Clinical Trials Group (PACTG 076) was the first major randomized, placebo-controlled study to demonstrate that zidovudine administered PO antepartum (between 14 and 34 weeks’ gestation), intravenously intrapartum, and PO to the infant for 6 weeks could significantly reduce the risk of perinatal transmission of HIV (25.5% in the placebo group vs. 8.3% in the zidovudine treated group, P < 0.001). Follow-up results confirmed these findings without evidence of any long-term toxicity, other than transient anemia, in infants up to 5 years of age.

Subsequent clinical trials and observational studies have demonstrated that further reductions in vertical transmission, to rates as low as < 1% can be achieved with the antenatal administration of cART (with at least 2 or 3 agents) to the pregnant woman. In the entire Canadian cohort, the rate of vertical transmission was as low as 0.4% (6 out of 1585) when the mother received at least 4 weeks of cART before delivery.

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

It is important to note, however, that while lowering maternal viral load is important, antiretroviral prophylaxis 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).

Two primary treatment strategies have been evaluated in resource-poor countries and are relevant in the developed world for managing women living with HIV with absent or delayed prenatal care who are not receiving recommended antenatal cART. The first strategy involves use of shorter course regimens of either mono or dual antiretroviral therapy (e.g., zidovudine or zidovudine-lamivudine) or intrapartum single-dose nevirapine. The second strategy involves administration of cART to infants who are born in high transmission risk settings. Overall, both strategies have demonstrated benefit in reducing transmission; however, transmission rates are still significantly higher than those reported with antenatal cART, intrapartum and infant prophylaxis.

In a large African randomized trial (HIVNET 012), pregnant women living with HIV received either:

1. 1 single-dose nevirapine 200 mg in labour and 1 dose of nevirapine to their infant within 72 hours of birth, or
2. Oral zidovudine while in labour and the same to their infant for one week after birth.

Nevirapine significantly reduced the risk of vertical HIV transmission at 14 to 16 weeks of age by approximately 50% (13% vs. 25%, P < 0.001) compared with zidovudine. It is important to note that none of the women received antenatal antiretroviral therapy and almost all women in this study breastfed their infants. Because single-dose nevirapine...
Table 3. Summary of antiretroviral drugs in pregnancy with dosing recommendations

<table>
<thead>
<tr>
<th>Nucleoside reverse transcriptase inhibitors (NRTIs)</th>
<th>NRTI class concerns</th>
<th>Recommendations for use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended for use as part of combination regimens, usually including 2 NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended.</td>
<td>Causal relationship between mitochondrial toxicity and NRTI exposure in utero has not been established (see text for details).</td>
<td><strong>Zidovudine (ZDV)</strong></td>
</tr>
<tr>
<td><strong>FDA pregnancy category C</strong></td>
<td></td>
<td>ZDV plus 3TC is a recommended dual NRTI backbone for pregnant women.</td>
</tr>
<tr>
<td>High placental transfer (cord-to-maternal blood ratio 0.80)</td>
<td></td>
<td>Do not combine with stavudine (antagonistic mechanism of action); discontinue stavudine at time of administration of intrapartum intravenous ZDV.</td>
</tr>
<tr>
<td><strong>Animal data</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td>Vaginal carcinoma reported in mice and rats at 3 times and 24 times the usual human dose</td>
<td></td>
<td>Retrovir 300 mg twice daily or 200 mg 3 times daily</td>
</tr>
<tr>
<td>Embryotoxic in rats and rabbits at high doses</td>
<td></td>
<td>Combiqir (ZDV 300 mg/3TC 150 mg) 1 tablet twice daily</td>
</tr>
<tr>
<td>No evidence of teratogenicity in rats or rabbits unless given at extremely high doses to rats (e.g., 300 times usual human dose)</td>
<td></td>
<td>Trizivir (ZDV 300 mg/3TC 150 mg/ABC 300 mg) 1 tablet twice daily</td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td></td>
<td>Pharmacokinetics similar in third trimester of pregnancy and non-pregnant patients; no dose alteration required in pregnancy&lt;sup&gt;157&lt;/sup&gt;</td>
</tr>
<tr>
<td>PACTG 076 randomized, placebo-controlled trial in pregnant women showed no increase in congenital abnormalities&lt;sup&gt;19,155&lt;/sup&gt;; the WITS cohort study reported 10-fold increase in risk of hypospadias in women receiving ZDV in the first trimester.&lt;sup&gt;156&lt;/sup&gt;</td>
<td></td>
<td><strong>Adverse events/concerns in pregnancy</strong></td>
</tr>
<tr>
<td>No evidence of human teratogenicity; APR birth defects with first trimester exposure 3.3% (124 of 3789 births, 95% CI 2.7%–3.9%)&lt;sup&gt;42&lt;/sup&gt; Infants exposed in utero have shown no differences in immunology, neurology, or growth to infants receiving placebo, based on approximately 6 years of follow-up.</td>
<td></td>
<td>Overall, well tolerated in pregnancy and infants; higher incidence of anemia reported in neonates; however, reversible within 6 weeks of discontinuing ZDV&lt;sup&gt;19,155&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Lamivudine (3TC)</strong></td>
<td></td>
<td><strong>3TC plus ZDV is a recommended dual NRTI backbone for pregnant women.</strong></td>
</tr>
<tr>
<td>FDA pregnancy category C</td>
<td></td>
<td>A preferred NRTI for dual NRTI backbone (in combination with TDF) for pregnant women with chronic HBV infection</td>
</tr>
<tr>
<td>High placental transfer (cord-to-maternal blood ratio 0.86)&lt;sup&gt;158&lt;/sup&gt;</td>
<td></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td><strong>Animal data</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>3TC 150 mg twice daily or 300 mg once daily</td>
</tr>
<tr>
<td>No evidence of toxicity or teratogenicity in rabbits or rats at 35 to 130 times usual human dose</td>
<td></td>
<td>Combiqir (ZDV 300 mg/3TC 150 mg) 1 tablet twice daily</td>
</tr>
<tr>
<td>Embryotoxic in rabbits at doses similar to human doses, however no indication of this effect in rats at 35 times usual human dose</td>
<td></td>
<td>Trizivir (ZDV 300 mg/3TC 150 mg/ABC 300 mg) 1 tablet twice daily</td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td></td>
<td>Kivexa (3TC 300 mg/ABC 600 mg) 1 tablet once daily</td>
</tr>
<tr>
<td>No adequate or well-controlled studies in pregnant women</td>
<td></td>
<td>A phase I study, evaluating both daily and twice-daily dosing, showed pharmacokinetics were similar in the third trimester of pregnancy and postpartum&lt;sup&gt;159&lt;/sup&gt;; larger study reports 22% higher drug clearance in pregnant women; however, level of exposure was therapeutic.&lt;sup&gt;158&lt;/sup&gt; No dose alteration is required in pregnancy.</td>
</tr>
<tr>
<td>No evidence of human teratogenicity; APR birth defects with first trimester exposure 3.1% (127 of 4088 births, 95% CI 2.6%–3.7%)&lt;sup&gt;42&lt;/sup&gt;</td>
<td></td>
<td><strong>Adverse events/concerns in pregnancy</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall, well tolerated in pregnancy; also active against HBV</td>
</tr>
<tr>
<td><strong>Abacavir (ABC)</strong></td>
<td></td>
<td><strong>Alternative NRTI for dual NRTI backbone of combination regimens</strong></td>
</tr>
<tr>
<td>FDA pregnancy category C</td>
<td></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td>High placental transfer (cord-to-maternal blood ratio 1.0)&lt;sup&gt;160&lt;/sup&gt;</td>
<td></td>
<td>Ziagen 300 mg twice daily or 600 mg once daily</td>
</tr>
<tr>
<td><strong>Animal data</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>Kivexa (3TC 300 mg/ABC 600 mg) 1 tablet once daily</td>
</tr>
<tr>
<td>Developmental toxicity (decreased fetal weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats, at 35 times usual human dose; toxic effects to embryo and fetus in rats at 8 times usual human dose</td>
<td></td>
<td>Phase I study showed drug area under the curve concentrations were similar in pregnant, postpartum, and non-pregnant individuals. No dose alteration is required in pregnancy.&lt;sup&gt;161&lt;/sup&gt;</td>
</tr>
<tr>
<td>No evidence of developmental toxicity or increase in fetal malformation observed in rabbits at 8.5 times usual human dose</td>
<td></td>
<td><strong>Adverse events/concerns in pregnancy</strong></td>
</tr>
<tr>
<td>Carcinogenic in rats at 6 to 32 times usual human dose</td>
<td></td>
<td>Severe hypersensitivity reaction that may be fatal has been reported; testing for the HLA-B<em>5701 allele identifies patients at risk of reaction; patients with the HLA</em>B-5701 allele should not be given ABC.</td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td></td>
<td><strong>continued</strong></td>
</tr>
<tr>
<td>No adequate or well-controlled studies in pregnant women</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3. Continued

**Emtricitabine (FTC)**

- **FDA pregnancy category B**
- **High placental transfer (cord-to-maternal blood ratio 1.2)**

**Animal data**

- No evidence of carcinogenicity in mice or rats at doses up to 26 times and 31 times usual human dose, respectively
- No evidence of developmental toxicity or teratogenicity in mice or rabbits at doses 60 times and 120 times usual human dose, respectively

**Human data**

- No adequate or well-controlled studies in pregnant women
- No evidence of human teratogenicity: APR birth defects with first trimester exposure 2.3% (21 of 899 births; 95% CI 1.4%–3.5%)

**Recommendations for use in pregnancy**

- Alternative NRTI for dual NRTI backbone of combination regimens
- One of preferred NRTI for dual NRTI backbone (in combination with TDF) for women with chronic hepatitis B infection

**Dosing**

- Emtriva (not available in Canada) 200 mg once daily
- Truvada (TDF 300 mg/FTC 200 mg) 1 tablet once daily
- A phase II pharmacokinetic study showed that FTC concentrations were lower in the third trimester than postpartum, however, current data is insufficient to recommend a dosage adjustment in pregnancy.

**Adverse events/concerns in pregnancy**

- Overall, well tolerated in pregnancy; also active against HBV

**Tenofovir (TDF)** (nucleotide analogue reverse transcriptase inhibitor)

- **FDA pregnancy category B**
- **High placental transfer (cord-to-maternal blood ratio 0.6-1.03)**

**Animal data**

- Carcinogenic in female mice at 16 times usual human dose; however, there is no indication of this effect in rats at 5 times usual human dose.
- No evidence of gross structural abnormalities observed in fetal monkeys at 25 times usual human dose; however, low birth weights and reduction in fetal bone porosity were observed.
- Chronic administration of TDF at high doses to immature animals of multiple species has resulted in reversible bone abnormalities (ranging from decreased bone mineral density and content to severe pathologic osteomalacia) and evidence of nephrotoxicity in monkeys at doses 12 to 50 times usual human dose.

**Human data**

- No evidence of human teratogenicity: APR birth defects with first trimester exposure 2.3% (31 of 1370 births; 95% CI 1.5%–3.2%).
- Currently no evidence of nephrotoxicity or decreased growth and development in infants exposed in utero
- Cross-sectional study in HIV-exposed uninfected infants reported comparable outcomes (low birth weight and length measurements, quantitative bone ultrasound, and parameters of bone metabolism) between infants with and without in utero exposure to TDF.
- A cohort study in HIV-exposed uninfected infants compared outcomes of low birth weight and small for gestational age, newborn length for age, and head circumference for age in infants with or without in utero exposure to TDF. At age 1 year, infants exposed to TDF had lower length for age and head circumference for age. The clinical significance of these findings has not been determined.

**Recommendations for use in pregnancy**

- Alternative NRTI for dual NRTI backbone of combination regimens
- Preferred NRTI in combination with 3TC or FTC in women with chronic hepatitis B infection

**Dosing**

- Viread 300 mg once daily
- Truvada (TDF 300 mg/FTC 200 mg) 1 tablet once daily
- Atripla (TDF 300 mg/FTC 200 mg/EFV 600 mg) 1 tablet once daily at nighttime; not recommended in pregnancy (see Efavirenz below)
- A pharmacokinetic study showed that TDF AUC is lower in third trimester than postpartum; however, trough concentrations were similar in both groups. No dose alteration is required in pregnancy.

**Adverse events/concerns in pregnancy**

- Overall, well tolerated in pregnancy; clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance is unknown.

**Didanosine (DDI)**

- **FDA pregnancy category B**
- **Moderate placental transfer (cord-to-maternal blood ratio 0.38)**

**Animal data**

- No evidence of toxicity or teratogenicity in rats or rabbits

**Human data**

- No adequate or well-controlled studies in pregnant women
- APR birth defects with first trimester exposure 4.6% (19 of 409 births; 95% CI 2.8%–7.2%). No pattern of defects was discovered.

**Recommendations for use in pregnancy**

- Alternative NRTI for dual NRTI backbone of combination regimens
- Do not prescribe with stavudine (possible fatal lactic acidosis).

**Dosing**

- Videx EC or Videx oral solution: ≥ 60 kg: 400 mg once daily (with tenofovir give 250 mg PO daily); < 60 kg: 250 mg once daily (with tenofovir give 200 mg once daily)
- Take 30 minutes before or 2 hours after a meal.
- Phase I study showed pharmacokinetics were similar in third trimester of pregnancy and postpartum. No dose alteration is required in pregnancy.

**Adverse events/concerns in pregnancy**

- Fatal lactic acidosis has been reported in pregnant women who received the combination of DDI and d4T; physicians should avoid prescribing this combination.

continued
<table>
<thead>
<tr>
<th>Table 3. Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stavudine (d4T)</strong></td>
</tr>
<tr>
<td>FDA pregnancy category C</td>
</tr>
<tr>
<td>High placental transfer (cord-to-maternal blood ratio 0.5–0.8 in macaques)169</td>
</tr>
<tr>
<td><strong>Animal data</strong></td>
</tr>
<tr>
<td>No evidence of developmental toxicity or teratogenicity in rats at 399 times usual human dose or rabbits at 183 times usual human dose</td>
</tr>
<tr>
<td>No adequate or well-controlled studies in pregnant women</td>
</tr>
<tr>
<td>No evidence of human teratogenicity: APR birth defects with first trimester exposure 2.5% (20 of 801 births; 95% CI 1.5%–3.8%)42</td>
</tr>
<tr>
<td><strong>Human data</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Non-nucleoside reverse transcriptase inhibitors</strong></td>
</tr>
<tr>
<td>NNRTIs are recommended for use in combination regimens with 2 NRTI drugs (alternative to using a PI).</td>
</tr>
<tr>
<td><strong>Nevirapine (NVP)</strong></td>
</tr>
<tr>
<td>FDA pregnancy category B</td>
</tr>
<tr>
<td>High placenta transfer (cord-to-maternal blood ratio 0.90)26</td>
</tr>
<tr>
<td><strong>Animal data</strong></td>
</tr>
<tr>
<td>Hepatocellular adenoma and carcinoma reported in mice and rats; relevance to humans not known</td>
</tr>
<tr>
<td>No evidence of teratogenicity in rats and rabbits at twice the usual human dose; however, low birth weights observed</td>
</tr>
<tr>
<td><strong>Human data</strong></td>
</tr>
<tr>
<td>Limited well-controlled studies of NVP in pregnant women; no evidence of human teratogenicity; antiretroviral pregnancy registry 2.7% (28 of 1020 births, 95% CI 1.8%–4.0%)85</td>
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### Table 3. Continued

<table>
<thead>
<tr>
<th><strong>Efavirenz (EFV)</strong></th>
<th><strong>Recommendations for use in pregnancy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category D</td>
<td>Contraindicated in first trimester of pregnancy</td>
</tr>
<tr>
<td>Moderate placenta transfer (cord blood concentrations similar to maternal plasma concentration in rats, rabbits, primates)³</td>
<td>Women receiving EFV should be instructed to avoid pregnancy; recommend barrier contraception in combination with other hormonal contraceptives.</td>
</tr>
<tr>
<td><strong>Animal data³</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma and adenoma and pulmonary alveolar/bronchiolar adenomas reported in female mice; however, no indication of this effect in male mice or in rats</td>
<td></td>
</tr>
<tr>
<td>Significant central nervous system malformations (anencephaly, anophthalmia, cleft palate) reported in monkeys receiving EFV in first trimester at doses comparable to human therapeutic exposure</td>
<td></td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td></td>
</tr>
<tr>
<td>Limited well-controlled studies in pregnant women: a meta-analysis of birth defects observed in cohorts of infants with first trimester exposure (1437 live births) found no increased risk of overall birth defects than in infants exposed to non-EFV-based regimens (RR 0.85; 95% CI 0.61–1.20), with one neural tube defect observed⁴; a large prospective study of a cohort of antiretroviral-exposed infants (13 124 live births) found significant association between EFV exposure in the first trimester and neurological defects (adjusted OR 3.15; 95% CI 1.09–9.09).⁴⁴</td>
<td></td>
</tr>
<tr>
<td>APR 2.7% (18 of 679 births, 95% CI 1.6%–4.2%); 6 retrospective case reports of central nervous system defects (including 3 cases of meningomyelocele), 1 prospective case report of neural tube defect, and 1 prospective case report of bilateral facial clefts and anophthalmia in humans receiving EFV in first trimester⁴²</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Etravirine (ETR)</strong></th>
<th><strong>Recommendations for use in pregnancy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category B</td>
<td>Insufficient safety and pharmacokinetic data to recommend use during pregnancy</td>
</tr>
<tr>
<td>Placental transfer unknown (cord-to-maternal blood ratio from case report data 0.33)¹⁷⁴</td>
<td></td>
</tr>
<tr>
<td><strong>Animal data³</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma and adenoma reported in mice; however, no indication of this effect in rats</td>
<td></td>
</tr>
<tr>
<td>No evidence of embryotoxicity or teratogenicity in rabbits or rats at doses comparable to human therapeutic exposure</td>
<td></td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td></td>
</tr>
<tr>
<td>No adequate or well-controlled studies and few case report data in pregnant women</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Rilpivirine (RPV)</strong></th>
<th><strong>Recommendations for use in pregnancy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category B</td>
<td>Insufficient safety and pharmacokinetic data to recommend use during pregnancy</td>
</tr>
<tr>
<td>Placental transfer unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Animal data³</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma reported in mice; however, no indication of this effect in rats</td>
<td></td>
</tr>
<tr>
<td>No evidence of embryotoxicity or teratogenicity in rats or rabbits at doses 15 times and 70 times usual human dose, respectively</td>
<td></td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td></td>
</tr>
<tr>
<td>No published data for human pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

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continued
### Table 3. Continued

<table>
<thead>
<tr>
<th>Protease inhibitors</th>
<th>PI class concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs are recommended for use in combination regimens with 2 NRTI drugs (alternative to using an NNRT).</td>
<td>Hyperglycemia and new onset or exacerbation of existing diabetes have been reported with PIs; unclear whether pregnancy increases risk. Data regarding preterm delivery in women receiving PIs are conflicting (see text for details).</td>
</tr>
</tbody>
</table>

### Lopinavir-ritonavir (LPV/r)

**FDA pregnancy category C**

Low placental transfer (cord-to-maternal blood ratio LPV 0.20, RTV minimal)

**Animal data**

Hepatocellular carcinoma and adenoma reported in mice at doses 2 times (LPV) and 5 times (RTV) usual human dose

Embytotoxic in rats; no evidence of teratogenicity in rats or rabbits

**Human data**

There are no adequate or well-controlled studies in pregnant women.

No evidence of human teratogenicity; APR 2.4% (21 of 883 births, 95% CI 1.5%–3.6%)\(^4\)

**Recommendations for use in pregnancy**

Preferred PI for use in combination with dual NRTI backbone

**Dosing**

Kaletra (LPV/r 200 mg/50 mg; LPV/r 100 mg/50 mg; oral solution LPV/r 400 mg/100 mg in each 5 mL) 400 mg LPV twice daily; take with food to reduce stomach upset.

Pharmacokinetic studies show AUC is increased in third trimester.\(^{175,176}\) Increasing the dose of LPV/r from 400 mg/100 mg twice a day to 600 mg/150 mg twice a day resulted in AUC similar to non-pregnant adults taking the standard dose\(^{177,178}\); may consider increased dose to LPV/r 600 mg/150 mg twice daily in third trimester, particularly in women who have previously had PI. No data exist evaluating LPV/r drug levels using once-daily dosing in pregnancy; once-daily dosing is not recommended.

**Adverse events/concerns in pregnancy**

Well tolerated; short-term safety data in Phase I/II clinical studies

### Atazanavir (ATV)

**Approved by FDA for use in pregnancy**

FDA pregnancy category B

Low placental transfer (cord-to-maternal blood ratio 0.10–0.20)

**Animal data**

Benign hepatocellular adenomas reported in female mice at 3 times usual human dose; no evidence of teratogenicity in rats or rabbits at similar or 2 times usual dose respectively; weight loss or weight gain suppression observed at 1.3 times usual human dose

**Human data**

No adequate or well-controlled studies have been reported in pregnant women.

No evidence of human teratogenicity; APR 1.9% (13 of 669 births; 95% CI 1.0%–3.3%)\(^4\)

**Recommendations for use in pregnancy**

Alternative PI for use in combination with dual NRTI backbone

**Dosing**

Must be combined with low-dose RTV (ATV/r) in pregnancy

Reyataz ATV/r 300/100 mg once daily

Take with food to increase absorption and minimize stomach upset.

Three pharmacokinetic studies evaluating ATV/r 300 mg/100 mg (without any interacting medications) have shown lower plasma concentrations in the third trimester than in non-pregnant adults; however, most women achieved an HIV viral load < 50 copies/mL and did not require dose adjustment.\(^{50,52,53}\) Two pharmacokinetic studies evaluating ATV/r 400 mg/100 mg (without any interacting medications) in the third trimester have shown drug ATV AUC similar to non-pregnant controls.\(^{52,53}\) TDF reduces ATV exposure 25% in pregnant women; increasing the dose to ATV/r 400 mg/100 mg in women receiving TDF has shown ATV AUC similar to that in non-pregnant control subjects.\(^53\) Standard dose ATV/r 300 mg/100 mg can be used in pregnancy; consider increasing the dose in third trimester to ATV/r 400 mg/100 mg if combined with either an H\(_2\)-receptor antagonist or tenofovir. Data are insufficient to support combined use of ATV + TDF + H\(_2\)-receptor antagonist.

**Adverse events/concerns in pregnancy**

ATV increases indirect (unconjugated) bilirubin; the theoretical concern that increased bilirubin may exacerbate physiologic hyperbilirubinemia in infants has not yet been indicated in clinical trials.\(^{179}\)

Continued
### Guidelines for the Care of Pregnant Women Living With HIV and Interventions to Reduce Perinatal Transmission

#### Table 3. Continued

<table>
<thead>
<tr>
<th><strong>Ritonavir (RTV)</strong></th>
<th><strong>Recommendations for use in pregnancy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category B</td>
<td>Use only at low-dose in combination with a second PI to increase the serum drug levels of the second PI.</td>
</tr>
<tr>
<td>Minimal placental transfer</td>
<td></td>
</tr>
<tr>
<td><strong>Animal data</strong></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td>Hepatocellular carcinoma and adenomas observed in male mice at high doses; developmental toxicity (decreased body weight, ossification delays) observed at high doses</td>
<td>Ritonavir 100–400 mg PO per day in 1–2 divided doses (depending on combination with specific PI)</td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td>Take with food to minimize stomach upset.</td>
</tr>
<tr>
<td>Limited experience at full dose in human pregnancy; when used for low-dose RTV boosting there is no evidence of human teratogenicity; APR 2.2% (39 of 1741 births, 95% CI 1.6%–3.0%).42</td>
<td>Phase I and II pharmacokinetic studies using therapeutic RTV dosing and studies of other PIs using RTV as a low-dose booster have shown lower RTV levels in pregnancy than postpartum53,180; no dose adjustments are recommended in pregnancy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Darunavir (DRV)</strong></th>
<th><strong>Recommendations for use in pregnancy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category C</td>
<td>Insufficient safety and pharmacokinetic data to recommend use during pregnancy</td>
</tr>
<tr>
<td>Placental transfer unknown (cord-to-maternal blood ratio based on case reports 0.24)181</td>
<td></td>
</tr>
<tr>
<td><strong>Animal data</strong></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td>Hepatocellular carcinoma and adenomas observed in mice and rats; no evidence of embryotoxicity or teratogenicity in mice, rats, or rabbits at doses 50% and 5% that of usual human doses</td>
<td>Darunavir 800 mg/100 mg once daily for antiretroviral-naive patients or antiretroviral-experienced patients without DRV resistance mutations; DRV/r 600 mg/100 mg twice daily for antiretroviral-experienced patients with resistance mutations: DRV/r 600 mg/100 mg twice daily</td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td>Take with food to minimize stomach upset.</td>
</tr>
<tr>
<td>No adequate or well-controlled studies in pregnancy</td>
<td>Pharmacokinetic studies evaluating DRV/r as 600 mg/100 mg twice daily or 800 mg/100 mg once daily have shown 17%–35% reductions in DRV levels in third trimester of pregnancy compared to postpartum.180–182 DRV/r 600 mg/100 mg twice daily provides adequate drug exposure during pregnancy. Until more data are available, twice-daily DRV is suggested. If once-daily dosing is used, virological response and DRV concentration if available should be monitored.</td>
</tr>
<tr>
<td>Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Saquinavir (SQV)</strong></th>
<th><strong>Recommendations for use in pregnancy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category B</td>
<td>Alternative PI for use in combination with dual NRTI backbone</td>
</tr>
<tr>
<td>Minimal placental transfer</td>
<td></td>
</tr>
<tr>
<td><strong>Animal data</strong></td>
<td><strong>Dosing</strong></td>
</tr>
<tr>
<td>No evidence or carcinogenicity, embryotoxicity, or teratogenicity in mice, rats, or rabbits at doses 21%–26% of usual human doses</td>
<td>Saquinavir SQV/r 1000 mg/100 mg twice daily</td>
</tr>
<tr>
<td><strong>Human data</strong></td>
<td>Take with meals or within 2 hours after a meal.</td>
</tr>
<tr>
<td>No adequate or well-conducted clinical studies have been conducted in pregnant women.</td>
<td>Pharmacokinetic study data is conflicting; one study evaluating SQV/r 1000 mg/100 mg twice daily has shown comparable drug levels in second and third trimesters and postpartum183; a second study using the same dosing has shown a 50% decrease in third trimester levels without loss of virologic control184; data is insufficient to recommend a dosage adjustment in pregnancy and too limited to recommend once-daily dosing.</td>
</tr>
<tr>
<td>Few pregnancy exposures have been reported to the APR; no conclusion can be made about the risk of birth defects.</td>
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</tr>
</tbody>
</table>

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**Adverse events/concerns in pregnancy**

Well tolerated, short-term safety demonstrated for mothers and infants; baseline ECG is recommended before starting because PR and/or QT interval prolongation have been observed; no evidence that pregnancy increases risk
Table 3. Continued

<table>
<thead>
<tr>
<th>Nelfinavir (NVF)</th>
<th>Recommendations for use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category B</td>
<td>Use in special circumstances when alternative agents are not tolerated in combination with dual NRTI backbone.</td>
</tr>
<tr>
<td>Minimal placental transfer</td>
<td></td>
</tr>
</tbody>
</table>

**Animal data**

Thyroid follicular cell adenoma and carcinoma has been observed in rats receiving similar to 3 times usual human dose; no evidence of embryonic or teratogenicity has been observed in rats or rabbits.

**Human data**

No evidence of human teratogenicity; APR 3.9% (47 of 1204 births, 95% CI 2.9%–5.2%)\(^2\) 42

Well tolerated; short-term safety has been demonstrated for mothers and infants.

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<table>
<thead>
<tr>
<th>Fosamprenavir (FPV)</th>
<th>Recommendations for use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category C</td>
<td>Safety and pharmacokinetic data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td>Placental transfer unknown</td>
<td></td>
</tr>
</tbody>
</table>

**Animal data**

Hepatocellular carcinoma and adenoma have been observed in rats at doses comparable to human doses.

**Human data**

No adequate or well-controlled studies have been conducted in pregnant women.

Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects.

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<table>
<thead>
<tr>
<th>Indinavir (IDV)</th>
<th>Recommendations for use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA pregnancy category C</td>
<td>For use in special circumstances when alternative agents cannot be used in combination with dual NRTI backbone</td>
</tr>
<tr>
<td>Minimal placental transfer</td>
<td></td>
</tr>
</tbody>
</table>

**Animal data**

Thyroid adenomas observed in rats at 1.3 times usual human dose; however, no indication of any tumour types in mice.

No evidence of embryotoxicity or teratogenicity in rabbits or dogs at 3% and 50% of maternal levels; increased incidence of supernumerary and cervical ribs observed in rats at doses comparable to human doses.

Exacerbation of physiologic neonate hyperbilirubinemia did not occur in Rhesus monkeys with third trimester in utero exposure.

**Human data**

No adequate or well-controlled studies in pregnant women.

No evidence of human teratogenicity; APR 2.1% (6 of 286 births, 95% CI 0.8%–4.5%)\(^2\) 42

Well tolerated; short-term safety has been demonstrated for mothers and infants.

---

**Adverse events/concerns in pregnancy**

IDV increases indirect (unconjugated) bilirubin; evidence for a theoretical concern regarding increased bilirubin exacerbating physiologic hyperbilirubinemia in infants has not been reported; there is a potential for renal stones; it is unclear if pregnancy increases risk.

**Dosing**

Must be combined with low-dose RTV (IDV/r) in pregnancy.

Crixivan IDV/r 800 mg/100–200 mg twice daily

Two pharmacokinetic studies evaluating IDV without RTV have shown IDV concentrations are lower in the third trimester than in postpartum and non-pregnant patients, and 2 pharmacokinetic studies evaluating IDV 400 mg twice daily combined with low-dose RTV have shown decreases in IDV levels during pregnancy without loss of virologic control.\(^3\)

Optimal dose in pregnancy is not established; HIV levels and trough IDV concentration should be monitored; must be combined with low-dose RTV.

**Adverse events/concerns in pregnancy**

IDV increases indirect (unconjugated) bilirubin; evidence for a theoretical concern regarding increased bilirubin exacerbating physiologic hyperbilirubinemia in infants has not been reported; there is a potential for renal stones; it is unclear if pregnancy increases risk.

**Dosing**

Must be combined with low-dose RTV (IDV/r) in pregnancy.

Two pharmacokinetic studies evaluating IDV without RTV have shown IDV concentrations are lower in the third trimester than in postpartum and non-pregnant patients, and 2 pharmacokinetic studies evaluating IDV 400 mg twice daily combined with low-dose RTV have shown decreases in IDV levels during pregnancy without loss of virologic control.\(^3\)

Optimal dose in pregnancy is not established; HIV levels and trough IDV concentration should be monitored; must be combined with low-dose RTV.

**Adverse events/concerns in pregnancy**

IDV increases indirect (unconjugated) bilirubin; evidence for a theoretical concern regarding increased bilirubin exacerbating physiologic hyperbilirubinemia in infants has not been reported; there is a potential for renal stones; it is unclear if pregnancy increases risk.

**Dosing**

Recommended to be combined with low-dose RTV (FPV/r) in pregnancy.

Lexiva antiretroviral naïve patients: FPV 1400 mg twice daily or FPV/r 1400 mg/100–200 mg once daily; Telzir antiretroviral naïve patients: FPV/r 700 mg/100 mg twice daily; PI experienced patients: FPV 700 mg/100 mg twice daily

Limited pharmacokinetic data are available; one study evaluating FPV/r 700 mg/100 mg twice daily has shown lower amprenavir (active moiety) concentrations during pregnancy than in postpartum and non-pregnant patients; however, levels were considered adequate for patients without PI resistance mutations\(^19\); no data are available for using FPV in pregnancy without low-dose RTV; preliminary evidence suggests no dose adjustment is required in pregnancy and data is too limited to recommend once-daily or unboosted FPV.

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continued
Table 3. Continued

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendations for use in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tipranavir (TPV)</strong></td>
<td>Safety and pharmacokinetic data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td>FDA pregnancy category C</td>
<td></td>
</tr>
<tr>
<td>Placental transfer unknown; moderate transfer reported in one case report (cord-to-maternal blood ratio 0.41)</td>
<td></td>
</tr>
<tr>
<td>Animal data&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma and adenoma was observed in mice; this effect was not observed in rats.</td>
<td></td>
</tr>
<tr>
<td>No evidence of embryotoxicity or gross structural abnormalities in rats or rabbits at doses 0.2 to 1.1 times usual human dose have been reported; however, growth in inhibition was observed in rats at 0.8 times human doses.</td>
<td></td>
</tr>
<tr>
<td>Human data</td>
<td></td>
</tr>
<tr>
<td>No adequate or well-controlled studies in pregnant women have been reported.</td>
<td></td>
</tr>
<tr>
<td>Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects.</td>
<td></td>
</tr>
<tr>
<td><strong>Entry Inhibitors</strong></td>
<td>Safety and pharmacokinetic data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td><strong>Enfuvirtide (T20)</strong></td>
<td></td>
</tr>
<tr>
<td>FDA pregnancy category B</td>
<td>Safety and pharmacokinetic data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td>No placental transfer based on single case report&lt;sup&gt;189&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>No evidence of teratogenicity in rats or rabbits at 27 or 3 times the usual human dose, respectively&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>No adequate or well-documented studies in pregnant women have been reported.</td>
<td></td>
</tr>
<tr>
<td><strong>Maraviroc (MVC)</strong></td>
<td>Safety and pharmacokinetic data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td>FDA pregnancy category B</td>
<td></td>
</tr>
<tr>
<td>Placental transfer unknown</td>
<td></td>
</tr>
<tr>
<td>Animal Data&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>No evidence of embryotoxicity, carcinogenicity, or teratogenicity has been found in rats or rabbits at 20 times and 5 times usual human dose, respectively.</td>
<td></td>
</tr>
<tr>
<td>Human Data</td>
<td></td>
</tr>
<tr>
<td>No adequate or well-documented studies in pregnant women have been reported.</td>
<td></td>
</tr>
<tr>
<td>Few pregnancy exposures have been reported to the APR; no conclusion can be made about the risk of birth defects.</td>
<td></td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td>Safety and pharmacokinetic data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td><strong>Raltegravir (RAL)</strong></td>
<td></td>
</tr>
<tr>
<td>FDA pregnancy category C</td>
<td>Safety and pharmacokinetic data are insufficient to recommend use during pregnancy.</td>
</tr>
<tr>
<td>Placental transfer unknown (cord-to-maternal blood ratio from case reports 1.0)&lt;sup&gt;190&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Animal Data&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>There has been no evidence shown of embryotoxicity, carcinogenicity, or teratogenicity in rats or rabbits at 3 to 4 times the usual human dose; however, an increase in incidence of supernumerary ribs was reported in rats at 3 times usual human dose.</td>
<td></td>
</tr>
<tr>
<td>Human Data</td>
<td></td>
</tr>
<tr>
<td>No adequate or well-documented studies in pregnant women have been reported.</td>
<td></td>
</tr>
<tr>
<td>Few pregnancy exposures have been reported to the APR; no conclusion can be made about the risk of birth defects.</td>
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Table 3. Continued

<table>
<thead>
<tr>
<th>Elvitegravir (EVG)-Cobicistat (COBI)</th>
<th>Recommendations for use in pregnancy</th>
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<td>FDA pregnancy category B</td>
<td>Safety and pharmacokinetic data are insufficient to recommend use during pregnancy.</td>
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<tr>
<td>Placental transfer unknown</td>
<td><strong>Dosing</strong></td>
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<td>Animal Data1,2</td>
<td>Stribild (TDF 300 mg/FTC 200 mg/EVG 150 mg/COBI 150 mg)</td>
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<tr>
<td>EVG: No evidence of teratogenicity or an effect on reproductive function has been reported in rats or rabbits at doses 23 and 0.2 times higher, respectively, than the usual human dose.</td>
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</tr>
<tr>
<td>COBI: No evidence of teratogenicity or effect on reproductive function has been reported in rats or rabbits at doses 1.8 and 4.3 times higher, respectively, than the usual human dose.</td>
<td></td>
</tr>
<tr>
<td>Human Data</td>
<td>No adequate or well-documented studies have been reported in pregnant women.</td>
</tr>
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</table>

APR: Antiretroviral Pregnancy Registry; IV: intravenous, FTC: emtricitabine; EVF: efavirenz; RR: relative risk; OR: odds ratio; AUC: area under the curve; RPV: ritonavir; LPV/r: lopinavir/ritonavir; SQV: saquinavir; ECG: electrocardiogram; CYP: cytochrome P450; EMS: ethyl methane sulfonate

rapidly crosses the placenta and achieves adequate infant blood levels,26,27 is easily administered, and is well tolerated in both women and infants, it has been recommended as a treatment strategy for women living with HIV who present in labour and are not receiving antenatal antiretroviral therapy. Nevirapine possesses a long half-life, however, and therefore use of even a single dose exposes women to an extended period of nevirapine monotherapy, potentially increasing the risk of nevirapine drug-resistant mutations.28 One strategy to limit the emergence of nevirapine resistance after single-dose nevirapine is to provide the woman with an antiretroviral tail (e.g., postpartum addition of 2 NRTIs for a period of 3 to 14 days).29-33

The HPTN 040/PACTG 040 study evaluated the alternative treatment strategy of administering prophylactic cART to infants born to women living with HIV who were not receiving antenatal antiretroviral therapy.25 Forty-one percent of women in this study received intrapartum intravenous zidovudine and the majority of infants were formula-fed. This study demonstrated that the cART (the addition of either 3 doses of infant nevirapine or 2 weeks of lamivudine/lopinavir to 6 weeks of zidovudine) was superior in reducing the risk of vertical HIV transmission (2.2% and 2.4%, respectively) to 6 weeks of infant zidovudine therapy alone (4.8%, \( P = 0.046 \)). The rate of neutropenia was higher in the 3-drug regimen (27.5% with zidovudine/lopinavir/lamivudine) than in the 2-drug (14.9% with zidovudine/nevirapine) and 1-drug (16.4% with zidovudine) regimens.

Principles behind using combination antiretroviral therapy in pregnancy

Antiretroviral treatment recommendations for the pregnant woman living with HIV are based on the principle that therapies of known benefit to the woman should be offered and not withheld during pregnancy. The benefits of cART for the overall health of the woman and for prevention of vertical transmission are known; however, there is need for improved understanding of the short- and long-term effects of antiretroviral drug therapy in pregnancy; therefore parameters of maternal and fetal well-being need to be closely monitored. Overall, the benefit of prevention of 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.

Selection of a specific antiretroviral drug therapy regimen in a pregnant woman living with HIV must take into account the inter-related 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.

Timing of initiation of combination antiretroviral therapy in pregnancy

The timing of initiation will depend on the woman’s HIV disease status (e.g., CD4-cell count and HIV viral load), her
preparedness to start cART, and her degree of nausea and vomiting of pregnancy. Adult HIV treatment guidelines are available elsewhere and are not discussed in detail here. In brief, they recommend initiation of cART for all individuals regardless of CD4-cell counts. In the obstetrical setting there are controversies about the timing of cART initiation in pregnant women who have not already been treated. While cART may reduce the risk of HIV vertical transmission, there may also be risks in exposing the fetus to cART.

Women with CD4-cell counts < 200 cells/mm³ are at high risk of opportunistic infections; therefore, cART should be started immediately, regardless of gestational age, in conjunction with prophylaxis for opportunistic infections as described below. Women with CD4-cell counts between 200 to 350 cells/mm³ may be at risk of experiencing more common infections (e.g., herpes zoster, bacterial pneumonia), therefore cART should be initiated as soon as possible—usually after the first trimester is completed (week 14). In other cases, although 14 weeks is the general recommendation for cART initiation, delayed initiation of cART until the detailed anatomy ultrasound (i.e., week 18) may be considered in women with CD4-cell counts > 350 cells/mm³ on a case-by-case basis.

Antiretroviral drug resistance testing should be performed before starting an antiretroviral regimen; however, if it is determined that cART needs to be started urgently, decisions to start can be made based on the woman’s antiretroviral history and adjusted later if necessary. All women should be counselled about the importance of adherence to the regimen, and should be recommended to continue therapy after delivery.

Detailed guidelines regarding management and prophylaxis of opportunistic infections, including specific recommendations for pregnant women, are available and are not discussed in detail here. In brief, consideration for antibiotic prophylaxis against the following opportunistic infections must be made based on CD4-cell count: < 200 cells/mm³ requires prophylaxis against PCP; < 100 cells/mm³ requires additional prophylaxis against Toxoplasmosis gondii (if Toxoplasmosis immunoglobulin G serology is positive and an agent other than cotrimoxazole is used as prophylaxis for PCP); < 50 cells/mm³ requires additional prophylaxis against MAC after obtaining MAC blood cultures and an ophthalmology referral to rule out CMV retinitis. Treatment and prophylaxis of all opportunistic infections must be provided as required with consideration of potential toxicities in pregnancy. While this is well discussed in available guidelines, agents of note to avoid, particularly in the first trimester of pregnancy, include continuous oral fluconazole and clarithromycin. Cotrimoxazole (a folate antagonist which readily crosses the placenta) may be safely used throughout pregnancy; however, consideration should be given to increasing the folic acid dose to 5 mg per day in the first trimester and monitoring infants postpartum due to increased risk of neonatal hyperbilirubinemia.

**Continuation of therapy in women already receiving combination antiretroviral therapy prior to pregnancy**

In most cases, the current antiretroviral regimen should be continued if the regimen is effective in suppressing HIV viral load and is tolerated by the woman. Significant nausea and vomiting of pregnancy may complicate a woman’s ability to adhere to medication and needs to be addressed and aggressively managed.

There are two main populations of women in whom switching of antiretroviral medications may be considered. The first is pregnant women living with HIV who are receiving efavirenz and present pre-conception or very early for care in the first trimester. As discussed below and more thoroughly in Appendix 2, efavirenz is not a desirable choice in the first trimester due to its association with neural tube defects in primates and in case reports in humans. Because most women will present after the 5- to 6-week gestational age time window for neural tube closure, the NIH guidelines endorse continuation of efavirenz in all pregnant woman including those who present for care in the first trimester. However because women may not always present after neural tube closure, and because there is a risk of women remaining on a potentially teratogenic medication postpartum, particularly those who do not receive adequate contraception, these guidelines still recommend considering switching the woman from efavirenz to an alternative antiretroviral agent that has greater safety and efficacy data in pregnancy. If efavirenz is received during the first trimester, however, ultrasound evaluation of neural tube closure is very important.

Changing antiretroviral medications may also be considered in women who are receiving an antiretroviral agent for which there is little known safety and efficacy data for use in pregnancy (see Appendix 2). It is important to consider the safety and risk of continuing each antiretroviral medication, and prior to any changes to medication there should be discussion between the woman, her HIV care provider, and her obstetrical care provider.

**Selection of cART regimen in pregnancy**

Antiretroviral drug resistance testing should be performed as described above before starting cART and test results used to help determine the optimal regimen. A cART regimen should usually include a dual NRTI backbone...
that includes one or more NRTIs with high levels of transplacental passage (e.g., zidovudine, lamivudine, emtricitabine, tenofovir, abacavir) and an additional boosted protease inhibitor (see Appendix 2).

Consistent adherence to antiretroviral therapy is critical to its efficacy and to preventing the development of resistance. In particular, with complications in pregnancy such as nausea and vomiting of pregnancy, there may be circumstances when cART needs to be discontinued. In this case, regardless of reason, the woman should be advised to discontinue all drugs at once, and to resume all drugs simultaneously to minimize the risk of viral resistance developing during therapy (unless on an NNRTI, then a tail of 2 NRTIs is recommended for 1 week). Resume antiretroviral therapy as quickly as possible after discontinuing, to minimize the risk of rebound viremia and the potentially increased risk of vertical transmission.

In the antiretroviral naive and in a presumed or proven pan-sensitive virus the recommended NRTI backbone is zidovudine-lamivudine 300 mg/150 mg 1 tablet PO twice daily with lopinavir-ritonavir 200 mg/50 mg 2 tablets PO twice daily. This regimen requires twice-daily dosing and monthly hemoglobin monitoring as zidovudine can cause pure red cell aplasia.45 If women are unable to tolerate or adhere to a twice-daily dosing regimen an alternative regimen is abacavir-lamivudine 600 mg/300 mg 1 tablet PO once daily and boosted atazanavir (atazanavir 300 mg plus ritonavir 100 mg PO once daily). Testing for, and confirmation of the absence of the inherited HLA*B5701 gene must be done prior to initiation of any abacavir-containing medication to reduce the risk of a severe allergic reaction.46 Atazanavir is associated with increased maternal indirect bilirubin. Although the clinical significance has not been determined, bilirubin should be monitored monthly in the mother and the infant after delivery.47,48 It is important to note that both of the above listed boosted protease inhibitor regimens may require increased dosing (e.g., abacavir-lamivudine 3 tablets PO twice daily, atazanavir 400 mg PO once daily with ritonavir 100 mg PO once daily) in the third trimester as a result of increased volume of distribution of pregnancy.43,45–47 These empiric dose increases should be considered, particularly if the woman's HIV viral load becomes detectable, cART adherence has been verified and HIV resistance has been ruled out. If available, therapeutic drug level monitoring may also be considered in the third trimester to guide the need for protease inhibitor dose adjustment.44

In pregnant women with HIV and HBV co-infection, the dual NRTI backbone should include 2 NRTI agents that are also active against HBV (e.g., lamivudine, emtricitabine, tenofovir)2,3,55,56; therefore, the recommended first-line regimen in these women is tenofovir-emtricitabine and boosted atazanavir/ritonavir as described above. HBV DNA levels should be monitored and should become undetectable on this regimen. Because chronic administration of tenofovir to pregnant monkeys has resulted in a slight reduction in fetal bone porosity (a finding which has conflicting results in human studies) and is associated with nephrotoxic effects, tenofovir is not recommended as a first-line agent in pregnancy except with an HBV co-infection, drug resistance, and/or medication adherence issues.3,56,57

If women are unable to tolerate or are resistant to the PIs lopinavir and/or atazanavir, alternative cART regimens may need to be considered including (a) boosted darunavir/ritonavir (darunavir 800 mg PO daily with ritonavir 100 mg PO daily or darunavir 600 mg PO twice daily with ritonavir 100 mg PO twice daily), or (b) efavirenz 600 mg PO at nighttime, if the virus is sensitive and after the early first trimester of pregnancy, ideally after a detailed ultrasound and screening have confirmed the absence of a neural tube defect. Nevirapine initiation in pregnancy has been associated with 10% life-threatening toxicity (fetal rash and hepatotoxicity) and its initiation in pregnancy is not recommended if there is a suitable alternative.2,3 Although some data have suggested that nevirapine may be safe if a woman's CD4 cell count is > 250 cells/mm3, Canadian data have suggested that toxicity has occurred at a wide range of CD4-cell counts in women exposed to nevirapine for the first time during pregnancy.58 Women who have been receiving and tolerating nevirapine prior to becoming pregnant (regardless of CD4-cell count) can continue to receive this agent.53 All other antiretroviral agents used in adult HIV care must be individually assessed on a case-by-case basis, depending on the woman's clinical and personal circumstances, co-infections, HLA*B5701 results, genotype of virus, and available options. Detailed information on each antiretroviral agent is provided in Appendix 2; however, it is recommended that consultation be made with experts in the areas of HIV and obstetric care.

Because antiretroviral medications are used as a part of combination regimens it is difficult to ascertain the contribution that an individual agent has on potential maternal and/or fetal toxicity. Studies that have evaluated the results of cART have shown variable results. Some early studies have reported serious maternal toxicities including hepatotoxicity,59–61 higher rates of neonatal malformations,62,63 increased risk of prematurity and low birth weight,64–70 or serious neonatal complications including mitochondrial toxicity.68–75 Other studies, however, suggest that there are generally few serious effects for the mother or infant associated with cART.17,76–82
The concerns surrounding the use of efavirenz (teratogen), nevirapine (rash and hepatotoxicity), tenofovir (bone abnormalities, nephrotoxicity), and atazanavir (hyperbilirubinemia) in pregnancy have been discussed. Women living with HIV who are on antiretroviral therapy are also at a higher risk of preterm delivery than those who are not (18% vs. 9% in Canada).83,84 There is conflicting evidence about whether cART further increases this risk.67,85–92 Data to suggest an association between antiretroviral drug therapy (including protease inhibitor use) and premature delivery or low birth weight infants are mixed; however, a causal relationship has not been established.88,93–95 A causal relationship has not been established and PIs should not be withheld during pregnancy. There is also conflicting evidence as to whether women taking regimens that include PI are at increased risk for impaired glucose tolerance or gestational diabetes in pregnancy.64,96–98 Standard glucose screening at 24 to 28 weeks is recommended in pregnant women living with HIV; if a woman is receiving a PI-based regimen, the clinician may choose to perform this screening test earlier.3,99

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-naïve) 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-2D)
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, non-judgemental care to women living with HIV and their children, in the spirit of professionalism.100

• Addressing early and systematically the woman’s need for social support, with at least one interview with a social worker. Pregnant women living with HIV in Canada commonly experience challenging social and economic environments, with 25% of infections linked to drug use.10,11 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.100

• Encouraging the testing of partners and previous children if their HIV status is unknown.101 The medical and psychological needs of the fathers should be addressed, and the men referred to other health care providers if necessary.102

• Advising on the use of, and facilitating access to, condoms for the purpose of preventing transmission of HIV and other sexually transmitted infections.103 If both members of the couple are living with HIV, they should be informed of the possible risk of superinfection associated with unprotected sex.104

• 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.100

Inclusion of de-identified data of the mother and infant pairs in provincial and national surveillance programs is highly recommended. The CPHSP, an initiative of the Canadian Pediatric AIDS Research Group (CPARG) collects important public health data, which inform allocation of resources and management of future pregnancies.10,11

First Trimester (Weeks 0 to 13)

Early pregnancy offers the opportunity for complete HIV and obstetrical assessments and permits planning for prenatal genetic screening. In addition to the standard antenatal assessments for all pregnant women, assessment should include the following: documentation of history of prior HIV-related illnesses and past CD4-cell counts and plasma HIV viral loads; assessment for symptoms of opportunistic infections; complete physical examination including a pelvic examination and cervical Pap smear; screening for sexually transmitted infections (including chlamydia, gonorrhea, syphilis); screening for HBV (using HBsAg, anti-HBs, and anti-HBc), HCV (HCV antibody and HCV PCR status if antibody positive) and tuberculosis (induration of \( \geq 5 \text{ mm} \)

using purified protein derivative); and evaluation of immunization status. In addition to standard prenatal blood work, the following blood work should also be obtained: CD4-cell count (absolute count and fraction), HIV viral load, baseline CBC and differential, and liver (AST, ALT, LDH) and renal (urea, serum creatinine) function testing (see Table 4 and Table 5).

All pregnant women who are 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. Timely referral is critical to ensure women are able to undergo the type of screening test they have chosen. Ideally, first trimester biochemical screening and nuchal translucency measurements (at 11 to 14 weeks) should be obtained to integrate with second trimester biochemical screening, and these results should be used to inform the need for invasive testing.105 If integrated prenatal screening is not accessible, then pregnant women living with HIV should be offered the non-invasive screening for aneuploidy based on gestational age that is available in the area. As maternal serum testing of fetal aneuploidy becomes more available, this method of testing will be preferred over amniocentesis, particularly in this population.

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,40 is necessary to facilitate the initiation and/or continuation of antiretroviral medications. Important considerations when evaluating nausea and vomiting of pregnancy in a woman living with HIV should include antiretroviral-related lactic acidosis or pancreatitis, as well as opportunistic infections including intestinal protozoa if the woman is at risk (e.g., CD4-cell count < 200 cells/mm\(^3\)) and symptoms are accompanied by diarrhea. In particular, in women with very advanced HIV disease, alternative causes for nausea should be considered (e.g., gastric lymphoma, central nervous system lesions, or infections causing increased intracranial pressure).35

As outlined above, the timing of initiation of antiretroviral therapy will depend on current CD4-cell count and maternal conditions including nausea and vomiting. Antiretroviral therapy and prophylaxis or treatment of opportunistic infections should be started immediately if CD4-cell count is < 200 cells/mm\(^3\) and/or there are AIDS-defining illnesses requiring therapy. In other cases, it is advisable to ensure...
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*Integrate initial visit laboratory tests and investigations (as indicated) with all others if the visit occurs after 10 weeks’ gestation.

†HIV genotypic drug testing is recommended at time of first HIV plasma viral load, at time of initiation of antiretrovirals, and if and when treatment fails or viral load suppression is incomplete (> 250 HIV copies/mL).

‡HIV genotypic testing is recommended at baseline or if not previously done before initiating therapy with abacavir.

§Phosphatemia should be monitored in women receiving tenofovir-based regimens because it is a potential cause of tubular toxicity.56-57

∥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).99 If a woman is receiving a PI-based regimen, particularly if initiated before pregnancy, consideration can be given to performing this screening test earlier.

¶Confirm positive result of 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 herpes simplex virus at delivery.

**Group B streptococcus anorectal swab is recommended at 35 to 37 weeks, or sooner if delivery is anticipated within 5 weeks.
Assessment of the status of the woman's HIV, review of antiretroviral drug therapy should be completed during the second trimester. The women's re-evaluation of antiretroviral drug therapy should be reviewed for safety in pregnancy, particularly in the first trimester period of embryogenesis.

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. If necessary, in cases of food insecurity, resources should be offered to improve nutrition. Notably, malnutrition and micronutrient deficiencies have been linked to vertical transmission risk.106 Live vaccines (varicella zoster and measles, mumps and rubella) are contraindicated in pregnancy.107 Women with negative serologies for these infections should be considered for immunization postpartum, depending on their CD4 count, and the schedule of recommended immunization for adults living with HIV should be followed.33 In particular, HBV, pneumococcus, and influenza vaccines can be safely administered in pregnancy. Within a harm reduction model, women should be encouraged to stop smoking, drinking alcohol, and using recreational drugs and should be referred for appropriate counselling support and/or treatment.1,108,109 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 drug therapy should be completed during the second trimester. The women's clinical, virological, and immunologic status including CD4-cell count, HIV viral load, CBC, AST, ALT, LDH, bilirubin, blood urea nitrogen, creatinine, as well as any other blood work as indicated by clinical history and specific cART regimen, should be assessed every 4 to 8 weeks throughout pregnancy (see Table 4). Because comorbidities affect many women living with HIV, more frequent evaluations may be appropriate. Consideration for repeat urine cultures in second and third trimester should be made given the higher rates of hospitalization for urinary tract infections in women living with HIV.110 All women should be screened for gestational diabetes between 24 and 28 weeks as recommended in most recent guidelines.99 As discussed above, there is conflicting evidence on whether cART regimens containing PIs increase the risk of hyperglycemia or new-onset or exacerbated diabetes in pregnancy (see also Appendix 2). If a woman is receiving a PI-based regimen, particularly one initiated before pregnancy, consideration can be given to earlier screening for gestational diabetes.

The second part of the integrated prenatal screening tests (i.e., second trimester biochemical screening) should be performed at 15 to 19 weeks.105 A detailed ultrasound at 18 to 20 weeks is recommended to assess growth and fetal anatomy.105 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 statistical risk of the condition is higher than the risk of the procedure, taking into consideration the biochemical, serologic, and ultrasound results.105 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. In the pre-cART era, the risk of vertical transmission in women who underwent
amniocentesis was twice as high as those who did not (30% vs. 16%, RR = 1.85; 95% CI 0.69–4.98). Since the initiation of cART and the recommendation to treat all pregnant women, there have been no documented transmissions. However, it is impossible to rule out a residual small increase in risk of transmission with amniocentesis in women on cART with a fully suppressed plasma viral load. Non-invasive molecular prenatal testing should be considered as an option to avoid invasive testing.

General obstetrical management with referral of the woman to support services as needed is appropriate at this time. A review of the care providers involved and the delivery plan, including location of delivery, can be initiated at this time (at the 19- to 20-week and 23- to 24-week visits).

**Third Trimester (Weeks 28 to 40)**

The efficacy and toxicity of the particular cART regimen for each woman should be determined by CD4-cell count, HIV viral load, and hematologic, liver, and renal parameters in the third trimester, approximately every 4 to 8 weeks (see Table 4). Given the risk of placental dysfunction associated with increased rates of intrauterine growth restriction and oligohydramnios in the pregnancies of women living with HIV, follow-up growth ultrasound should preferably be done monthly, but 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, 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 pregnancy; however, this is critical in the third trimester because virologic suppression (HIV viral load < 50 copies/mL) should be achieved at this time. If the woman’s viral load has not been suppressed or has appeared to rebound, a number of factors must be considered. Health care providers should reassess overall adherence, clarify any reasons for non-adherence, and attempt to implement strategies or provide tools to assist the woman in taking her medication. Inpatient directly observed therapy may be considered. Clinicians should also reassess dosing adequacy and consider the need for increased dosing of antiretroviral medications in the third trimester. Therapeutic drug level monitoring may also be considered to guide the need for dose adjustment. In all cases viral genotype history should be reassessed and current HIV viral load sample sent for repeat genotyping if applicable.

Between 30 to 35 weeks it is important that a plan for location and mode of delivery is established and 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 post-natal transmission of HIV through breast milk, breastfeeding is not recommended. The risk of disclosure that may arise when a women 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 should also be established at this time (see Postpartum Management).

**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, facilities at her regional hospital, and the comfort and experience of the local care providers. If delivery is being considered outside a regional tertiary care facility, information on pregnancy history and management plans should be provided to the facility prior to the woman’s estimated date of delivery, communication with local care providers should be established, and arrangements should be made to ensure that required intrapartum and postpartum antiretroviral drugs are available at the designated facility.

Mode of delivery has been reviewed extensively with both cohort studies and a randomized controlled trial of intended mode of delivery. The burden of evidence supports a vaginal delivery if obstetrially appropriate and if virologic suppression has been achieved. The initial studies that identified elective Caesarean section as a method to reduce vertical transmission were conducted in women who were not receiving any antiretroviral drug therapy or who received monotherapy with zidovudine only. Evidence to support elective Caesarean section in the current cART era, when all women (even with viral loads < 1000 copies/mL) are recommended to initiate cART in pregnancy, is absent. European surveillance data did not show a significant benefit of elective Caesarean delivery in the cohort of women with undetectable viral loads while on cART. Therefore, the evidence supports elective Caesarean section at 38 weeks to minimize the risk of presentation in spontaneous labour only in women who have an unknown viral load, who have a viral load > 1000 copies/mL, or who are not on cART regardless of viral load. The booking time of 38 weeks for Caesarean section, rather than the usual 39 weeks, is proposed because avoidance of labour in this setting is paramount. Considering the potential complications of operative...
delivery, however, women who receive antepartum cART, are adherent to therapy, and have an HIV viral load < 1000 copies/mL near term (i.e., obtained within 4 weeks of delivery) can be delivered vaginally, reserving Caesarean sections for obstetrical indications only. It is also important to note that the benefit of Caesarean section shown in early studies appears to have been found exclusively in pre-labour elective Caesarean sections; no benefit was shown for emergency Caesarean sections.123

**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 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 Caesarean 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., any antiretroviral therapy, monootherapy only, or with an incompletely suppressed viral load) should be offered a scheduled pre-labour Caesarean section at approximately 38 weeks' 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 the labour and delivery department 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, should be continued for as long as possible during labour. Stavudine should not be administered concomitantly with IV zidovudine because of an antagonistic drug interaction.46 There are no randomized controlled trial data on the additional benefit of intrapartum IV zidovudine in women who have been receiving antenatal cART. A large cohort study of > 5000 pregnant women living with HIV, who received intrapartum IV zidovudine in addition to various (mono, dual, triple) antenatal antiretroviral therapy regimens, reported a significant benefit of IV zidovudine in reducing vertical transmission among those women with HIV viral loads > 10 000 copies/mL (5.3% vs. 22.7%, P = 0.009) at delivery.126,127 However, there was no additional benefit of IV zidovudine reported among women with HIV viral loads < 400 copies/mL at delivery (0.6% vs. 0%, P > 0.99), and data were not provided for women with viral loads from 400 to 9999 copies/mL. Based on this cohort data, the most recent perinatal guidelines published by the NIH in the United States endorse intrapartum IV zidovudine for women living with HIV who are receiving antenatal cART and have an HIV viral load > 400 copies/mL (or unknown viral load) near delivery; however, they do not recommend its administration for those women on cART with an HIV viral load ≤ 400 copies/mL.3 Canadian data, however, show that 8.7% of women with previously suppressed viral load have unpredictably elevated viral loads at time of delivery.128 On the basis of this evidence, intrapartum IV zidovudine (2 mg/kg IV loading dose followed by 1 mg/kg/hour until delivery) continues to remain the standard of care in Canada and is recommended for all women, regardless of mode of delivery, current antiretroviral regimen, or viral load. Intravenous zidovudine 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. If in the future rapid HIV viral load measurements become available on day of delivery, decisions regarding the need for IV zidovudine could be modified.

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 Caesarean section. This recommendation also differs somewhat from that
in the NIH perinatal guidelines,\(^3\) where intrapartum IV zidovudine (but not single-dose oral nevirapine) and combination infant antiretroviral with zidovudine plus 3 doses of nevirapine is recommended for women who were not receiving antepartum antiretroviral therapy (or those with incomplete viral load suppression). However, 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 zidovudine difficult or impossible. Because single-dose oral nevirapine has been demonstrated to reduce vertical transmission of HIV,\(^{2,29}\) it continues to be recommended for intrapartum administration to women living with HIV who have not received antenatal therapy, in addition to administration of cART to their infants. The addition of 7 days of lamivudine-zidovudine postpartum for the mother is recommended in order to mitigate the risk of nevirapine resistance.\(^{31}\)

Mode of delivery has been described in detail above. Elective Caesarean section at 38 weeks of gestation to reduce the risk of vertical transmission of HIV is recommended for women with a viral load > 1000 copies/mL at delivery or those with an unknown viral load (e.g., have not accessed care and/or are not taking antiretroviral drug therapy) near the time of delivery. Importantly, there are limited data to support the benefit of emergency Caesarean section for the purpose of reducing the risk of vertical HIV transmission. 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 Caesarean section is recommended for obstetrical indications, this can be conducted at 39 weeks usual for those indications.

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 transmission.\(^{129–132}\) Extrapolating these data into the present era of cART, it is recommended that interventions that potentially increase fetal exposure, including scalp electrodes, intrauterine catheters,\(^{133}\) prolonged rupture of membranes, operative vaginal deliveries, and episiotomies, should be avoided if possible. However, some Canadian data have been reassuring about the risk of HIV transmission in HIV-suppressed women with prolonged membrane rupture.\(^{133}\) Additional important considerations during the intrapartum period include, among others: epidural anaesthesia is not contraindicated; if a woman is group B streptococcus positive, continue to initiate antibiotic prophylaxis according to protocol; and, if a woman has ruptured membranes and is not in labour, initiate oxytocin induction of labour in addition to intravenous zidovudine (the medications are compatible).

**Intrapartum management for woman 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 with appropriate pre- and post-test counselling. 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 (intravenous zidovudine and single-dose oral nevirapine) plus postpartum zidovudine-lamivudine (Combivir, 1 tablet orally twice daily for 7 days; see Postpartum Management) and infant prophylactic cART (see Infant Management) should be initiated pending results of the confirmatory test. If the confirmatory test is negative, maternal and infant antiretroviral drugs may be discontinued.

It is recommended that all women who have not been tested in pregnancy, particularly those who are recognized to be at high and ongoing risk for HIV infection, be offered HIV testing as soon as possible, with appropriate pre- and post-test counselling. Women involved in ongoing high-risk HIV transmission activities who are HIV negative on initial testing should be retested each trimester,\(^{12}\) and if possible again near term. HIV testing should also occur with the woman’s knowledge and verbal consent, and appropriate pre- and post-test counselling should accompany each 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 (IV zidovudine, single-dose oral nevirapine, Combivir)
antiretroviral drugs therapy should be offered to the woman, and all infants should receive prophylactic antiretroviral therapy pending results (see Infant Management). If the HIV antibody test is negative and the woman is out of the seroconversion period (e.g., has not engaged in high-risk activities within the previous 4 weeks) and/or HIV PCR is negative, infant antiretroviral prophylactic therapy and maternal zidovudine-lamivudine may be discontinued. If the woman at risk is found to be living with HIV, a full 6-week course of infant antiretroviral prophylactic therapy should be completed and the woman should receive a complete 7-day course of oral zidovudine-lamivudine to prevent the emergence of nevirapine-resistant virus. A referral should be made for ongoing HIV assessment and care for both the mother and the infant for all women who are determined to be living with HIV during labour or delivery. Appendix 3 summarizes intrapartum and postpartum recommendations and includes a management algorithm for women known to be living with HIV or in whom HIV infection has not been ruled out.

**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. (II-2B)

**POSTPARTUM MANAGEMENT**

Postpartum care involves collaborative efforts between obstetric care providers, HIV specialists, and other multidisciplinary 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 of substance use.

The use of ergotamine should be avoided because of the risk of exaggerated vasoconstriction in women receiving protease inhibitor therapy. 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. Some studies report higher rates of endometritis and pneumonia following Caesarean section in women living with HIV than in women without, but others do not. Endometritis does, however, occur in a higher percentage of all women following Caesarean section, and routine preoperative prophylactic antibiotics have been demonstrated to decrease postoperative infection. Preoperative antibiotics are therefore recommended for all women who undergo elective or emergent Caesarean section, including women living with HIV, to decrease infectious postoperative complications. 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 zidovudine-lamivudine, 1 tablet orally twice daily, to reduce the risk of developing nevirapine resistance. Zidovudine-lamivudine therapy can be discontinued before completion of the 7-day treatment period if confirmatory HIV testing results show that the woman is not living 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 and support is important.

There is a risk of HIV transmission through breast milk; therefore breastfeeding is contraindicated regardless of maternal antiretroviral therapy or viral load. Management of the effects of not breastfeeding should include measures such as acetaminophen, ibuprofen, and cold compresses to minimize pain from engorgement. Bromocriptine and cabergoline, the classical therapies used for lactation suppression, are ergot derivatives, whose co-administration with PIs 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 advised to pump their breast milk, but they should not feed it to the infant unless a confirmatory HIV test 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 is reported to be as high as 14% as commonly used. 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 for potential interactions between specific antiretroviral agents and oral contraceptives. This information is available in the NIH Perinatal HIV Guidelines and on the Motherisk website. Non-oral contraceptive methods including DMPA (Depo-Provera), contraceptive patch or vaginal ring, and levonorgestrel IUD are also options; however, data for them in combination with antiretroviral medications is not available. The side effect profile of DMPA has been shown to be the same in women living with and without HIV; however, consideration should be given to the bone loss seen in women using DMPA, since bone loss in women living with HIV is already faster than in their uninfected counterparts. Data on copper or levonorgestrel IUD use in women living with HIV are limited, but given the value of this method for successful contraception IUD use in women living with HIV are limited, but given the value of this method for successful contraception and low general rates of infection, use in women with CD4-cell counts > 200 cells/mm\(^3\) is appropriate. Linkage to care is important for all women living with HIV, particularly those who are 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**

Mothers should be offered antiretroviral prophylaxis for their infants regardless of maternal antenatal or intrapartum antiretroviral therapy, viral load, or mode of delivery. The recommended regimen will depend on the presumed level of risk. Infants born to a mother known to be living with HIV and a viral load < 1000 copies/mL should be offered prophylactic therapy with oral zidovudine for 6 weeks. Intravenous zidovudine may be used if the infant is unable to tolerate oral intake. The dose of zidovudine is determined based on gestational age, with a twice-daily dosing regimen now recommended for all infants (see Appendix 4). The infant zidovudine prophylaxis should be started as soon as possible, no later than 6 to 12 hours after birth.

Infants born to a mother known to be living with HIV and who has 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 (this includes a mother who is presumed to be living with HIV based on a positive rapid HIV antibody test result) should receive prophylactic cART with a 3-drug regimen including zidovudine for 6 weeks combined with 3 doses of nevirapine in the first week of life (at birth, day 2, and day 6 of life) and twice-daily oral lamivudine for 2 weeks. This recommendation is made on the basis of the HPTN040/PACTG 1043 trial which enrolled women living with HIV who were not receiving antenatal antiretrovirals and demonstrated that combination regimens had better efficacy (2.2%) in reducing vertical transmission to infants intrapartum than zidovudine alone (4.8%). While this trial does not address whether prophylactic cART provides additional protection against transmission in infants born to mothers who have suboptimal viral suppression near delivery (i.e., > 1000 copies/mL), extrapolation of those results suggests that prophylactic cART should be recommended, particularly in situations involving vaginal delivery. Although the HTPN040/PACTG 1043 trial evaluated a 2-drug zidovudine and nevirapine combination regimen, the addition of a third agent, lamivudine, is recommended in order to prevent the emergence of nevirapine resistance should the infant be infected with HIV. The rationale for this recommendation is to provide a highly active antiretroviral regimen throughout the first 2 weeks of life when nevirapine is expected to be circulating at decreasing but significant levels, due to its very long half-life (median 30 hours, range 18 to 50 hours in newborns). 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; therefore combination infant prophylaxis (with zidovudine, 3-dose nevirapine, and lamivudine) is recommended until confirmatory HIV test results are available. Surveillance and poll-result data reported out of the United Kingdom, Ireland, and United States indicate increasing use of prophylactic cART for infants in high-risk situations. Until HIV-negative status can be confirmed, pumping breast milk, but not feeding it to the infant is recommended.

Dosing recommendations and commercial names for the prophylactic antiretroviral agents are specified in Appendix 4. Of note, hepatic clearance is slower in preterm infants, but pharmacokinetic data informing dosing are limited, particularly in infants with a birth weight below 1.5 kg.
Breastfeeding remains contraindicated for mothers living with HIV regardless of maternal viral load, antepartum cART regimen, and continuation of postpartum antiretroviral therapy. In Malawi, peripartum HIV transmission through breastfeeding was found to be as high as 4% at 48 weeks when mothers were prescribed cART or infants received daily nevirapine prophylaxis versus 7% in the absence of maternal or infant antiretrovirals. Canadian surveillance data and a meta-analysis also show high rates of postpartum virologic rebound due to non-adherence among women who are prescribed ongoing cART.

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, 4 weeks, and 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 up to 18 to 24 months of age. A confirmatory HIV EIA test is recommended to document seroconversion 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 be infected with HIV, antiretroviral prophylaxis should be discontinued, and an urgent referral to an HIV specialist should be made for HIV therapy and comprehensive care. Early initiation of cART has been shown to improve long-term outcomes and may prevent the establishment of viral reservoirs in infected infants.

Infants should also be monitored with a CBC and differential at baseline and at 4 weeks of age. Zidovudine prophylaxis is generally well tolerated, but low grade anemia or neutropenia with elevated platelet count are not uncommon after receipt of 4 weeks of zidovudine prophylaxis. If hemoglobin levels are below 100 g/L and expected to be further decreased with continued zidovudine exposure, early discontinuation of zidovudine prophylaxis at 4 weeks may be considered. Hematologic toxicity may be more common with exposure to cART; however, data are limited. In high-risk newborns receiving cART prophylaxis for the first 2 weeks of life, clinicians should consider obtaining an earlier CBC to monitor for toxicity. There is no evidence for nevirapine associated rash or hepatic toxicity in infants receiving either single-dose or extended-dose nevirapine. Infants rarely present symptoms of mitochondrial toxicity; however, if an infant presents with unexplained neurologic or gastrointestinal symptoms, hepatic function (ALT, AST) and serum lactate should be measured.

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 HIV-exposed uninfected 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. Family physicians and pediatricians play an essential role in identifying and addressing such issues in uninfected HIV-exposed infants and children, and they should facilitate referrals to specialists and developmental resources.

Long-term follow-up of children who were perinatally exposed to HIV and antiretrovirals is recommended into adulthood, due to unknown and theoretical concerns regarding the potential for carcinogenicity of nucleoside analogue antiretroviral drugs or other long-term effects of antiretroviral medications.

Including all HIV-exposed mother-infant pairs in the national surveillance program (CPHSP) is essential to keep generating important epidemiological data and to support continued access to resources for these vulnerable families.

**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 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)

REFERENCES


38. Viread (Tenofovir Disoproxil Fumarate). Foster City, CA; 2012.


Appendix begins on next page
### APPENDIX 1. RECOMMENDATIONS AND MANAGEMENT ALGORITHM FOR WOMEN WITH UNKNOWN HIV STATUS OR ONGOING RISK OF HIV INFECTION

**Indications of High-risk for HIV Infection**
- Self-identifies as being at high risk of HIV
- Sex partner of an HIV-infected person
- Ongoing use of injection drugs or sex with a person using injection drugs
- Diagnosis of a sexually transmitted infection during pregnancy
- Belonging to a population with a high prevalence of HIV (e.g., recent incarceration, recent immigrant, or refugee from an HIV-endemic country)

**Recommendations for Testing**

#### In institutions where rapid HIV antibody testing is NOT available:
1. Contact the provincial centre for disease control to access prenatal HIV serology results. If laboratory results are not available proceed to #2.
2.  
   a. If the woman's HIV status is not available or if she is at ongoing risk of HIV infection since her last serology test result:  
      i. draw STAT HIV EIA (antibody) and send blood (4 mL) in a gold top tube to local CDC laboratory;  
      ii. draw STAT diagnostic HIV PCR test and send blood (4 mL) in an EDTA tube to local CDC laboratory.
   b. If the woman is unavailable for testing:  
      i. draw HIV EIA (antibody) from the infant within 48 hours of age as a first priority and send blood (minimum 2 mL) in a gold top tube to local CDC laboratory;  
      ii. draw diagnostic HIV PCR from the infant within 48 hours of age and send blood (minimum 2 mL) in an EDTA tube to local CDC laboratory.
3. Until HIV test results are known:
   a. Initiate maternal and infant treatment for prevention of HIV vertical transmission.
   b. If any test is positive in mother or infant, refer to local multidisciplinary HIV clinic.
   c. If all HIV EIA and HIV PCR tests drawn are negative in the mother and infant, discontinue all antiretroviral drug therapy.

#### In institutions where rapid HIV antibody testing is available
1. Contact provincial centre for disease control to access prenatal HIV serology results. If laboratory results are not available proceed to #2.
2.  
   a. All women should be offered rapid HIV antibody testing. A protocol for rapid HIV testing should be established in each institution.
   b. For women considered at high risk of HIV with undocumented prenatal HIV serology or who have ongoing risk of HIV since their most recent HIV serology result, also draw a confirmatory prenatal diagnostic HIV PCR test and send blood (4 mL in EDTA tube) and appropriate requisition to local CDC.

**Pre-test discussion points**
Offer information about:
- HIV and the nature of the test;
- the reasons HIV testing is recommended (risk of transmission, long-term health of the woman);
- the expected benefits of testing (treatment of woman and infant, decreased transmission);
- the voluntary nature of testing.
Answer any questions.

**Post-test discussion points**
Inform the woman of the test result.

**Non-reactive (negative test): no antibodies to HIV were detected**
Discuss any needs for harm reduction or further testing and the possibility of acute infection if there was high-risk behaviour in the last 4 weeks (i.e., the implications of the “window period” of infection when antibodies have not yet been produced).
Inform the woman that confirmatory test results will be available in approximately one week.
Inform the woman of treatment recommendations to prevent HIV vertical transmission.
Invalid: test will not work with blood sample provided
Inform the woman:
– that there may be a possibility of infection if high-risk behaviour at any time during pregnancy;
– that confirmatory testing results will be available in approximately one week;
– about treatment recommendations to prevent HIV vertical transmission.

Preliminary reactive (preliminary positive): antibodies to HIV were detected OR indeterminate: unable to interpret result
Discuss with woman:
– the possibility of HIV infection;
– the need for a confirmatory blood test (diagnostic HIV PCR results available in approximately one week);
– immediate treatment recommendations to prevent HIV vertical transmission;
– steps to prevent transmission;
– the follow-up care and support available to her.

Post-test documentation
Notify the local health authority of any preliminary positive result.
Document discussions in the woman’s Health Record.
Ensure contact information for the woman is available in the Health Record.

Recommended intervention based on rapid HIV test result

<table>
<thead>
<tr>
<th>HIGH risk of HIV and undocumented prenatal HIV serology (or ongoing risk of HIV risk since most recent HIV test)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary reactive or Indeterminate or Invalid:</td>
<td>Initiate treatment for prevention of HIV vertical transmission</td>
</tr>
<tr>
<td>Non-reactive but involved in high-risk HIV transmission activity in previous 4-weeks (within possible ‘window’ period of infection):</td>
<td>Initiate treatment for prevention of HIV vertical transmission</td>
</tr>
<tr>
<td>Non-reactive and no identifiable risk within the past 4 weeks</td>
<td>No further intervention.</td>
</tr>
</tbody>
</table>

LOW risk of HIV and undocumented prenatal HIV serology

| Preliminary reactive or Indeterminate | Initiate treatment for prevention of HIV vertical transmission |
| Non-reactive or Invalid | No further intervention |

continued
MANAGEMENT ALGORITHM FOR WOMAN OF UNKNOWN HIV STATUS OR ONGOING HIV RISK
in institutions where rapid HIV antibody test is AVAILABLE
(ZDV = Zidovudine, 3TC = Lamivudine, NVP = Nevirapine)

Unknown HIV status or ongoing HIV risk since last HIV serology was performed
Contact local health services authority to access serology results if available

HIGH HIV risk

Rapid HIV test and diagnostic HIV PCR

Preliminary reactive OR indeterminate OR invalid

Mother: IV ZDV loading dose and infusion during labour
and
Single-dose NVP
and
ZDV-3TC (Combivir®) x 7 days postpartum

Recent high-risk activities in previous 4 weeks?

Yes
No

Infant: ZDV x 6 weeks
and
3-doses NVP (day 0, 2, 6)
and
3TC x 2 weeks

No Therapy

LOW HIV risk

Rapid HIV test

Preliminary reactive OR indeterminate

Mother: IV ZDV loading dose and infusion during labour
and
Single-dose NVP
and
ZDV-3TC (Combivir®) x 7 days postpartum

Infant: ZDV x 6 weeks
and
3-doses NVP (day 0, 2, 6)
and
3TC x 2 weeks

No Therapy

Non-reactive

OR

OR

OR

No

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

APPENDIX 1. Continued

**MANAGEMENT ALGORITHM FOR WOMAN OF UNKNOWN HIV STATUS OR ONGOING HIV RISK**
institutions where rapid HIV antibody test is NOT AVAILABLE
(ZDV = Zidovudine, 3TC = Lamivudine, NVP = Nevirapine)

Unknown HIV status or ongoing HIV risk since last HIV serology was performed
Contact local health services authority to access serology results if available

**HIGH HIV risk**

Mother: STAT HIV EIA (antibody) and diagnostic HIV PCR

Mother: IV ZDV loading dose and infusion during labour

and

Single-dose NVP

and

ZDV-3TC (Combivir®) x 7 days postpartum

Infant: if mother is unavailable for testing:

HIV EIA (antibody) and diagnostic HIV PCR within 48 hr of age

Note: if difficult to obtain sample HIV EIA is priority test

Infant: consider administering combination prophylactic therapy*:

ZDV x 6 weeks

and

3-doses NVP (day 0, 2, 6)

and

3TC x 2 weeks

**LOW HIV risk**

No Therapy

A) If any test is POSITIVE in mother or infant:
Refer to local multidisciplinary HIV clinic

B) If all HIV EIA and HIV PCR tests drawn are NEGATIVE in mother and infant:
DISCONTINUE ALL antiretroviral drug therapy

*Alternative consideration is single agent prophylactic therapy: ZDV x 6 weeks

High risk: self identifies, ongoing injection drug use, sex partner of person infected with HIV or using injection drugs, diagnosis of a sexually transmitted infection during pregnancy, from a population with a high prevalence of HIV (e.g., recent incarceration of refugee from an HIV endemic country)
Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs)

Drugs in this class function as a group of competitive substrate inhibitors that are intracellularly phosphorylated to form the active triphosphate nucleoside moiety and incorporated into HIV DNA, which terminates the action of the reverse transcriptase enzyme and prevents the conversion of viral RNA into DNA.\(^{3,92,151}\) NRTIs are recommended for use as part of combination regimens, which usually include a backbone of 2 NRTIs with the addition of either a non-NRTI (NNRTI) or one or more PIs. The use of single or dual NRTIs alone is not recommended for treatment of HIV infection because rapidly developing resistance outpaces their ability to suppress viral replication for prolonged periods.\(^{2,3}\)

Among this class of drugs the first-line agents for use in the dual NRTI backbone in pregnancy are zidovudine (ZDV) and lamivudine (3TC); alternative agents include abacavir (ABC), emtricitabine (FTC; not available in Canada as a single agent), and tenofovir (TDF). TDF would be a preferred NRTI, in combination with 3TC or FTC, for pregnant women with chronic hepatitis B infection. DDI and stavudine (d4T) are reserved for use only in special circumstances because they are more toxic than other available agents.

Various combinations of NRTIs can be employed. Clinical safety and efficacy data in pregnancy have been most reported for the first-line recommended combination of ZDV and 3TC. This combination is formulated as a fixed-dose combination tablet, Combivir, and is generally well tolerated in pregnancy. It does, however, require twice-daily dosing, and resistance to either ZDV or 3TC is common in antiretroviral-experienced women.\(^{193}\)

Alternative agents or combinations of agents (ABC, FTC, TDF) may be considered in a number of situations including when there is resistance to first-line agents; a woman conceives on an effective treatment regimen containing alternative agents; tolerability is a concern; and regimen simplification is desirable. When selecting combination regimens it is important to consider HIV resistance profiles; the potential for adverse events related to the additive; any co-morbid medical conditions including HBV; concomitant medications and the potential for drug-drug interactions; and convenience of dosing. Two notable combinations that should be avoided are d4T in combination with ZDV, because they have competing intracellular mechanisms of activation,\(^{124}\) or d4T with DDI, because the combination has a higher reported risk of a potentially fatal lactic acidosis and hepatic steatosis reaction.\(^{194}\)

NRTI pharmacokinetics are similar in pregnant and non-pregnant women and dosing adjustments are not required in pregnancy. All NRTIs, with the exception of DDI, readily cross the placenta and have high cord-to-maternal blood ratios greater than 0.60.\(^{3,41}\)

All NRTI agents are categorized as either FDA pregnancy category B (TDF, DDI) or C, and none have been demonstrated to be associated with any known human teratogenic syndrome in pregnancy. Although not considered to be a teratogen, animal studies have demonstrated that chronic administration of high doses of TDF to pregnant monkeys has resulted in a slight reduction in fetal bone porosity. Continued administration of high dose TDF to infant monkeys (and other species) has resulted in reversible bone abnormalities ranging from reduction in bone mineral density to severe pathologic osteomalacia. Evidence of renal toxicity has also been observed in newborn monkeys given high doses of TDF.\(^{4,41,54}\) Because of the limited data on use in human pregnancy and concern regarding potential fatal effects and nephrotoxicity, TDF is recommended as an alternative (vs. first-line) drug for use in pregnancy, unless the woman is co-infected with HBV.\(^{3}\)

Additional Considerations in Pregnancy

Bone marrow toxicity is a concern with the NRTIs. In the ACTG 076 study there were no significant toxicities noted in the women who received ZDV monotherapy;\(^{18}\) and in short and longer term follow-up studies (up to 5 years of age post in utero exposure) transient anemia in the neonate is the only significant adverse effect reported.\(^{71-79}\) Overall, transient and mild hemoglobin reductions have been observed in most infants exposed to antiretroviral drugs and these resolve by age 3 to 6 months after discontinuation of antiretroviral prophylaxis.\(^{92,151}\)

In utero exposure to cART appears to be associated with increased severity of anemia. Neutropenia and/or lymphopenia have also been reported, with resolution at age 8 to 24 months.\(^{3,92,151}\) The clinical significance of this is not established and there is no evidence of an increase in antibiotic use or an increase in the frequency or severity of infections in these infants.\(^{193,196}\)

Mitochondrial toxicity/dysfunction has been reported. NRTIs are able to bind to mitochondrial gamma DNA polymerase in different organ systems, resulting in mitochondrial toxicity.\(^{25,106}\) The clinical effects in adults can include myopathy, bone marrow suppression, pancreatitis, peripheral neuropathy and hepatic steatosis. Serum lactate, which accumulates when mitochondrial function is significantly altered, has been used as an indirect marker of mitochondrial toxicity. Mitochondrial toxicity has been most strongly associated with d4T, DDI, zalcitabine (no longer marketed in Canada), and ZDV.\(^{25}\) As described above, the combination of d4T and DDI should be avoided because of a higher incidence of fatal lactic acidosis in people receiving cART; it is unknown whether pregnancy increases the risk further.\(^{151}\) Data for an association between mitochondrial dysfunction and in utero exposure to NRTI therapy are conflicting. In the French Pediatric Cohort study, the total incidence of clinical symptoms of mitochondrial dysfunction at 18 months was 0.26% (95% confidence interval [CI] 0.10 to 0.54) in exposed children compared with 0.01% in the general population, and the mortality rate was 0.07%.\(^{198}\) These findings have not been duplicated in other studies,\(^{31,109,203}\) and severity of maternal illness has been identified as a potential confounding factor.\(^{201,202}\) Antiretroviral-exposed infants may have transiently elevated lactic acid levels for up to 6 months; however, the clinical significance of this has not been determined.\(^{70,77}\) Overall, it appears that severe clinically evident mitochondrial diseases secondary to in utero antiretroviral exposure are likely to be rare.

Abacavir hypersensitivity—ABC has been associated with a severe, potentially fatal hypersensitivity reaction.\(^{45,203}\) Testing for carriage of the HLA-B*5701 allele identifies patients at risk of reaction, and patients with the allele should not be given ABC.\(^{46}\) Re-challenge with ABC in patients who have experienced ABC hypersensitivity is contraindicated. To date, there is no evidence that in utero exposure to ABC increases the risk of any hypersensitivity reaction in the infant.
Non-Nucleoside Reverse Transcriptase Inhibitors

Drugs in this class 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.135 NNRTIs are recommended for use in pregnancy in combination with a dual NRTI backbone.

Initiation of nevirapine (NVP) is not recommended in pregnancy because of the risk of potentially fatal rash and hepatotoxicity. Women who are tolerating NVP and who become pregnant may continue taking NVP. While a preferred agent in the non-pregnant adult, efavirenz (EFV) is contraindicated in the first trimester of pregnancy because of its association with neural tube defects in primates and in case reports in humans.40 However, if given inadvertently during this period, the overall risk posed by EFV is low; ultrasound evaluation of neural tube closure should be done to guide counselling on fetal status. The use of EFV in later trimesters should be reserved for when other agents cannot be used or are not tolerated. Currently available safety and pharmacokinetic data are insufficient to support the use of etravirine (ETR) or rilpivirine (RPV) in pregnancy.

NNRTI pharmacokinetics are similar in pregnant and non-pregnant women, and dose adjustments are not required in pregnancy. The extent of placental transfer varies within the class, ranging from high with NVP (which also rapidly crosses the placenta) to moderate with EFV. The extent of placental transfer with the newer NNRTIs, ETR, and RPV, is currently unknown.

Teratogenicity data for NNRTIs is more limited and variable than for NRTIs. There is no evidence of animal or human teratogenicity with NVP (FDA pregnancy category B), and no evidence of teratogenicity in animals with ETR or RPV (FDA pregnancy category B); however, there is very limited information on these agents in human pregnancy.3,41

Effavirenz, however, is classified as FDA pregnancy category D, and should not be used in the first trimester of pregnancy. Non-pregnant women who are receiving EFV should be counselled to avoid pregnancy. Central nervous system malformations including anencephaly, cleft palate, and anophthalmia were reported in 3 of 20 (15%) of monkeys exposed to efavirenz plasma concentrations similar to human therapeutic concentrations in the first trimester.41 While the Antiretroviral Pregnancy Registry has reported a birth defect incidence of only 2.7% (comparable to the baseline population risk),41 there have been a total of 7 (1 prospective, 6 retrospective) reported cases of central nervous system defects, including 3 cases of meningomyelocele, in humans following first trimester EFV exposure.4,41 Meta-analysis of cohort studies reporting first trimester EFV exposure in 1437 women did not detect an increased risk of birth defects.42 However, a report from a large French perinatal cohort did find a significant association between exposure to EFV in the first trimester and neurological defects.43

Additional Considerations in Pregnancy

Nevirapine (NVP) has been reported to cause severe, life threatening and in some cases fatal hepatotoxicity and hypersensitivity skin reactions.203,204 The risk of toxicity is higher in women than men; however, it does not appear that pregnancy increases the risk.3,195,204 There are data to suggest that the greatest risk of toxicity occurs during the first 6 to 18 weeks of therapy and increases approximately 10-fold when NVP is initiated at baseline CD4-cell counts greater than 250 cells/mm3.3,195,204 However, a Canadian study found that toxicity occurred at a wide range of CD4-cell counts in women exposed to NVP for the first time in pregnancy.52 Neither rash nor hepatotoxicity have been reported in women or infants receiving intrapartum single-dose or extended-dose NVP therapy for prevention of vertical transmission.22,205 As described above, NVP should not be initiated in pregnancy regardless of CD4-cell count; however, women who become pregnant while receiving and tolerating NVP may continue without interruption.

Protease Inhibitors

Drugs in this class function as competitive inhibitors that bind to the HIV protease enzyme and prevent the conversion of HIV viral particles into mature infectious forms.153 PIs are recommended in pregnancy in combination with a dual NRTI backbone. Individual PIs are most commonly administered together with low-dose ritonavir (r), which functions as a pharmacokinetic booster to increase serum drug levels of the first PI.

Short-term studies have demonstrated the safety and tolerance of the co-formulated combination of lopinavir/ritonavir (LPV/r), and as a result of this and clinical experience with its use, LPV/r is considered the first-line agent for use in pregnancy. Alternative agents for use include boosted atazanavir (ATV/r), which has growing short-term safety and efficacy data in pregnancy; boosted darunavir (DRV/r), and boosted saquinavir (SQV/r), which has also been shown to be well tolerated and safe in short-term studies, but requires a baseline electrocardiogram prior to the start of therapy. Because of associated adverse effect profiles and/or pharmacokinetic limitations in pregnancy, boosted indinavir (IDV/r) and nevirapine (NVP) should be reserved for use in special circumstances when other agents cannot be used. Current data in pregnancy are insufficient to recommend use of the newer agents including boosted fosamprenavir (FPV/r) or tipranavir (TPV/r).

The pharmacokinetics of PIs are variable in pregnancy, particularly in the second and third trimester. Current data suggest that exposure to LPV/r, ATV, and NVP is decreased during the second and third trimesters. However, the clinical significance of reduced exposure to antiretroviral drugs during pregnancy is not clear. The need for a dose increase in pregnancy will depend on the treatment experience of the specific woman, the use of concomitant interacting medications (e.g., TDF or histamine receptor antagonists with ATV), and virologic response to the prescribed dose throughout pregnancy. HIV viral load must be followed closely, particularly in the second and third trimesters, to ensure virologic failures due to increased plasma volumes, and subsequent reduced PI concentrations, do not occur. Consideration should be given to a PI dose increase in this situation. 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 PI dose adjustment.51 All PIs have minimal to low placental transfer to the fetus, with cord-to-maternal blood ratios < 0.3. All PIs are classified as FDA pregnancy category B or C. None of the PIs have been demonstrated to cause gross structural abnormalities in animals; however, minor skeletal variations (e.g., increase in supramaxillary ribs, ossification delays) and growth inhibition has been reported with high dose ritonavir (RTV), IDV, TPV/r, and FPV. The majority of PIs have not been demonstrated to be teratogenic in human studies; however, data with the use of DRV, FPV or TPV/r in human pregnancy are limited.3,41
Additional Considerations in Pregnancy

**Preterm delivery** could be a greater risk with combination antiretroviral therapy (vs. none, mono or dual NRTI therapy), but evidence to date is conflicting. Some studies have suggested an approximate 2-fold increase risk of preterm delivery (<37 weeks) with combination antiretroviral therapy than with no treatment, particularly when therapy is initiated prior to pregnancy versus in the third trimester. A 2007 meta-analysis of 14 published clinical studies suggested that combination regimens that include a PI (vs. no PI) may be at highest risk of preterm delivery, and data from the Antiretroviral Pregnancy Registry has suggested an increase in low birth weight infants since the introduction of combination therapy, with PI-containing regimens identified as a significant risk factor. Other studies, however, have not detected an association between antepartum antiretroviral therapy or PI use and preterm delivery or low birth weight infants. Overall, data to suggest an association between in utero antiretroviral therapy (including PI use) and prematurity or low birth weight infants are mixed. However, a causal relationship has not been established, and PIs should not be withheld because of the possibility of an increased risk of preterm delivery.

**Glucose intolerance/diabetes** could be a greater risk with combination antiretroviral regimens containing PIs in pregnancy, but evidence is conflicting. The risk of glucose intolerance was reported to be increased by PIs in one retrospective study, but was not observed in others. Secondary analysis of data from 2 prospective cohorts found an increased risk of gestational diabetes only when PIs were initiated prior to pregnancy or during the first trimester. Overall, it is recommended that women living with HIV and taking antiretroviral drugs during pregnancy should receive standard glucose screening (i.e., 1 h 50 g glucose loading test at 24–28 weeks’ gestation); if a woman is receiving a PI-based regimen, particularly if initiated before pregnancy, the clinician may choose to perform this screening test earlier.

**Hyperbilirubinemia** commonly occurs in patients, including pregnant women, who receive the PIs ATV and IDV. These agents increase indirect (unconjugated) bilirubin from directly inhibiting uridine diphosphate-glucuronosyl transferase (UGT), the enzyme responsible for the conversion of indirect to direct (conjugated) bilirubin. There is a theoretical concern that in utero exposure to IDV or ATV may exacerbate physiologic hyperbilirubinemia in neonates as a result of the transfer of indirect bilirubin from the mother and/or a direct transplacental drug effect on bilirubin metabolism in the fetus. Hyperbilirubinemia has been observed in neonates following in utero exposure to atazanavir; however, there is no evidence of severe hyperbilirubinemia elevations or clinical signs of acute or chronic bilirubin encephalopathy. Exacerbation of physiologic neonatal hyperbilirubin has not been reported with in utero exposure to IDV. It is recommended that all infants exposed to ATV (and IDV) should be monitored for development of hyperbilirubinemia in the first few days of life.

**Postpartum hemorrhage** should not be managed with ergot derivatives (e.g., ergonovine maleate), because the combined use of this drug class with PIs may result in serious and potentially life threatening vasoconstriction reactions characterized by peripheral vasospasm and ischemia of the extremities and other tissues. Other alternatives including oxytocin and/or prostaglandins may be used if required.

**Entry (fusion) Inhibitors**

This class of drugs includes 2 agents, enfuviride and maraviroc, that act extracellularly to prevent HIV from attaching to the target cell surface and entering the host target cell. Enfuviride binds to glycoproteins (gp41) on the viral surface to inhibit virus–cell membrane fusion. Maraviroc prevents virus binding to the CCR5 co-receptor on host cells to prevent the entry of virus into the cell. Because HIV can use other co-receptors, such as CXCR4, an HIV tropism test must be performed to determine whether maraviroc will be effective.

Current data is insufficient to recommend the use of fusion inhibitors in pregnancy. Data regarding their pharmacokinetics in pregnancy are minimal, and it is not known whether dose adjustments are required. Placental transfer to the fetus is also unknown. Both agents are classified as FDA pregnancy category D because animal studies have not demonstrated any evidence of teratogenicity; however, there is no (maraviroc) or very limited (enfuviride) experience of their use in human pregnancy.

**Integrate Inhibitors**

This class of drugs includes 2 agents, raltegravir and elvitegravir (EVG), that 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). Elvitegravir is currently only available as part of a fixed-dose combination tablet with the pharmacokinetic enhancer cobicistat (COBI) and the NRTIs tenofovir and emtricitabine (TDF 300 mg/FTC 300 mg/EVG 150 mg/COBI 150 mg).

Current data are insufficient to recommend the use of integrate inhibitors in pregnancy. No pharmacokinetic data or placental transfer information is available for elvitegravir-cobicistat. Limited pharmacokinetic data suggest that although raltegravir shows extensive variability in the third trimester, postpartum and historical data show consistent exposure, and standard dosing appears appropriate in pregnancy. Case report data suggest a high placental transfer rate to the fetus, with a reported cord-to-maternal blood ratio of approximately 1.0.

Raltegravir is classified as FDA pregnancy category C; animal studies have not found evidence of gross developmental abnormalities; however, increases in the incidence of supernumerary ribs have been observed in rats receiving raltegravir doses 3 times the recommended human dose. There is only limited experience with raltegravir in human pregnancy; case report data show the addition of raltegravir in the third trimester to rapidly decrease viral load at the time of delivery. Elvitegravir and cobicistat (as components of the combination antiretroviral Stribild®) are classified as FDA pregnancy category B; animal studies have not shown evidence of teratogenicity or gross structural abnormalities. There are no reported data in human pregnancies.
This Appendix applies to women with known HIV infection, to women with potential HIV infection based on rapid HIV antibody test results, and (when rapid HIV antibody testing is not available) to women considered at high risk of HIV infection, but whose HIV status is unknown.

1. **Maximal confidentiality** of the woman’s HIV status should be maintained.

2. **Standard universal precautions** should be undertaken for protection from blood and bodily fluids (use gown, mask, eye protection, and gloves during delivery) according to details available in an infection control manual. No additional precautions are required.

3. **Laboratory tests**:
   a. On admission, tests should be performed for
      • CBC, differential, creatinine, urea, AST, ALT, bilirubin, and glucose;
      • HIV viral load; and
      • CD4-cell count.
   b. Performance of prenatal blood tests, including HBV and HCV serology, RPR, rubella, and varicella IgG, should be verified.
   c. The placenta should be sent to pathology for examination after delivery.
   d. Appropriate blood test results should be obtained for any study in which the woman has previously consented to participate.

4. **General management of labour and delivery**:
   a. Epidurals are not contraindicated.
   b. Artificial rupture of membranes should be avoided unless necessary for obstetrical management.
   c. Prolonged rupture of membranes should be avoided if possible.
   d. Oxytocin should be administered as per protocol if there is rupture of membranes and the woman is not in labour.
   e. The use of scalp electrodes, fetal scalp sampling, or intrauterine pressure catheters should be avoided unless absolutely necessary.
   f. Intermittent auscultation or external fetal monitoring should be used based on usual obstetrical guidelines for fetal surveillance.
   g. Group B streptococcus prophylaxis should be offered as per standard guidelines.
   h. Because of the risk of exaggerated vasoconstriction in women receiving PIs, ergonovine maleate should be avoided in the management of postpartum hemorrhage.

5. **Mode of delivery** should be discussed in detail with women known to be living with HIV.
   a. Women on optimal antenatal antiretroviral therapy with a recent (within last 4 weeks) HIV viral load ≤ 1000 copies/mL are recommended to have a **vaginal delivery** if obstetrically appropriate and the woman was adherent to antenatal antiretroviral therapy.
   b. Women not on optimal antiretroviral therapy (e.g., no antenatal antiretroviral therapy or with a recent [within last 4 weeks] HIV viral load or projected viral load > 1000 copies/mL) should be offered a **pre-labour Caesarean section** at approximately 38 weeks of completed gestation. If the woman is in labour or there has been rupture of membranes, Caesarean section has not been shown to reduce transmission.

6. **Antenatally prescribed antiretroviral therapy** should usually be continued for as long as possible during labour; however, oral stavudine (d4T or Zerit) should be discontinued because of its antagonistic interaction with intravenous zidovudine.

7. **Intrapartum antiretroviral therapy** should be initiated
   • with rupture of membranes at any time;
   • with onset of labour—spontaneous or induced, even if preterm;
   • at induction of labour if rapid progression is anticipated;
   • at least 2 hours prior to planned Caesarean section; and
   • in any situation when delivery is anticipated.
   a. All women throughout labour and delivery, regardless of their antepartum antiretroviral regimen and mode of delivery, should be given
      • zidovudine 2 mg/kg IV loading dose over 1 hour, followed by
      • zidovudine 1 mg/kg/hr IV infusion until delivery.
      If the labour stops and the infusion is discontinued for greater than 6 hours, the loading dose should be re-administered and continuous infusion resumed when labour recommences.
   b. Women who did not receive any antenatal antiretroviral therapy during pregnancy should also be given one single-dose of nevirapine 200 mg orally as soon as possible at onset of labour or presentation to labour/delivery suite.

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**APPENDIX 3. SUMMARY OF RECOMMENDATIONS AND MANAGEMENT ALGORITHM FOR WOMEN WITH KNOWN HIV INFECTION OR WOMEN IN WHOM HIV INFECTION HAS NOT BEEN RULED OUT**

This Appendix applies to women with known HIV infection, to women with potential HIV infection based on rapid HIV antibody test results, and (when rapid HIV antibody testing is not available) to women considered at high risk of HIV infection, but whose HIV status is unknown.
8. *Postpartum antiretroviral therapy*
   a. Women who have been receiving antenatal antiretroviral therapy should have their complete regimen resumed after delivery as soon as oral intake is tolerated, unless otherwise indicated.
   b. Women who have not been receiving antenatal antiretroviral therapy but have received single-dose nevirapine during labour should receive 7 days of Combivir (zidovudine-lamivudine), 1 tablet orally twice daily, to reduce the risk of the development of nevirapine resistance. An adult HIV care provider should be consulted to determine the need to continue the therapy or begin an alternate antiretroviral regimen.

9. *Prophylaxis against opportunistic infections* should be offered to women who are immunocompromised.

10. *Assessment and discussion* of contraception, mental health, need for social services, or treatment of substance use indicated should be undertaken prior to discharge.

11. *Breastfeeding* is contraindicated in women with known HIV infection regardless of maternal antiretroviral therapy and viral load. In women in whom HIV infection has not been ruled out, breast milk pumping and avoidance of breast milk infant feeding is recommended until HIV negative status is confirmed.

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**APPENDIX 3. Continued**

**MANAGEMENT ALGORITHM FOR HIV INFECTED WOMAN AND HER INFANT**

(†VL = viral load, ART = antiretroviral therapy, ZDV = Zidovudine, 3TC = Lamivudine, NVP = Nevirapine)

- **Mother**
  - **Received antenatal ART and VL ≤ 1000 copies/mL**
    - Continued combination antenatal ART
    - IV ZDV loading dose and infusion during labour
  - **Received antenatal ART but VL > 1000 copies/mL (known or projected)**
    - Continue combination antenatal ART
    - IV ZDV loading dose and infusion during labour
    - Caesarean section if not in active labour
  - **Did not receive ART in pregnancy**
    - IV ZDV loading dose and infusion during labour
    - Single-dose NVP and ZDV-3TC (Combivir®) x 7 days postpartum
    - Caesarean section if not in active labour

- **Infant**
  - **ZDV x 6 weeks**
  - **Combination ART:**
    - ZDV x 6 weeks and 3-doses NVP (day 0, 2, 6) and 2-weeks 3TC

*Use of combination ART for prophylaxis may be warranted in circumstances when infant is born to a mother with poor adherence to antenatal ART and/or with non-suppressed VL (i.e., VL 40-999 copies/mL) particularly when delivered vaginally. Consult with pediatrician with expertise in HIV.*
This Appendix applies to infants born to mothers with known HIV infection, mothers with potential HIV infection based on rapid HIV antibody test result, and mothers considered at high risk of HIV infection but with unknown HIV status when rapid HIV antibody test is not available.

1. **Maximal confidentiality** of the woman’s HIV status should be maintained.

2. **Standard universal precautions** should be undertaken for protection from blood and bodily fluids (use gown, mask, eye protection, and gloves during delivery) according to details available in an infection control manual. No additional precautions are required.

3. **Wash injection site** prior to intramuscular injections or blood sampling.

4. **Breastfeeding** is contraindicated in women with known HIV infection regardless of maternal antiretroviral therapy and viral load. In women in whom HIV infection has not been ruled out, breast milk pumping and avoidance of breast milk infant feeding is recommended until HIV negative status is confirmed.

5. **Prophylaxis** should be offered to prevent HIV vertical transmission to the infant, whether or not the mother received antiretroviral therapy at delivery.
   a. All infants should be given oral or intravenous zidovudine beginning immediately after birth. Oral therapy is preferred, but if the infant is unable to tolerate oral feeds, intravenous therapy may be used.

### Zidovudine (ZDV, AZT, Retrovir) Dosage

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Recommended (twice daily dosing for all infants)</th>
<th>Alternate (three times daily dosing for preterm infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term (≥ 35 weeks’ gestation)</td>
<td>ZDV 4 mg/kg/dose PO every 12 hours for 6 weeks or ZDV 3 mg/kg/dose IV* every 12 hours</td>
<td>ZDV 2 mg/kg/dose PO (or 1.5mg/kg/dose IV*) every 12 hours for 2 weeks, then every 8 hours until 6 weeks.</td>
</tr>
<tr>
<td>30–34 weeks’ gestation</td>
<td>ZDV 2 mg/kg/dose PO every 12 hours for 2 weeks, then 3 mg/kg/dose PO every 12 hours until 6 weeks or ZDV 1.5 mg/kg/dose IV* every 12 hours for 2 weeks, then 2.3 mg/kg/dose IV* every 12 hours until 6 weeks.</td>
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<tr>
<td>≤ 29 weeks’ gestation</td>
<td>ZDV 2 mg/kg/dose PO every 12 hours for 4 weeks, then 3 mg/kg/dose PO every 12 hours until 6 weeks or ZDV 1.5 mg/kg/dose IV* every 12 hours for 4 weeks, then 2.3 mg/kg/dose IV* every 12 hours until 6 weeks.</td>
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</tbody>
</table>

*Use IV formulation only when the infant is unable to tolerate oral feeds.

b. Combination antiretroviral therapy with nevirapine and lamivudine (in addition to zidovudine) is given to infants born to mothers who were not on optimal antiretroviral therapy (e.g., received no antenatal antiretroviral therapy) or with a recent HIV viral load (measured within last 4 weeks) or projected HIV viral load greater than 1000 copies/mL.

**Note:** For infants born to mothers considered at high risk of HIV infection, but with unknown HIV status, when the rapid HIV antibody test is not available prophylaxis with only single agent zidovudine may still be considered.

### Nevirapine Dosage

Nevirapine dosage (there is no IV formulation available):

- Infant > 2 kg: 12 mg PO for a total of 3 doses. First dose given immediately after birth (day 0), second dose given at 2 days of age, third dose given at 6 days of age.
- Infant 1.5–2 kg: 8 mg PO for a total of 3 doses. First dose given immediately after birth (day 0), second dose given at 2 days of age, third dose given at 6 days of age.

### Lamivudine (3TC) Dosage

Lamivudine (3TC) dosage (there is no IV formulation available):

- Infant > 2 kg: 6 mg PO every 12 hours for 2 weeks.
- Infant 1.5–2 kg: 4 mg PO every 12 hours for 2 weeks.

6. **Laboratory tests** to be ordered within 48 hours after birth:
   - CBC, differential, creatinine, urea, AST, ALT, bilirubin
   - For infants born to mothers with known HIV infection or potential HIV infection based on rapid HIV antibody testing, infant diagnostic HIV PCR should be performed with blood (minimum 2 mL in EDTA tube) and appropriate requisition sent to the local CDC.
For infants born to mothers with unknown HIV status (where rapid HIV antibody testing is not available), HIV EIA (antibody) is the priority test over HIV PCR if a blood sample from the infant is difficult to obtain. Blood (minimum 2 mL in gold top tube) and appropriate requisition should be sent to the local CDC. Infant diagnostic HIV PCR should be conducted within 48 hours, with blood (minimum 2 mL in EDTA tube) and appropriate requisition sent to the local CDC.

7. **Check maternal hepatitis B status.** If the mother tests positive for hepatitis B surface antigen or has unknown status, administer first dose of hepatitis B vaccine and hepatitis B immune globulin to the infant within 12 hours after birth.

8. **The remainder of the zidovudine** bottle should be supplied to the parent/guardian on discharge to treat the infant for the entire 6-week course. If nevirapine and lamivudine (3TC) are required for the infant, adequate medication should be provided to the parent/guardian on discharge from hospital to complete the treatment course.

9. **Infants born to mothers considered at high risk of HIV infection,** but with unknown HIV status (when the rapid HIV antibody test is not available) should be referred to the local multidisciplinary HIV clinic if any HIV test (HIV EIA or HIV PCR) drawn is positive in mother or infant. If all HIV tests (HIV EIA and HIV PCR) drawn are negative in both mother and infant all antiretroviral drug therapy may be discontinued.

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### APPENDIX 4. Continued

<table>
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<tr>
<th><strong>For infants born to mothers with unknown HIV status (where rapid HIV antibody testing is not available), HIV EIA (antibody) is the priority test over HIV PCR if a blood sample from the infant is difficult to obtain. Blood (minimum 2 mL in gold top tube) and appropriate requisition should be sent to the local CDC. Infant diagnostic HIV PCR should be conducted within 48 hours, with blood (minimum 2 mL in EDTA tube) and appropriate requisition sent to the local CDC.</strong></th>
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