
**BRITISH COLUMBIA GUIDELINES FOR THE CARE OF
HIV POSITIVE PREGNANT WOMEN AND
INTERVENTIONS TO REDUCE PERINATAL
TRANSMISSION**

July 23, 2013

TABLE OF CONTENTS:

Summary of recommendations

Introduction

I. Background

II. Preconception planning

III. New diagnosis of HIV in a pregnant woman

IV. New diagnosis of pregnancy in a known HIV positive woman

V. Recommendations for Antiretroviral Drug Therapy During Pregnancy

VI. Antepartum management

VII. Intrapartum management

VIII. Postpartum management

IX. Infant management

Other Guidelines

Contact List

Appendices

Acknowledgements

Principal Authors

References

SUMMARY OF RECOMMENDATIONS

1. All HIV infected women who are planning a pregnancy or become pregnant should have their individual situation discussed with experts in the area with referral to both HIV treatment programs and obstetrical care providers, and an overall plan for pregnancy care made. (Level II-2A)
2. All pregnant women should be offered HIV testing, with appropriate pre and post-test counseling as part of their routine prenatal care in each pregnancy. This test should be repeated in each trimester in women who are recognized to be at high and ongoing risk for HIV infection. (Level II-2A)
3. HIV infected pregnant women should be made aware that with the consistent use of combination antiretroviral therapy and by abstaining from breastfeeding the risk of perinatal transmission is <1%. (Level I-A)
4. All HIV infected pregnant women should be treated with combination antiretroviral therapy regardless of baseline CD4 and viral load. (Level II-2A).
5. Antiretroviral therapy should not be discontinued during the first trimester for obstetrical reasons, but if not on therapy, and no immediate medical indication for urgent cART, then therapy can be delayed until after 14 weeks gestation. (Level III-B)
6. All HIV-infected women (Antiretroviral exposed women with detectable viral load, and antiretroviral-naïve) should have genotyping (and if possible phenotypic resistance testing) of their virus in order to assist in optimizing antiretroviral therapy. It is advisable to discuss interpretation of genotype testing and antiretroviral therapy changes with experienced clinicians. Testing for HLA B5701 is recommended if not done previously, (in case abacavir use will be required). (Level II-2B).
7. A combination antiretroviral therapy regimen including a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one of more NRTIs with addition of a boosted protease inhibitor should be favored, due to higher confidence of safety and efficacy in pregnancy. Whenever possible, antiretrovirals known to cross the placenta to the fetal compartment should be utilized. (Level II-2B)

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8. Avoid whenever possible drugs with no safety data during the period of organogenesis. Efavirenz (Sustiva®/Atripla®) should not be deliberately prescribed in the first trimester of pregnancy due to its possible teratogenicity. However if exposure has occurred and the timing of neural tube closure is passed, then efavirenz can be continued. Nevirapine should not be started in pregnancy unless required based on resistance patterns due to the high rate of serious adverse outcomes in this situation. Ongoing, pre-pregnancy treatment with nevirapine can be continued through pregnancy if tolerance and efficacy established.(Level II-3B)
 9. If antiretroviral therapy is discontinued for any reason during pregnancy, discontinue all drugs at once, and resume all drugs simultaneously to minimize the risk of viral resistance developing on therapy (unless on NNRTI, then a tail of 2 NRTI is recommended for 1 week). Resume antiretroviral therapy as quickly as possible after discontinuing, to minimize the risk of rebound viremia, and potentially increased risk of vertical transmission. (Level II-1A)
 10. If a pregnant woman has significant nausea of pregnancy, do not begin antiretroviral therapy until nausea is adequately controlled. Most anti-nauseants 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 on NNRTI, then a tail of 2 NRTI is recommended for 1 week to prevent future NNRTI resistance). (Level II-2B)
 11. Therapy should be individualized in order to maximize adherence to the prescribed antiretroviral regimen. (Level III-A)
 12. Routine dose adjustment of the combination antiretroviral therapy is not recommended in pregnancy. (Level III –B)
 13. The woman’s clinical, virologic and immunologic status should be assessed every 4-8 weeks, and again 6 weeks post partum. Routine criteria of response to and failure of antiretroviral therapy should be employed. Toxicity to the antiretrovirals should also be monitored at these times. Specific

testing should be individualized to the known toxicities of the woman's antiretroviral therapy regimen. (Level III-B)

14. All HIV infected pregnant women, 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. (Level III-A)
15. A detailed obstetrical ultrasound at 19-20 weeks of gestation is recommended. Additional ultrasounds, for fetal growth and amniotic fluid volume, are recommended (at least each trimester, or as guided by obstetrical indications). (Level II-3B)
16. As for all pregnant women, HIV positive women should be screened periodically for substance use and drug addiction should be addressed in conjunction with HIV management as needed (Level 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 1,000 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 C-section). If caesarian section is recommended for obstetrical indications, this can be conducted at 39 weeks as per usual indications. (Level I-A)
 - b. Women not on optimal antiretroviral therapy (e.g. no antiretroviral therapy, monotherapy only, or with incompletely suppressed viral load) should be offered pre-labour scheduled caesarian section at approximately 38 weeks of completed gestation. (Level II-2A)
18. Intravenous zidovudine should be initiated as soon as labor onset until delivery, in addition to oral combination antiretroviral regimen, regardless of mode of delivery, current antiretroviral regimen or viral load. (Level III-B)
19. Intrapartum single dose of oral nevirapine (200mg) remains an option for the unusual circumstance of a woman who is HIV positive and not received antenatal antiretroviral therapy in pregnancy. (Level II-B)

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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 adult HIV care providers. (Level II-1A)
 21. HIV exposed newborns should receive antiretroviral therapy for 6 weeks to prevent vertical transmission of HIV. (Level I-A)
 22. Health care practitioners who care for HIV-exposed newborns should provide timely diagnostic HIV testing (HIV PCR at birth, 1 month and 3-4 months and HIV serology at 18 months) (Level II-A) and should monitor both short- and long-term outcomes, including screening for adverse effect of antiretroviral therapy and development delay. (Level III-A).
 23. Breast-feeding is not recommended irrespective of plasma HIV viral load and use of antiretroviral therapy. (Level I-A)
 24. Registration of the pregnancy with surveillance programs should be done to allow for collection of provincial and national data to guide future pregnancy policies (Canadian Perinatal HIV Surveillance Program – CPHSP). In addition, any woman undergoing antiretroviral therapy in pregnancy should be offered inclusion in appropriate studies when available. (Level III-B)

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

Quality of Evidence Assessment*	Classification of Recommendations‡
<p>I: Evidence obtained from at least one properly randomized controlled trial</p> <p>II-1: Evidence from well-designed controlled trials without randomization</p> <p>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group</p> <p>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 the category</p> <p>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees</p>	<p>A. There is good evidence to recommend the clinical preventive action</p> <p>B. There is fair evidence to recommend the clinical preventive action</p> <p>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</p> <p>D. There is fair evidence to recommend against the clinical preventive action</p> <p>E. There is good evidence to recommend against the clinical preventive action</p> <p>L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making</p>
<p>* 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.</p> <p>‡ Recommendations included in these guidelines have been adapted from the Classification of recommendations criteria described in The Canadian Task Force on Preventive Health Care.</p>	

INTRODUCTION

Supportive non-directive counseling 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 HIV infected woman and her infant. The provision of pregnancy and reproductive health care in HIV infected women should involve a collaboration with individuals experienced in the management of high risk pregnancy and HIV care of women and infants.

In British Columbia (BC), the Women and Family HIV Centre (Oak Tree Clinic), a program of BC Women's Hospital and Health Centre, provides clinical care and guidance for this population of HIV infected and exposed adults and children. The interdisciplinary team at the Oak Tree Clinic works in partnership with the BC Centre for Disease Control for surveillance and with the BC Centre for Excellence in HIV/AIDS for drug therapy and overall provincial coordination. Longitudinal surveillance on pregnancy outcomes in HIV positive women are tracked in BC through information provided by clinicians throughout the province who care for HIV positive pregnant women and their infants. This is vital for the continuous quality improvement of antiretroviral prescribing in pregnancy.

I. Background

A. *Scope of Document*

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, guidelines addressing HIV care of non-pregnant women are available elsewhere^{2,3} and are not discussed in this document. Management of HIV in pregnant women with co-morbidities is addressed in brief, readers are referred to available guidelines⁴ for detailed discussion.

B. *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.⁵ Between 23 to 28% of Canadians living with HIV/AIDS are women and according to 2009 statistics, women account for approximately 26% of the total new HIV/AIDS diagnoses in Canada.⁶ Cumulative surveillance data reports that two thirds of HIV positive test results occurred in women of reproductive age, with 37.6% and 32.5% occurring in women between 30 to 39 years and 20 to 29 years respectively.⁶

Combination antiretroviral therapy (cART) has been demonstrated to prolong the lives of people living with HIV⁷ and also has significantly reduced the rate of vertical transmission of HIV from a baseline risk of 25% without intervention, to less than 2% in the context of comprehensive pregnancy care and cART administered antenatally, intrapartum and to the infant in the early neonatal period.^{8,9} As a result of these factors more HIV positive women are considering their reproductive options and choosing to become pregnant.¹ However the vertical transmission of

HIV from mother to newborn remains a great concern globally as an estimated 26% of HIV infected women remain unaware of their HIV status⁶ and the majority of childhood HIV infections are acquired in this manner.⁴

The Canadian Perinatal HIV Surveillance program (CPHSP) identified a total of 2,692 HIV infected women known to care providers who delivered infants between 1990 and 2010.¹⁰ Based on rates of spontaneous and therapeutic abortions in Canada, it is estimated that there is an equal number of women who have been pregnant for which there has not been a live birth. The incidence of pregnancies in HIV positive women in Canada has been gradually increasing with variable rates of increase from province to province.¹⁰ In BC, the majority of HIV positive pregnancies occur in the setting of known HIV infection prior to conception, while in an estimated 18% of cases, HIV is diagnosed during the pregnancy.¹¹ With the implementation of cART for pregnant women in late 1990s, the CPHSP documented a substantial reduction in HIV transmission rates from 20.2% (1990-1996) to 2.9% (1997-2010). Overall, HIV vertical transmission rate in women who have accessed care is 0.4% in Canada.¹⁰ However, despite 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 2010.¹² Over the past twelve years, there have been seven cases of vertical transmission of HIV in BC¹¹; two occurred in women who did not have any HIV testing performed during pregnancy; while five occurred in women who tested negative for HIV immediately prior to, or in early pregnancy, however later seroconverted during the pregnancy.

II. Preconception Planning

Detailed information and recommendations regarding preconception 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 (NIH) Perinatal Guidelines.⁴ In brief, the following important clinical issues need to be considered with respect to pregnancy planning and counseling in HIV-positive individuals: 1) use of effective methods of birth control if not desiring pregnancy; 2) preconceptional health including intake of folic acid; 3); transmission between partners during conception; 4) antiretroviral and other drugs in pregnancy planning.

III. New Diagnosis of HIV in a Pregnant Woman

All pregnant women should be offered HIV testing, with appropriate pre and post-test counseling as part of their routine prenatal care in each pregnancy.¹³ Women involved in ongoing high risk HIV transmission activities (see *Appendix C*) 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 outcome 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 implemented as an important last opportunity to identify HIV-infected women before delivery and to provide emergency prophylaxis to prevent vertical transmission.^{13, 14} (see *Appendix C*)

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 with the provision of support and counseling for the woman and her family. Woman should be made aware of the improved natural history of the HIV, specifically that with compliance to care and therapy, individuals living with HIV are now experiencing an improved quality of life and prolonged life expectancy.¹⁵ Women should also be made aware that with the use of cART and abstaining from breastfeeding the risk of vertical transmission is <1%. Referral to the Oak Tree Clinic is recommended.

Immediate assessment of risk transmission to others is important, and the woman should be counseled regarding the need for safe sexual practices. All previous children that may have been exposed in the past and sexual or drug use sharing partners should be offered testing. Public Health can assist with anonymous contact tracing if the woman is not prepared to contact prior

partners. HIV is a reportable disease in BC, public health consultation should be sought to adhere to provincial regulations. Disclosure to family and friends not at risk of HIV is not required and should be considered carefully due to the unfortunate persistence of stigmatization. Non-judgmental counseling regarding continuation of the pregnancy based on a complete understanding of the women's medical and social circumstance is important.

IV. New Diagnosis of Pregnancy in an HIV-Infected Woman

A clinician familiar with HIV management should evaluate each HIV positive woman who becomes pregnant. Medical care recommendations for the HIV infected pregnant woman will depend on whether the woman wishes to continue the pregnancy, her HIV disease status, and whether she is already receiving antiretroviral drug therapy. Pregnancy dating should occur through careful history and a dating ultrasound.

Women should be made aware that with the use of cART and abstaining from breastfeeding the risk of vertical transmission is <1% in Canada.¹⁰ In the event that the woman does not wish to continue the pregnancy, facilitation of access to termination of pregnancy services should be provided. Health care providers should use this opportunity to continue to engage in and optimize HIV care and provide reproductive health counseling, including contraception, to reduce the future occurrence of an unintended pregnancy. The HIV status of the exposed sexual partner should also be queried and if not known to be HIV positive, testing of this partner is recommended.

If the woman desires to continue the pregnancy, immediate review of HIV status including recent CD4 T-lymphocyte (CD4-cell) count, HIV viral load and antiretroviral medication use is warranted. A number of clinical scenarios may apply including woman is antiretroviral naive, is currently receiving cART, or is not currently receiving but has received cART in the past.

Specific recommendations regarding antiretroviral drug therapy management and trimester specific information are discussed further in *sections V* and *VI* below. Overall it is important to consider that HIV positive pregnant women present high-risk pregnancies. Their medical therapy requires coordination and communication between HIV specialists and obstetrical providers.

V. Recommendations for Antiretroviral Drug Therapy During Pregnancy

A. Background

Antiretroviral drug therapy is indicated for HIV infected pregnant women, both for women's own health and for the prevention of vertical transmission of HIV. In general, the recommendations for the use of antiretroviral therapy for the benefit of maternal health during pregnancy are similar as for women regardless of pregnancy status.^{2,3} However there are a number of important considerations based on limited experience and/or specific concerns with some antiretroviral drugs in pregnancy.⁴ While optimizing maternal care and health is of prime importance, it is important that whenever possible, exposure of the developing fetus to potentially toxic medications, is minimized. There is still minimal data available on the pharmacokinetics and safety of many antiretroviral drugs, particularly the newer agents, in pregnancy (see *Appendix A, tables 5 and 6*), and therefore all treatment decisions during pregnancy require full discussion between the patient and her physician with regard to the known and unknown benefits and risks.

Antiretroviral agents administered in pregnancy have demonstrated a reduction in the risk of vertical transmission of HIV.⁴ Published literature and analysis of our Canadian data informs treatment in pregnancy in two ways; literature from resource-rich countries informs on optimization of antiretroviral therapy for both maternal health and the prevention of vertical transmission, while literature from resource-poor countries provides insight on recommendations for care for HIV-infected pregnant women with absent or delayed prenatal care. A detailed table describing results of major studies on antiretroviral prophylaxis to prevent vertical transmission of HIV is available in the NIH Perinatal Guidelines.⁴

The Pediatric AIDS Clinical Trials Group 076 (PACTG 076) was the first major randomized, placebo-controlled study to demonstrate that zidovudine administered orally antepartum (between 14 to 34 weeks gestation), intravenously intrapartum, and orally to the infant for 6 weeks could significantly reduce the risk of vertical transmission of HIV (25.5% in placebo group vs. 8.3% in zidovudine treated group, $p=0.00006$).¹⁶ Follow-up results confirmed these findings with no evidence of any long-term toxicity, other than transient anemia, in infants up to 5 years of age.¹⁷⁻¹⁹

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 administration of cART (with at least 2 or 3 agents) given antenatally to the woman.⁴ 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 four weeks of cART before delivery.^{10, 12}

Antiretroviral agents reduce the risk of vertical transmission through a number of mechanisms, including: (a) lowering maternal viral load using antenatal cART, (b) providing infant pre-exposure prophylaxis using intrapartum antiretroviral therapy that rapidly crosses the placenta in order to achieve adequate systemic drug levels in the infant, and (c) providing infant post-exposure prophylaxis.⁴ 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 compared to those did not (1.0% vs. 9.8% respectively $p<0.001$).²⁰

Two primary treatment strategies have been evaluated in resource-poor countries and are relevant in the developed world for managing HIV-infected women 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, zidovudine-lamivudine)^{21,22} or use of intrapartum single-dose nevirapine.^{23,24} The second strategy involves administration of cART to infants²⁵ 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) HIV-infected pregnant women received either single-dose nevirapine 200 mg in labour and their infant received one dose of nevirapine within 72 hours of birth, or oral zidovudine in labour and for one week to their infant. Nevirapine significantly reduced the risk of vertical HIV transmission at 14 to 16 weeks of age by approximately 50% (13% vs. 25%, $p=0.0006$) compared to the zidovudine group.²³ It is important to note that none of the women were receiving antenatal antiretroviral therapy and almost all women were breastfeeding their infants in this study. Because single-dose nevirapine 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 HIV-infected women whom 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 development of nevirapine drug resistant mutations.²⁸ One strategy to limit the emergence of nevirapine resistance in the woman after single-dose nevirapine is to provide the woman with an antiretroviral tail (e.g., postpartum addition of two nucleoside-reverse transcriptase inhibitors for a period of 3 to 14 days) (30-33).²⁹⁻³³

The HPTN 040/PACTG 040 study evaluated the alternative treatment strategy of administering prophylactic cART to infants born to HIV-infected women 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 three doses of infant nevirapine or two weeks of lamivudine/nelfinavir to six weeks of zidovudine) was superior in reducing the risk of vertical HIV transmission (2.2% and 2.4% respectively) compared to six weeks of infant zidovudine therapy alone (4.8%, p=0.046). The rate of neutropenia was increased in the 3-drug regimen (27.5% with zidovudine/nelfinavir/lamivudine) compared to the 2-drug (14.9% with zidovudine/nevirapine) and 1-drug (16.4% with zidovudine) regimens.

B. *Principles behind using combination antiretroviral therapy in pregnancy*

Antiretroviral treatment recommendations for the HIV infected pregnant woman are based on the principle that therapies of known benefit to the woman should be offered and not withheld during pregnancy. 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 an HIV-infected pregnant woman 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) 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) social status and intravenous drug use, and 7) ability of the women to cope with antiretroviral drug therapy pill burden.

C. Timing of initiation of combination antiretroviral therapy in pregnancy

All HIV-infected pregnant women, regardless of HIV viral load or CD4-cell count should receive cART for maternal health and to prevent vertical transmission of HIV. The timing of initiation will depend on HIV disease status (e.g. CD4-cell count and HIV viral load), preparedness to start cART, as well as degree of nausea and vomiting of pregnancy. Detailed adult HIV treatment guidelines are available^{2,3} and are not discussed in detail here.

In brief, guidelines recommend initiation of cART for all individuals regardless of CD4-cell counts. Women with CD4-cell counts <200 cells/mm³ are at high risk of opportunistic infections,^{34,35} 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 for experiencing more common infections (e.g., herpes zoster, bacterial pneumonia) thereby 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 (e.g., 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 antiretroviral history and adjusted later if required. All women should be counseled 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^{34,35} 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 prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP); <100 cells/mm³ additional prophylaxis against *Toxoplasmosis gondii* (if *Toxoplasmosis* IgG serology is positive and using agent other than cotrimoxazole as prophylaxis for PCP); <50 cells/mm³ additional prophylaxis against *Mycobacterium avium* complex (MAC) after obtaining MAC blood cultures, and an ophthalmology referral to rule out cytomegalovirus (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,³⁴ agents of note to avoid particularly in the first trimester of pregnancy include continuous oral fluconazole and clarithromycin.^{36,37} 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 post partum due to increased risk of neonatal hyperbilirubinemia.³⁸

D. 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.³⁹

There are two main populations of women in whom consideration for switching of antiretroviral medications may be considered. The first is HIV-infected pregnant women receiving efavirenz who present pre-conception or very early for care in the first-trimester. As discussed below and more thoroughly in *Appendix A*, efavirenz is not a desirable choice in the first trimester due to association with neural tube defects in primates and in case reports in humans.⁴⁰⁻⁴³ 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.⁴ However because this may not always be the case, and because there is a risk of women remaining on a potentially teratogenic medication post-partum, particularly those who do not receive adequate contraception, these guidelines still recommend consideration to switch efavirenz to an alternative antiretroviral agent that has greater safety and efficacy data in pregnancy. It is emphasized however that if efavirenz is received during (and beyond) the first trimester, ultrasound evaluation of neural tube closure is important.

Consideration for changing antiretroviral medications may also be made in the population of women whom are receiving an antiretroviral agent for which there is little known safety and efficacy data available in pregnancy (see *Appendix A*). Overall, it is important that the safety and

risk of continuing each antiretroviral medication is considered and that prior to making any medication switches there should be discussion between the woman, her HIV care provider, and her obstetrical care provider. The Oak Tree Clinic is available to provide advice in this regard.

D. Selection of combination antiretroviral drug therapy regimen in pregnancy

As described above, antiretroviral drug-resistance testing should be performed before starting cART and results used to help determine optimal regimen. In general, a cART regimen should include a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one of more NRTIs with high levels of transplacental passage (e.g., zidovudine, lamivudine, emtricitabine, tenofovir, abacavir) with addition of a boosted protease inhibitor (see *Appendix A*). In antiretroviral naïve and presumed or proven pan-sensitive virus the recommended NRTI backbone is zidovudine-lamivudine 300 mg/150 mg (Combivir[®]) 1 tab orally (PO) twice daily with lopinavir-ritonavir 200 mg/50 mg (Kaletra[®]) 2 tablets PO twice daily. This regimen requires twice-daily dosing and monthly hemoglobin monitoring as zidovudine can cause pure red cell aplasia.⁴⁴ If women are unable to tolerate or adhere to a twice-daily dosing regimen an alternative regimen is abacavir-lamivudine 600 mg/300 mg (Kivexa[®]) 1 tab 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.⁴⁵ 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.^{46,47} It is important to note that both of the above listed boosted protease inhibitor regimens may require increased dosing (e.g., Kaletra[®] 3 tablets PO twice daily, atazanavir

400mg PO once daily with ritonavir 100mg PO once daily) in the third trimester as a result of increased volume of distribution of pregnancy.^{46, 48-52} Empiric dose increases may 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.⁵³

In HIV-infected pregnant women with hepatitis B virus (HBV) co-infection, the dual NRTI backbone should include two NRTI agents that are also active against HBV (e.g., lamivudine, emtricitabine, tenofovir),^{3, 4, 54, 55} therefore, the recommended first-line regimen in these women is tenofovir-emtricitabine (Truvada[®]) and boosted atazanavir/ritonavir as described above. HBV DNA levels should be monitored and 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 should not be used as a first-line agent in pregnancy unless HBV coinfecting, drug resistance, and/or medication adherence issues exist.^{4, 55, 56}

If women are unable to tolerate or are resistant to the protease inhibitors 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 (fatal rash and hepatotoxicity) and its initiation in pregnancy is not recommended if there is a suitable

alternative.^{3,4} Although some data has suggested that nevirapine may be safe if a woman's CD4 cell-count is >250 cells/mm³, Canadian data⁵⁷ has suggested that toxicity has occurred at a wide range of CD4-cell counts in women exposed to nevirapine for the first time during pregnancy. Women who have been receiving and tolerating nevirapine prior to becoming pregnant (regardless of CD4-cell count) can continue to receive this agent.^{3,4} All other antiretroviral agents utilized in adult HIV care must be individually assessed on a case by case basis, dependent on the woman's clinical and personal circumstances, co-infections, HLA*B5701 results, genotype of her virus and available options. Detailed information on each antiretroviral agent is provided in *Appendix A*, 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,⁵⁸⁻⁶⁰ higher rates of neonatal malformations,^{61,62} increased risk of prematurity and low birth weight,⁶³⁻⁶⁹ or serious neonatal complications including mitochondrial toxicity.⁶⁸⁻⁷⁴ Other studies however suggest that there are generally few serious effects associated with cART for the mother or infant.^{16, 75-81}

The concerns surrounding the use of efavirenz (teratogen), nevirapine (rash and hepatotoxicity), tenofovir (bone abnormalities, nephrotoxicity) and atazanavir (hyperbilirubinemia) in pregnancy have been discussed. HIV-infected women on antiretroviral therapy are also at an increased risk (18% vs. 9% in Canada) of pre-term delivery compared to baseline.^{82, 83} There is conflicting evidence whether cART increases this risk further.^{66, 82, 84-90} Overall there is mixed data to suggest an association between antiretroviral drug therapy (including protease inhibitor use) and

premature delivery or low-birth weight infants; however a causal relationship has not been established^{86, 91-93} and protease inhibitors should not be withheld during pregnancy. There is also conflicting evidence as to whether women taking regimens that include protease inhibitors are at increased risk for impaired glucose tolerance or gestational diabetes in pregnancy^{63, 94-96} Standard glucose screening at 24 to 28 weeks is recommended in HIV-infected pregnant women; if a woman is receiving a PI based regimen, the clinician may chose to perform this screening test earlier.^{4, 97}

VI. Antepartum Management

A. 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, nonjudgmental care to HIV-infected women and their children, in a spirit of professionalism.⁹⁸
- Early and systematically addressing the need for social support, with at least one interview with a social worker. HIV-positive pregnant women in Canada commonly experience challenging social and economic environments, with 25 % of infection linked to drug use and an increasing proportion of black and aboriginal women.^{10, 12} The aim of the comprehensive assessment by a social worker is to determine the needs and to propose support and follow-up if required.
- Maintaining confidentiality, including with relatives.⁹⁸
- Encouraging the testing of partners and previous children if their HIV status is unknown.⁹⁹ The medical and psychological needs of the fathers should be addressed, and the men referred to other health care provider if required.¹⁰⁰
- Advising on the use of, and facilitating access to condoms for the purpose of preventing transmission of HIV and other sexually transmitted infections.¹⁰¹ If both members of the couple are HIV positive, they should be informed of the possible risk of superinfection associated with unprotected sex.¹⁰²
- If a mother refuses antenatal cART, her wish should be respected. A plan for the care of the newborn should be prepared prenatally.⁹⁸

Registration of the mother and infant pairs with 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 on, which inform allocation of resources and management of future pregnancies.^{10, 12} In BC, registration into the surveillance program can be facilitated through the Oak Tree Clinic at BC Women's Hospital and Health Centre.

B. First Trimester (Weeks 0-13)

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), hepatitis C virus (HCV antibody and HCV PCR status if antibody positive) and tuberculosis (induration of ≥ 5 mm using purified protein derivative); and evaluation of immunization status. In addition to standard prenatal bloodwork, the following bloodwork should also be obtained: CD4-cell count (absolute count and fraction); HIV viral load, baseline complete blood count (CBC) and differential, liver (AST, ALT, LDH) and renal (urea, serum creatinine) function testing (see *table 2*).

All HIV infected pregnant women, 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 (at 11 to 14 weeks) measurements should be obtained to integrate with second trimester biochemical screening and these results should be used to inform the need for invasive testing.^{103, 104} If integrated prenatal screening is not accessible, then pregnant HIV infected women should be offered the available non-invasive option for screening for aneuploidy in the region based on gestational age.

Nausea and vomiting can be a significant issue for all pregnant women, and in HIV-infected women, it may affect their ability to adhere to the antiretroviral regimen prescribed. Evaluation of nausea and vomiting of pregnancy should be conducted and aggressive management of this condition, starting with prescription for doxylamine-pyridoxine (Diclectin[®]) as needed,³⁹ is necessary to facilitate the initiation and/or continuation of antiretroviral medications. Important considerations when evaluating nausea and vomiting of pregnancy in an HIV infected woman 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/mm³) 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 or central nervous system lesions or infections causing increased intracranial pressure).³⁴

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/mm³ and/or there are AIDS defining illnesses requiring therapy. In other cases, it is advisable to ensure nausea and vomiting is controlled prior to initiating antiretroviral therapy. Women who are receiving antiretroviral therapy prior to pregnancy should not

discontinue their medication regimen during the first trimester. All drug therapy should be reviewed for safety in pregnancy, particularly the first trimester period of embryogenesis. Women should be counseled 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 three months of their pregnancy. If necessary, in cases with food insecurity, resources should be offered to improve nutrition. Notably, malnutrition and micronutrient deficiencies have been linked to vertical transmission risk.¹⁰⁵ Live vaccines (Varicella zoster and measles, mumps and rubella) are contraindicated in pregnancy.¹⁰⁶ Women with negative serologies for these infections should be considered for immunization postpartum, depending on their CD4 count. With regard to this first consideration, the schedule of recommended immunization for HIV positive adults should be followed.³⁴ 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 counseling support and/or treatment as appropriate.^{1, 107, 108} Other harm reduction strategies can be offered if appropriate, including nicotine replacement treatment and linkage to a methadone clinic if narcotic use is a concern.

C. Second Trimester (Weeks 14-27)

Completion of 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 occur during the second trimester. The women's clinical, virological and immunologic status including CD4-cell count, HIV viral load, CBC, AST, ALT, LDH, bilirubin, BUN, creatinine, as well as any other blood work as indicated by clinical history and specific cART regimen should be assessed every 4-8 weeks throughout pregnancy (see *table 2*). Because of co-morbidities affecting many HIV

infected women in BC, 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 HIV positive women.¹⁰⁹ All women should be screened for gestational diabetes between 24-28 weeks as per most recent guidelines.⁹⁷ As discussed above, there is conflicting evidence regarding whether cART regimens containing protease inhibitors increases the risk of hyperglycemia or new onset or exacerbation of diabetes in pregnancy (see also *Appendix A*). If a woman is receiving a protease inhibitor based regimen, particularly if initiated before pregnancy, the consideration can be given to performing this screening test earlier.

The second part of the integrated prenatal screening tests (i.e., second trimester biochemical screening) should be obtained between 15 to 19 weeks.¹⁰³ A detailed ultrasound at 18 to 20 weeks is recommended to assess growth and fetal anatomy.¹⁰³ If there are concerns of aneuploidy or other fetal infection or syndrome that has prenatal diagnostics, invasive testing should be considered. Invasive testing should only occur if statistical risk is higher than the risk of the procedure taking into consideration the biochemical, serologic, and ultrasound results.^{103, 104} Ideally, amniocentesis should be done with the woman on cART, however timing may not permit full suppression of 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 (95% confidence interval) = 1.85 (0.69–4.98)).¹¹⁰ Since the initiation of cART and the recommendation to treat all pregnant women, there have been no documented transmissions.¹¹¹⁻¹¹⁴ However, it is impossible to rule out a residual small increase in risk of transmission with amniocentesis in women on cART with fully suppressed plasma viral load.

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

D. Third Trimester (Weeks 28-40)

Ongoing assessment of 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 2*). Given the risk of placental dysfunction associated with increased rates of intrauterine growth restriction and oligohydramnios in HIV positive pregnancies,¹¹⁵ follow-up growth ultrasound is suggested to be done monthly, but at a minimum, a third trimester scan can assist in determining if there has been placental or fetal compromise. Considering the higher rate of preterm birth in this population^{66, 82, 84-90}, close clinical follow-up is recommended and schedule of some of the 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 as virologic suppression (HIV viral load <50 copies/mL) should be achieved at this time. If the woman's viral load has not suppressed or has appeared to rebound, a number of considerations must be made. Health care providers should reassess overall adherence, clarify reasons for nonadherence, and attempt to implement strategies or tools to assist women in taking their medication. 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.⁵³ 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 an infant formula-feeding plan has been arranged. HIV infected women are recommended to formula feed their infants after giving birth and breast feeding is not recommended in order to avoid the 9.3 % (3.8-14.8) increased risk of post-natal transmission of HIV through breast milk.¹¹⁶⁻¹¹⁸ Risk of disclosure associated with not breastfeeding may be a challenge for some women. Health care providers should assist with a plan before delivery around what to say to family and friends that can help women feel more comfortable when addressing these questions. In BC, free infant formula to infants of HIV positive mothers is available¹¹⁹ and can be accessed with the assistance of the Oak Tree Clinic dietitian, regardless of mother's delivery location.

Plan for ongoing HIV care should also be established (see *Section VIII. Postpartum management*).

E. Delivery Plans and Mode of Delivery

Planning the hospital location for delivery should take into consideration the woman's gestational history, home location, ability to transport, 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 occur and arrangements should be made to ensure that required intrapartum and postpartum antiretroviral drugs are available at the designated facility. All facilities in BC with delivery rates of at least 250 births per year have a mother to child

transmission of HIV prevention kit containing adult intra- and post-partum and infant antiretroviral drug therapy (see *Appendices B through D*).

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 obstetrically appropriate and if virologic suppression has been achieved.^{8, 20, 120-123} The initial studies that identified elective cesarean section as a method to reduce vertical transmission were in women who were not receiving any antiretroviral drug therapy or who received monotherapy with zidovudine only. Evidence to support elective cesarean section in the current cART era, where all women (even with viral loads <1000 copies/ml)²⁰ are recommended to initiate cART in pregnancy, is less impressive however. European surveillance data^{122, 123} did not show a significant benefit to elective caesarian delivery in the cohort of women with undetectable viral loads while on cART. Thereby, there is evidence to support elective cesarean section in women who have an unknown viral load, a viral load > 1000 copies/mL, or women who were not on cART regardless of viral load. However, considering the potential complications of operative delivery, women who received antepartum cART, were 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 indications for cesarean sections for obstetrical indications only. It is also important to note that the benefit of caesarian delivery in early studies appear to have been exclusively with a pre-labour elective caesarian delivery compared to a lack of benefit shown with an emergency caesarian delivery.^{8, 121}

VII. Intrapartum Management

A. Intrapartum management for known HIV-infected women

All HIV-infected women should be instructed to attend labour and delivery immediately upon rupture of membranes or regular contractions so that measures can be taken to decrease the risk of vertical HIV transmission. All oral antenatal antiretroviral medications, with the exception of stavudine (d4T or Zerit[®]), should be continued for as long as possible during labor. Due to an antagonistic drug interaction with zidovudine, stavudine should not be administered concomitantly with IV zidovudine.¹²⁴ There is no randomized controlled trial data to inform on the additional benefit of intrapartum IV zidovudine in women who were receiving antenatal cART. A large cohort study which involved more than 5000 HIV-infected pregnant women who received intrapartum IV zidovudine in addition to various (mono, dual, triple) antenatal antiretroviral therapy regimens reported 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.¹²⁵ 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=1.000), and data was not provided for women with viral loads between 400 to 9,999 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 HIV-infected women receiving antenatal cART and an HIV viral load >400 copies/mL (or unknown viral load) near delivery however do not recommend its administration for those women on cART with an HIV viral load ≤400 copies/mL.⁴ BC data however shows that 8.7% of women with previously suppressed viral load have unpredictably elevated viral loads at time of delivery.¹²⁶ On the basis of this evidence,

intrapartum IV zidovudine (2 mg/kg IV load over 1 hour followed by 1 mg/kg/hour until delivery) continues to remain standard of care in BC 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 caesarian section. If in the future rapid HIV viral load measurements are available on day of delivery, decisions regarding 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 caesarian section. This recommendation also differs somewhat from that made by the NIH perinatal guidelines⁴, where intrapartum IV zidovudine (but not single-dose oral nevirapine) and combination infant antiretroviral with zidovudine plus three 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 there are a number of practicalities that must be considered when women present in labour, including the difficulty that often occurs with obtaining IV access, and thereby there is difficulty or inability to administer IV zidovudine. Because single-dose oral nevirapine has demonstrated to reduce vertical transmission of HIV²³, it continues to be recommended for intrapartum administration to HIV-infected woman whom have not received antenatal therapy in addition to administration of cART to their infants. The addition of seven-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 cesarean 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 unknown viral loads (e.g., have not accessed care and/or are not taking antiretroviral drug therapy) near the time of delivery. Importantly, there is limited data to support the benefit of emergency caesarian 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 1,000 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 caesarian section). If caesarian section is recommended for obstetrical indications, this can be conducted at 39 weeks as per usual indications.

Data from the pre-cART era have found 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.¹²⁷⁻¹³⁰ Extrapolating this data into the era where cART is used, it is recommended that interventions that potentially increase fetal exposure, including scalp electrodes, intrauterine catheters, prolonged rupture of membranes, operative vaginal deliveries and episiotomies should be avoided if possible. A number of additional important considerations during the intrapartum period include: epidural anesthesia is not contraindicated, continue to initiate antibiotic prophylaxis as per protocol if woman is Group B Streptococcus positive, and if woman has ruptured membranes and is not in labour, oxytocin induction of labor in addition to intravenous zidovudine (medications are compatible) should be initiated.

B. Intrapartum management for woman of unknown HIV status and/or ongoing HIV risk

There are many situations where 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 who are at particular risk of HIV infection include women who use injection drugs and have shared needles, had a recent illness suggestive of a seroconversion illness, have had regular

unprotected sex with a known HIV infected partner or partner with significant risk factors for HIV infection, or who had a diagnosis of a sexually transmitted infection during pregnancy.

Women who have been recently incarcerated or who have immigrated from HIV endemic areas are also at increased risk if they have not been recently screened.

It is recommended that all women who have not been tested in pregnancy, and 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 counseling. Women involved in ongoing high risk HIV transmission activities who are HIV negative on initial testing should be retested each trimester¹³, and if possible again near term. HIV testing should also occur with the woman's knowledge and verbal consents and appropriate pre- and post-test counseling should accompany each test.

If rapid HIV antibody testing is available within the institution, women with unknown HIV status or at continued risk of HIV infection since last negative HIV serology result should be offered rapid HIV antibody testing in the labour and delivery setting with appropriate pre- and post-test counseling. In the event that the rapid HIV antibody test result is positive, the woman should be informed of the result and confirmatory HIV PCR and antibody tests should be sent.¹⁴

Maternal intrapartum antiretroviral drug therapy (intravenous zidovudine and single-dose oral nevirapine) plus post-partum zidovudine-lamivudine (Combivir[®] 1 tablet orally twice daily for seven days; see *Section VIII. Postpartum management*) and infant prophylactic cART (see *Section IX. Infant management*) should be initiated pending results of the confirmatory test. If the confirmatory test is negative, maternal zidovudine-lamivudine (Combivir[®]) and infant antiretroviral drugs may be discontinued; if the test is positive, the infant should receive a complete 6-week course of antiretroviral drug therapy and the woman should receive a complete

7-day course of oral zidovudine-lamivudine (Combivir[®]) to prevent the emergence of nevirapine resistant virus.

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 sent.

Intrapartum and post-partum (IV zidovudine, single-dose oral nevirapine, Combivir[®]) antiretroviral drugs therapy should be offered to the woman and all infants should receive empiric prophylactic antiretroviral therapy pending results (see *Section IX. 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 four weeks) and/or HIV PCR is negative, infant antiretroviral prophylactic therapy and maternal zidovudine-lamivudine (Combivir[®]) may be discontinued; if the woman at risk is determined to be HIV-infected, 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 (Combivir[®]) to prevent the emergence of nevirapine resistant virus.

The evidence and rationale for administering single-dose nevirapine to the mother, in addition to other intrapartum and infant therapies, has been discussed above. 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 HIV-positive during labor or delivery.

VIII. Post partum 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. There are a number of comprehensive issues that must be addressed including contraception, continuation of and adherence to antiretroviral drug therapy regimens, infant feeding and pediatric care, and as well as need for services surrounding mental health, social services, and treatment of substance use.

Oxytocin, misoprostol or prostaglandin F2 alpha are recommended agents for management of postpartum hemorrhage, and the use of ergotamine should be avoided if possible due to the risk of exaggerated vasoconstriction in women receiving protease inhibitor therapy.¹³¹ A number of studies have evaluated the risk of infectious morbidity following delivery in HIV positive women.¹³²⁻¹³⁶ Some studies report increased rates of endometritis and pneumonia following caesarian section in HIV infected versus non-HIV infected women,¹³³ while others have not¹³². Endometritis does however occur in a higher percentage of all women following caesarian delivery and routine preoperative prophylactic antibiotics have been demonstrated to decrease postoperative infection.¹³⁷ Preoperative antibiotics are thereby recommended for all women, including HIV infected women, who undergo elective or emergent caesarian sections to decrease infectious postoperative complications.¹³⁸

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 whom received single-dose nevirapine during labor should receive 7-days of zidovudine-lamivudine (Combivir[®]) 1 tablet orally twice daily to reduce the risk of developing nevirapine resistance. Combivir[®] therapy can be discontinued prior to

completion of the 7-day treatment period in cases where confirmatory HIV testing results confirm that the woman is not infected with HIV.

Plans for ongoing HIV care should be established prenatally, and unless otherwise indicated, maternal antiretroviral therapy should be continued after delivery and reassessed for ongoing therapy by adult HIV care providers. Based on future pregnancy planning and adult HIV status, antiretroviral treatment modifications may be appropriate. Adherence in the post partum period can be challenging¹³⁹ and support is important.

There is a risk of HIV transmission through breast milk¹¹⁶⁻¹¹⁸; therefore breastfeeding is contraindicated irrespective of maternal antiretroviral therapy and/or viral load. Management of absence of breastfeeding should include comfort measures (acetaminophen, ibuprofen, cold compress) to minimize the pain that can occur with engorgement. Bromocriptine and cabergoline, the classical therapies used for lactation suppression, are ergot derivatives, whose co-administration with protease inhibitors is contraindicated. Women who test positive on rapid HIV antibody testing or whom are believed to be at high risk of HIV (when rapid HIV antibody testing is not available) should not breastfeed unless a confirmatory HIV test is negative.

An earlier return to fertility may be expected as a result of avoidance of breastfeeding. It is critical that safer sex practices and effective contraception methods are discussed with women. Condom use is recommended for all HIV infected women 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.¹⁴⁰ Oral contraceptives may also be used in HIV infected women, particularly also 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

contraceptive pill. This information is available in the NIH Perinatal HIV Guidelines⁴ as well as the Motherrisk website.¹⁴¹ Non-oral contraceptive methods including depo-provera, contraceptive patch or vaginal ring, and levonorgestrel interuterine device (IUD) are also options, however there is less available data in combination with antiretroviral medications. The side effect profile of depo-provera has been shown to be the same in HIV infected and uninfected women¹⁴²; however, consideration should be given to the bone loss seen in women using depo-provera and that women who are HIV positive have accelerated bone loss compared to their uninfected counterparts. Data on IUD use in HIV positive women is limited but given the value of this method for successful contraception and low general rates of infection, consideration for use in women with CD4-cell counts >200 cells/mm³ is reasonable.¹⁴⁰

Linkage to care is important for all HIV-infected women, particularly women whom are newly diagnosed with HIV during labor and delivery. All women should have arrangements to follow-up care providers experienced in the management of HIV and their infants referred for follow-up by a pediatrician.

IX. Infant Management

All infants should be offered antiretroviral prophylaxis 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 with known HIV infection and a viral load <1000 copies/mL should be offered prophylactic therapy with oral zidovudine for six weeks. Intravenous zidovudine may be used if 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 D*). 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 with known HIV-infection who has a known or projected viral load >1000 copies/mL or to a mother with known HIV-infection who did not receive any antepartum antiretroviral therapy (this includes a mother who is presumed to be HIV-infected based on a positive rapid HIV antibody test result) should receive prophylactic cART with a three-drug regimen including zidovudine for six weeks combined with three doses of nevirapine in the first week of life (at birth, day 2 and day 6 of life) and twice daily oral lamivudine for two weeks.

This recommendation is made on the basis of the HPTN040/PACTG 1043 trial which enrolled HIV-infected women who were not receiving antenatal antiretrovirals and demonstrated increased efficacy of combination regimens (2.2%) in reducing intrapartum transmission compared with use of zidovudine alone (4.8%) in infants.²⁵ 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 (e.g., >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 two-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 HIV infected. The rationale for this recommendation is to provide a highly active antiretroviral regimen throughout the first two 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 – 50 hours in newborns).²⁷

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 unnecessary antiretroviral exposure of the infant, 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 that the use of prophylactic cART for infants in high-risk situations is increasing.^{143, 144} Until HIV negative status can be confirmed, breast milk pumping and avoidance of breast milk infant feeding is recommended.

The dosing recommendations for the prophylactic antiretroviral agents are specified in *Appendix D*. Of note, hepatic clearance is slower in preterm infants but pharmacokinetic data informing dosing is limited, particularly in infants with birth weight below 1.5 kg.^{145, 146}

Breastfeeding remains contraindicated for HIV-infected mothers regardless of maternal viral load, antepartum cART regimen and continuation of postpartum antiretroviral therapy. 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 in Malawi (versus 7 % in

the absence of maternal or infant antiretrovirals).¹¹⁶ In addition, provincial BC surveillance data show high rates of virologic rebound post partum among women who are prescribed ongoing cART.¹³⁹ In BC, infant formula is available free of charge for the first year of life to infants born to HIV infected mothers through a provincially funded program.¹¹⁹ Applications to the program may be facilitated through the Oak Tree Clinic. It is important to discuss feeding practices with the mother during antenatal visits, using a sensitive approach and acknowledging the mother's cultural beliefs around infant feeding.

Since premastication of food by HIV-infected caregivers has been implicated as a potential route of HIV transmission to young infants, health care practitioners should also inquire about premastication and advise HIV-infected caregivers to avoid this practice.

Infants exposed to HIV should be tested for HIV infection by a virologic 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 NAT (nucleic acid amplification test) is the virologic test currently used for diagnostic purposes at the BC Centre for Disease Control Laboratories. When ordering this test please specify "Infant Diagnostic HIV PCR" on the requisition form. 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. Serologic EIA tests are not indicative of infant status due to the presence of detectable maternal HIV antibodies up to 18-24 months of age. A confirmatory HIV EIA test is recommended to document seroreversion after 18 months of age.

If an HIV PCR is reactive, a confirmatory RNA PCR test should be requested immediately.

When an infant is found to be HIV-infected, 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 outcomes¹⁴⁷ and may prevent the establishment of viral reservoirs in infected infants.¹⁴⁸

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.^{17, 18, 91, 149} 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 is limited.⁴ 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.^{70, 72}

All infants born to HIV-infected women 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 behavioral disorders. Family physicians and pediatricians play an essential role in identifying and addressing such issues in HIV exposed uninfected infants and children and they should facilitate referrals to specialists and developmental resources. Communications with public health nurses, immunization clinics, the Infant Development

Program (IDP), the Ministry of Children and Families (MCFD) and Vancouver Aboriginal Child and Family Services Society (VAC-FSS) are important for the well-being of these children, as is early referral to a pediatrician for developmental assessment if there are any concerns.

Management of HIV exposed infants born in BC is offered through the Oak Tree Clinic. Visits for HIV exposed, uninfected children are typically scheduled at 2, 4 and 6 weeks, 3, 6, 9, 12 and 18 months. A yearly visit is recommended thereafter.

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.⁴

Registration of mother-infant pairs with the provincial and national (CPHSP) surveillance programs is facilitated through the Oak Tree Clinic. Including all HIV exposed mother-infant pairs in those surveillance programs is essential to keep generating important epidemiological data and support continued access to resources for these vulnerable families.

Table 2: Recommended Laboratory Tests and Investigations by Visit/Gestational Age

		Initial visit ¹	10-13+6 weeks	15-17 weeks	19-20 weeks	24-26 weeks	28-30 weeks	32-36 weeks	Delivery	4-6 weeks Post partum
Immunologic assessment	CD4	√	√	√	√	√	√	√	√	√
HIV Plasma Viral Load	HIV viral load	√	√	√	√	√	√	√	√	√
Drug Resistance Testing & Other	HIV genotypic drug resistance ²	√								
	HLA-B*5701 ³	√								
Hematologic Assessment	CBC with differential	√	√	√	√	√	√	√	√	√
Liver Function Tests	AST, ALT, LDH, bilirubin	√	√	√	√	√	√	√	√	√
Renal Function	Creatinine, BUN	√	√	√	√	√	√	√	√	√
	Phosphatemia ⁴	√	√	√	√	√	√	√	√	√
	Urinalysis & Urine culture	√			√ opt			√ opt		
Blood Glucose	Fasting Glucose		√							
	Gestational diabetes screen ⁵					√				
Blood Type	Blood type	√								
Serology	CMV IgG	√								
	Rubella IgG	√								
	Toxoplasma IgG	√								
	Syphilis (RPR)	√					√ ¹⁵⁰			
	Varicella IgG	√								
	HAV IgG	√								
	HBsAg, anti-HBs, anti-HBc	√								
	HCV IgG ⁶	√								
Ultrasound & Prenatal Screening	Ultrasound	√ dating	√ 11-13 ⁺⁶ NT		√ detailed	√ growth	√ growth	√ growth		
	PAPP-A		√							
	uE3, hCG, AFP, Inhibin A			√ 15-20 ⁺⁶						
Sexually Transmitted Infection & Other	Cervix Chlamydia & Gonorrhea NAAT	√								
	Pap smear	√								√
	HSV history ⁷	√								
	GBS screen ano-rectal swab ⁸							√		

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

-
1. Integrate initial visit labs/investigations (as indicated) with all others if visit occurs later than 10 weeks
 2. HIV genotypic drug testing recommended at time of first HIV plasma viral load, at the time of initiation of antiretrovirals and if treatment failure or incomplete viral load suppression (>250 HIV copies/mL)
 3. HLA-B*5701 testing recommended at baseline or before starting or initiating therapy with abacavir if not previously done
 4. Phosphatemia should be monitored in women receiving tenofovir based regimens because it is a potential cause of tubular toxicity.^{4, 55, 56}
 5. Gestational diabetes screen 50g glucose challenge test (1h plasma glucose (PG)) or 75g oral glucose tolerance test (fasting PG, 1hPG, 2hPG)⁹⁷
 6. Hepatitis C: confirm positive result of HCV antibodies with HCV PCR
 7. If positive genital herpes history, recommend start prophylactic treatment (e.g., valacyclovir 500mg orally twice daily) at 34 to 36 weeks to prevent recurrent HSV at delivery
 8. Group B streptococcus ano-rectal swab recommended at 35 to 37 weeks or sooner if delivery within 5 weeks is anticipated

Table 3: Guidelines related to the care of HIV-positive individuals

Topic	Website	Issuing Agency
• Antiretroviral Treatment of Adult HIV Infection: 2012 Recommendations	https://www.iasusa.org/guidelines	International AIDS Society, US Panel
• Adult HIV Infection Therapeutic Guidelines	http://www.cfenet.ubc.ca/therapeutic-guidelines/adult	BC Centre for Excellence in HIV/AIDS
• Opportunistic Infections Therapeutic Guidelines	http://www.cfenet.ubc.ca/therapeutic-guidelines/opportunistic-infection	
• Primary Care Guidelines	http://cfenet.ubc.ca/therapeutic-guidelines/primary-care	
• Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents.	http://www.aidsinfo.nih.gov/guidelines	Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infections Diseases Society of America
• Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-infected Adults and Adolescents		
• 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		
• Canadian HIV Pregnancy Planning Guidelines	http://www.sogc.org/guidelines/documents/gui278-CPG1206E.pdf	Society of Obstetricians and Gynecologists of Canada
• Alcohol Use and Pregnancy Consensus Clinical Guidelines	http://www.sogc.org/guidelines/documents/gui245-CPG1008E.pdf	
• Substance Use in Pregnancy Clinical Practice Guidelines	http://www.sogc.org/guidelines/documents/gui256-CPG1104E.pdf	
• HIV Screening in Pregnancy Clinical Practice Guidelines	http://sogc.org/wp-content/uploads/2013/01/185E-CPG-December2006.pdf	
• The Management of Nausea and Vomiting of Pregnancy Clinical Practice Guidelines	http://sogc.org/wp-content/uploads/2013/01/120E-CPG-October2002.pdf	
• Canadian Contraception Consensus	http://sogc.org/wp-content/uploads/2013/01/143E-CPG1-February2004.pdf http://sogc.org/wp-content/uploads/2013/01/143E-CPG2-March2004.pdf http://sogc.org/wp-content/uploads/2013/01/143E-CPG3-April2004.pdf	

Table 4: CONTACT LIST

Organization	Local Number	Other Number	Website
Oak Tree Clinic Inquiries regarding specialized HIV care for positive woman, partners, children, and youth	604-875-2212	1-888-711-3030	www.oaktreeclinic.bc.ca
BC Centre for Excellence in HIV/AIDS For HIV treatment and management information, therapeutic guidelines, and information on anti-HIV medications	604-806-8477	HIV/AIDS Treatment Program Information Line 604-806-8515 24-hour Physician Hotline 604-681-5748 1-800-665-7677 Drug Resistance Testing 1-800-517-1119	www.cfenet.ubc.ca/
REACH Telephone Line Rapid Expert Advice and Consultation in HIV – for timely clinical advice on HIV/AIDS treatment and management from a physician or pharmacist experienced in HIV care. Operated by the BC Centre for Excellence in HIV/AIDS and open 24-hours a day, 7 days a week	604-681-5748	1-800-665-7677	www.cfenet.ubc.ca/REACH
BC Centre for Disease Control For consultation in prevention, diagnosis, testing, treatment and case management of HIV and STIs.	604-707-5600	-	www.bccdc.ca
PHSA Laboratory Contact PHSA to speak to a Medical Microbiologist – for questions about testing, test results and window periods	-	1-877-747-2522	
Toronto General Hospital Immunodeficiency Clinic Comprehensive antiretroviral drug information on antiretrovirals and drug interactions	-	-	http://www.hivclinic.ca/main/drugs_home.html
Sheway Pregnancy Outreach Program located in Vancouver, BC providing health and social service supports to pregnancy women and infants under eighteen months who are dealing with drug and alcohol issues	604-216-1699	-	http://sheway.vcn.bc.ca
BC Women’s Hospital and Health Centre FIR Square Care for substance using women and substance-exposed newborns	604-875-2229	-	http://www.bcwomens.ca/services/pregnancybirthnewborns/hospitalcare/substanceusepregnancy.htm

APPENDICES

APPENDIX A: Summary information on antiretroviral medications in pregnancy

Nucleoside/Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs)

- This class of drugs functions as 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.¹⁵¹ NRTIs are recommended for use as part of combination regimens, which usually include two NRTIs (i.e., backbone) with the addition of either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or one or more protease inhibitor (PI). The use of single or dual NRTIs alone is not recommended for treatment of HIV infection because of the inability to suppress viral replication for prolonged periods as resistance develops rapidly.^{3,4}
- 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)**. Tenofovir would be a preferred NRTI, in combination with 3TC or FTC, for pregnant women with chronic hepatitis B infection. **Didanosine (DDI)** and **stavudine (d4T)** are reserved for use only in special circumstances due to increased toxicity compared to other available agents.
- Various combinations of NRTIs can be employed. The bulk of clinical safety and efficacy data in pregnancy exists 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.¹⁵²

- Alternative agents/combination of agents (ABC, FTC, TDF) may be considered in a number of cases, including: when there is resistance to first-line agents, when a woman conceives on an effective treatment regimen, for tolerability issues and for regimen simplification. When selecting combination regimens, it is important to consider HIV resistance profiles, potential for additive adverse events, co-morbid medical conditions, including hepatitis B virus, concomitant medications and the potential for drug-drug interactions, and convenience of dosing. Two notable combinations that should be avoided include: d4T in combination with either ZDV, because both have competing intracellular mechanisms of activation,¹²⁴ or with DDI, because the combination has a higher reported risk of a potentially fatal lactic acidosis and hepatic steatosis reaction.¹⁵³
- 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.^{4,41}
- 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 fetal effects and nephrotoxicity, TDF is recommended as an alternative (vs. first-line) drug for use in pregnancy, unless the woman is co-infected with hepatitis B virus.⁴

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 monotherapy¹⁶ 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.¹⁷⁻¹⁹ Overall, transient and mild hemoglobin reductions have been observed in most infants exposed to antiretroviral drugs and resolve by age 3-6 months after discontinuation of antiretroviral prophylaxis.^{4, 91, 149} In utero exposure to cART appears to be associated with increased anemia severity. Neutropenia and/or lymphopenia have also been reported with resolution at age 8-24 months.^{4, 91, 149} 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.^{154, 155}

Mitochondrial toxicity/dysfunction - NRTIs are able to bind to mitochondrial gamma DNA polymerase found in different organ systems resulting in mitochondrial toxicity.^{91, 154} 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.⁹¹ As described above, the combination of d4T and DDI should be avoided because of a higher incidence of fatal lactic acidosis in individuals receiving cART; it is unknown if pregnancy increases the risk further.¹⁵⁶

Data are conflicting regarding whether mitochondrial dysfunction is associated with in utero exposure to NRTI therapy. In the French Pediatric Cohort study, the total incidence of clinical symptoms of mitochondrial dysfunction at 18 months was 0.26% (95% confidence interval 0.10-0.54) in exposed children compared with 0.01% in the general population, and mortality rate was 0.07%.¹⁵⁷ These findings have not been duplicated in other studies^{81, 158, 159} and severity of maternal illness has been identified as a potential confounding factor^{160, 161}. 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, 72} 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, 162} Testing for carriage of the HLA-B*5701 allele identifies patients at risk of reactions and patients with the HLA*B5701 allele should not be given ABC.⁴⁵ Rechallenge with ABC in patients who have experienced ABC hypersensitivity is contraindicated. To date, there is no evidence that in utero exposure to ABC has increased the risk of any hypersensitivity reaction in the infant.

Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- This class of drugs functions 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.¹⁵¹ 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 risk of potentially fatal rash and hepatotoxicity (see below). Women who are tolerating NVP and

become pregnant may continue taking NVP. While a preferred agent in the nonpregnant adult, **efavirenz (EFV)** is contraindicated in the first trimester of pregnancy due to association with neural tube defects in primates and in case reports in humans (see below)⁴⁰ However, if inadvertently given during this period the overall risk is low and ultrasound evaluation of neural tube closure should be done to guide counseling on fetal status. Its use in later trimesters should be reserved for when other agents cannot be used or are not tolerated. There is currently insufficient safety and pharmacokinetic data available 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. Extent of placental transfer is variable among the class and ranges from high with NVP (which also rapidly crosses the placenta) to moderate with EFV. The extent of placental transfer of the newer NNRTIs, ETR and RPV, is currently unknown.
- Compared to NRTI data, teratogenicity data using the NNRTIs is more limited and variable. 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 with these agents in human pregnancy.^{4,41} Efavirenz, however, is classified as FDA pregnancy category D, and should not be used in the first trimester of pregnancy. Nonpregnant women who are receiving EFV should be counseled to avoid pregnancy. Central nervous system malformations including anencephaly, cleft palate, and anophthalmia were reported in 3 of 20 (20%) of monkeys exposed to efavirenz plasma concentrations similar to human therapeutic concentrations in the first trimester.^{4, 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 seven (1 prospective, 6 retrospective) reported cases of CNS defects, including 3 cases of meningocele, 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 toxicity* –Nevirapine has been reported to cause severe, life threatening and in some cases fatal hepatotoxicity and hypersensitivity skin reactions.^{162, 163} The risk of toxicity is higher in women than men, however it does not appear that pregnancy increases the risk further.^{4, 154, 163} There is data to suggest that the greatest risk of toxicity occurs during the first 6-18 weeks of therapy and is increased approximately 10 fold when nevirapine is initiated at baseline CD4-cell counts greater than 250 cells/mm³.^{4, 154, 163} 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.⁵⁷ 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.^{23, 164} 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 (PIs)

- This class of drugs functions as competitive inhibitors that bind to the HIV protease enzyme and prevent the conversion of HIV viral particles into mature infectious forms.¹⁵¹ PIs are recommended in pregnancy in combination with a dual NRTI backbone. Individual PIs are most commonly administered together with low dose ritonavir, 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 also has been shown to be well-tolerated and safe in short term studies, however requires a baseline electrocardiogram prior to starting therapy. Because of associated adverse effect profiles and/or pharmacokinetic limitations in pregnancy, boosted **indinavir (IDV/r)** and **nelfinavir (NVF)** should be reserved for use in special circumstances when other agents cannot be used. There is currently insufficient data in pregnancy to recommend use of the newer agents including boosted **fosamprenavir (FPV/r)** or **tipranavir (TPV/r)**.
- Pharmacokinetics of PIs are variable in pregnancy, particularly in the second and third trimester. Current data suggest that exposure to LPV/r, ATV, and NVF is decreased during the second and third trimesters. The clinical significance of reduced exposure to antiretroviral drugs during pregnancy is however 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 virology failures due to increased plasma volumes and subsequent reduced PI concentrations do not occur. Consideration for PI dose increase should be made 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.⁵³ 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 supernumerary ribs, ossification delays) and growth inhibition has been reported with high dose RTV, IDV, TPV, and FPV. The majority of PIs have not demonstrated to be teratogenic in human studies however there is limited data with the use of DRV, FPV or TPR in human pregnancy.^{4,41}

Additional considerations in pregnancy:

- *Preterm delivery* - There is conflicting evidence regarding whether combination antiretroviral therapy (vs. none, mono or dual NRTI therapy) is associated with a higher risk of preterm delivery. Some studies have suggested approximately a 2-fold increase risk of preterm delivery (<37 weeks) with combination antiretroviral therapy compared with no treatment, particularly when initiated prior to pregnancy versus in the third trimester.^{86,91} A 2007 meta-analysis of 14 published clinical studies has suggested that combination regimens that include a PI (vs. no PI) may be at highest risk of preterm delivery^{84,92} 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.⁴¹ Other studies however have not detected an association between antepartum antiretroviral therapy or PI use and pre-term delivery or low-birth weight *infants*.^{82, 92} Overall, there is mixed data to suggest an association exists between in utero antiretroviral therapy (including PI use) and premature delivery or low birth-weight infants. However, a causal relationship has not been established and PIs should not be withheld because of the possibility of an increase risk of preterm delivery.

- *Glucose intolerance/diabetes* – There is also conflicting evidence regarding whether combination antiretroviral regimens containing PIs increases the risk of impaired glucose tolerance and gestational diabetes in pregnancy. The risk of glucose intolerance, has been reported to be increased by PIs in one retrospective study⁶³ but was not observed in others.⁹⁴⁻⁹⁶ Secondary analysis of data from two prospective cohorts found only an increased risk of gestational diabetes when PIs were initiated prior pregnancy or during the first trimester.¹⁶⁵ Overall, it is recommended that HIV-infected women taking antiretroviral drugs during pregnancy should receive standard glucose screening (e.g., 1 hour 50 gram glucose loading test of 24-28 weeks gestation); if a women is receiving a PI based regimen, particularly if initiated before pregnancy, the clinician may chose to perform this screening test earlier.⁴

- *Hyperbilirubinemia* - Hyperbilirubinemia commonly occurs in patients, including pregnant women, who receive the PIs, ATV and IDV.^{46, 166} These agents increase indirect (unconjugated) bilirubin from the direct inhibition of 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 the physiologic hyperbilirubinemia in neonates as a result of 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.^{46, 47} 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.⁴⁶

- *Management of postpartum hemorrhage*– Ergot derivatives (e.g., ergonovine maleate) should not be used for the management of postpartum hemorrhage, because the combined use of this drug class with protease inhibitors may result in serious and potentially life threatening vasoconstriction reactions characterized by peripheral vasospasm and ischemia of the extremities and other tissues.⁴⁸ Other alternatives including oxytocin and/or prostaglandins may be used if required.^{4, 167}

Entry (fusion) inhibitors

- This class of drugs includes two agents, **enfuviride** and **maraviroc**, which act extracellularly to prevent HIV from attaching to the target cell surface and entering the host target cell. Enfuviritide 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 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 if maraviroc will be effective.
- There is currently insufficient data to recommend the use of fusion inhibitors in pregnancy. There is minimal data regarding the pharmacokinetics in pregnancy and it is not known if

dose adjustments are required. Placental transfer to the fetus is also unknown. Both agents are classified as FDA pregnancy category D as animal studies have not demonstrated any evidence of teratogenicity, however there is no (maraviroc) or very limited (enfuvirtide) experience in human pregnancy.

Integrase inhibitors

- This class of drugs, includes two agents, **raltegravir** and **elvitegravir** 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 and the NRTIs tenofovir and emtricitabine (TDF 300mg/FTC 300mg/EVG 150mg/COBI 150mg).
- There is currently insufficient data to recommend the use of integrase inhibitors in pregnancy. There is no pharmacokinetic data or placental transfer information available for elvitegravir-cobicistat. Limited pharmacokinetic data suggests that although raltegravir shows extensive variability in the third trimester, exposure is not altered compared with postpartum and historical data and standard dosing appears appropriate in pregnancy. Case report data suggests a high placental transfer rate to the fetus with a reported cord-to-maternal blood ratio of approximately 1.0^{41, 168}
- 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 describe the addition of raltegravir in the third trimester to rapidly decrease viral load at the time of delivery.¹⁶⁹⁻¹⁷¹

- Elvitegravir and colbicistat (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 is no reported data in human pregnancies.¹⁷²

Table 5: Summary table on antiretroviral drugs in pregnancy

Nucleoside reverse transcriptase inhibitors	
Recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended.	NRTI class concerns: causal relationship between mitochondrial toxicity and NRTI exposure in utero has not been established (see text for details).
<p>Zidovudine (ZDV)</p> <ul style="list-style-type: none"> Approved by FDA and HPB for use in pregnancy FDA pregnancy category C High placental transfer (cord-to-maternal blood ratio 0.80) <p>Animal data⁴</p> <ul style="list-style-type: none"> Vaginal carcinoma reported in mice and rats at 3 times and 24 times the usual human dose. Embryotoxic in rats and rabbits at high doses No evidence of teratogenicity in rats or rabbits unless given at extremely high doses to rats (e.g., 300 times usual human dose). <p>Human data</p> <ul style="list-style-type: none"> PACTG 076 randomized, placebo-controlled trial in pregnant women showed no increase in congenital abnormalities^{18, 173}; WITS Cohort study reported 10-fold increase in risk of hypospadias in women receiving zidovudine in first trimester¹⁷⁴. No evidence of human teratogenicity; APR birth defects with first trimester exposure 3.3% (124 of 3,789 births, 95% CI 2.7-3.9%)⁴¹ Infants exposed in utero have shown no differences in immunologic, neurologic, or growth compared to infants receiving placebo, based on approximately 6 years of follow up. 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ZDV plus 3TC is a recommended dual-NRTI backbone for pregnant women Do not combine with stavudine (antagonistic mechanism of action); discontinue stavudine at time of administration of intrapartum intravenous zidovudine. <p>Dosing</p> <ul style="list-style-type: none"> <i>Retrovir</i>[®] 300 mg twice daily or 200 mg three times daily <i>Combivir</i>[®] (ZDV 300 mg/3TC 150 mg) 1 tablet twice daily <i>Trizivir</i>[®] (ZDV 300 mg/3TC 150 mg/ABC 300 mg) 1 tablet twice daily Pharmacokinetics similar in third trimester of pregnancy and nonpregnant patients; no dose alteration required in pregnancy¹⁷⁵ <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> Overall, well tolerated in pregnancy and infants; higher incidence of anemia reported in neonates however reversible within 6 weeks of discontinuing ZDV.^{18, 173}
<p>Lamivudine (3TC)</p> <ul style="list-style-type: none"> FDA pregnancy category C High placental transfer (cord-to-maternal blood ratio 0.86)¹⁷⁶ <p>Animal data⁴</p> <ul style="list-style-type: none"> No evidence of toxicity or teratogenicity in rabbits or rats at 35-130 times usual human dose. Embryotoxic in rabbits at doses similar to human doses, however no indication of this effect in rats at 35 times usual human dose <p>Human data</p> <ul style="list-style-type: none"> No adequate or well-controlled studies in pregnant women. No evidence of human teratogenicity: APR birth defects with first trimester exposure 3.1% (127 of 4,088 births, 95% CI 2.6-3.7%).⁴¹ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> 3TC plus ZDV is a recommended dual-NRTI backbone for pregnant women One of preferred NRTI for dual NRTI backbone (in combination with TDF) for pregnant women with chronic hepatitis B infection <p>Dosing</p> <ul style="list-style-type: none"> <i>3TC</i>[®] 150mg twice daily or 300mg once daily <i>Combivir</i>[®] (ZDV 300 mg/3TC150 mg) 1 tablet twice daily <i>Trizivir</i>[®] (ZDV 300 mg/3TC 150 mg/ ABC 300mg) 1 tablet twice daily <i>Kivexa</i>[®] (3TC 300 mg/ABC 600 mg) 1 tablet once daily Phase I study, evaluating both daily and twice daily dosing, showed pharmacokinetics were similar in third trimester of pregnancy and postpartum¹⁷⁷; larger study reports 22% higher drug clearance in pregnant women however level of exposure therapeutic¹⁷⁶; no dose alteration required in pregnancy. <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> Overall, well tolerated in pregnancy; also active against hepatitis B virus
<p>Abacavir (ABC)</p> <ul style="list-style-type: none"> FDA pregnancy category C High placental transfer (cord-to-maternal blood ratio 1.0)¹⁷⁸ <p>Animal data⁴</p> <ul style="list-style-type: none"> 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 No evidence of developmental toxicity or increase in fetal malformation observed in rabbits at 8.5 times usual human dose. 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Alternative NRTI for dual NRTI backbone of combination regimens <p>Dosing</p> <ul style="list-style-type: none"> <i>Ziagen</i>[®] 300 mg twice daily or 600 mg once daily <i>Kivexa</i>[®] (3TC 300 mg/ ABC 600 mg) 1 tablet once daily Phase I study showed drug area under the curve concentrations were similar between pregnant, post-partum, nonpregnant individuals; no dose alteration required in pregnancy¹⁷⁹ <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> Severe hypersensitivity reaction that may be fatal has been

<ul style="list-style-type: none"> ▪ Carcinogenic in rats at 6-32 times usual human dose. <p>Human data</p> <ul style="list-style-type: none"> ▪ No adequate or well-controlled studies in pregnant women. ▪ No evidence of human teratogenicity: APR birth defects with first trimester exposure 3.0% (25 of 823 births; 95% CI, 2.0-4.5%)⁴¹ 	<p>reported. Testing for the HLA-B*5701 allele identifies patients at risk of reactions; patients with the HLA*B-5701 allele should not be given abacavir.</p>
<p>Emtricitabine (FTC)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category B <p>High placental transfer (cord-to-maternal blood ratio 1.2)¹⁸⁰</p> <p>Animal data⁴</p> <ul style="list-style-type: none"> ▪ 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. <p>Human data</p> <ul style="list-style-type: none"> ▪ 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%)⁴¹ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ 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. <p>Dosing</p> <ul style="list-style-type: none"> ▪ <i>Emtriva</i>® (not available in Canada) 200 mg once daily ▪ <i>Truvada</i>® (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 compared to postpartum¹⁸¹ however current data is insufficient to recommend a dosage adjustment in pregnancy. <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> ▪ Overall, well tolerated in pregnancy; also active against hepatitis B virus.
<p>Tenofovir (TDF) (nucleotide analogue reverse transcriptase inhibitor)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category B <p>High placental transfer (cord-to-maternal blood ratio 0.6-1.03)¹⁸²⁻¹⁸⁴</p> <p>Animal data⁴</p> <ul style="list-style-type: none"> ▪ Carcinogenic in female mice at 16 times usual human dose; however 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 observed. ▪ Chronic administration of TDF at high doses to immature animals of multiple species has resulted in reversible bone abnormalities (range from decreased bone mineral density and content to severe, pathologic osteomalacia) and evidence of nephrotoxicity in monkeys at dose 12-50 times usual human dose. <p>Human data</p> <ul style="list-style-type: none"> ▪ No evidence of human teratogenicity: APR birth defects with first trimester exposure 2.3% (31 of 1,370 births; 95% CI 1.5-3.2%)⁴¹ ▪ 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 or without in utero exposure to TDF.⁵⁶ ▪ Cohort study in HIV-exposed uninfected infants reported outcomes of low birth weight, small-for-gestational age, newborn length-for-age, and head-circumference-for-age between infants with or without in utero exposure to TDF. No differences were found at birth between groups; at age 1 year, infants exposed to TDF had lower length-for-age and head-circumference for age. Clinical significance of findings has not been determined.¹⁸⁵ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ Alternative NRTI for dual NRTI backbone of combination regimens ▪ Preferred NRTI in combination with 3TC or FTC in women with chronic hepatitis B infection. <p>Dosing</p> <ul style="list-style-type: none"> ▪ <i>Viread</i>® 300 mg once daily ▪ <i>Truvada</i>® (TDF 300 mg/ FTC 200 mg) 1 tablet once daily ▪ <i>Atripla</i>® (TDF 300 mg/ FTC 200 mg/ EFV 600 mg) 1 tablet once daily at nighttime – not recommended in pregnancy (see Efavirenz below) ▪ Pharmacokinetic study showed that TDF AUC is lower in third trimester compared to postpartum however trough concentrations were similar in both groups¹⁸²; no dose alteration required in pregnancy <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> ▪ Overall well tolerated in pregnancy; clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown.
<p>Didanosine (DDI)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category B <p>Moderate placental transfer (cord-to-maternal blood ratio 0.38)¹⁷⁸</p> <p>Animal data⁴</p> <ul style="list-style-type: none"> ▪ No evidence of toxicity or teratogenicity in rats or rabbits <p>Human data</p>	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ Alternative NRTI for dual NRTI backbone of combination regimens ▪ Do not prescribe with stavudine (possible fatal lactic acidosis). <p>Dosing</p>

<ul style="list-style-type: none"> 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 discovered.⁴¹ 	<ul style="list-style-type: none"> <i>Videx EC</i>[®], <i>Videx oral solution</i>[®] ≥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 meal Phase I study showed pharmacokinetics were similar in third trimester of pregnancy and postpartum¹⁸⁶; no dose alteration required in pregnancy <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> Fatal lactic acidosis has been reported in pregnant women who received the combination of DDI and d4T; physicians should avoid prescribing this combination.
<p>Stavudine (d4T)</p> <ul style="list-style-type: none"> FDA pregnancy category C High placental transfer (cord-to-maternal blood ratio 0.5-0.8 in macaques)¹⁸⁷ <p>Animal data⁴</p> <ul style="list-style-type: none"> No evidence of developmental toxicity or teratogenicity in rats or rabbits at 399 times and 183 times usual human dose respectively. <p>Human data</p> <ul style="list-style-type: none"> No adequate or well-controlled studies in pregnant women No evidence of human teratogenicity: APR birth defects with first trimester exposure 2.5% (20 of 801 births; 95% CI 1.5-3.8%)⁴¹ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Alternate NRTI for dual NRTI backbone of combination regimens Do not combine with ZDV (antagonistic mechanism of action); discontinue d4T at time of administration of intrapartum IV ZDV. Do not combine with DDI (risk of fatal lactic acidosis) <p>Dosing</p> <ul style="list-style-type: none"> <i>Zerit</i>[®] ≥ 60 kg: 40mg twice daily, < 60 kg: 30mg twice daily Take without regard to meals A phase I/II study showed pharmacokinetics in pregnancy were similar to nonpregnant adults¹⁸⁸; no dose alteration required in pregnancy <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> Fatal lactic acidosis has been reported in pregnant women who received the combination of DDI and d4T; physicians should avoid prescribing this combination.
<p>Non-nucleoside reverse transcriptase inhibitors</p> <ul style="list-style-type: none"> NNRTIs are recommended for use in combination regimens with two NRTI drugs (alternative to using a PI) NRTI class concerns: hypersensitivity reactions, including hepatic toxicity, and rash more common in women; unclear if increased in pregnancy (see text for details) 	
<p>Nevirapine (NVP)</p> <ul style="list-style-type: none"> FDA pregnancy category B High placenta transfer (cord-to-maternal blood ratio 0.90)²⁶ <p>Animal data⁴</p> <ul style="list-style-type: none"> Hepatocellular adenoma and carcinoma reported in mice and rats; relevance to humans not known No evidence of teratogenicity in rats and rabbits at two times usual human dose; however low birth weights observed <p>Human data</p> <ul style="list-style-type: none"> Limited well-controlled studies of NVP in pregnant women. No evidence of human teratogenicity; Antiretroviral pregnancy registry 2.7% (28 of 1,020 births, 95% CI 1.8-4.0%)⁴¹ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Preferred NNRTI for use in combination with dual NRTI backbone Do not newly initiate in pregnancy due to risk of fatal rash and hepatotoxicity. Women who are tolerating NVP and become pregnant may continue taking NVP. <p>Dosing</p> <ul style="list-style-type: none"> <i>Viramune</i>[®] 200 mg once daily for 14 days then 200 mg twice daily. Repeat lead-in period if therapy is discontinued for greater than 7 days. A pharmacokinetic study has shown that pharmacokinetic parameters are similar in the second and third trimester compared to postpartum¹⁸⁹ however a second study has shown that NVP concentrations are lower in the third trimester compared nonpregnant women¹⁹⁰; current data is insufficient to recommend a dose adjustment in pregnancy. <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> Severe potentially fatal hepatotoxicity and hypersensitivity skin reactions have been reported; some data has suggested that women with CD4 counts > 250 cells/mm³ are at greater risk of reaction⁴; Canadian data has reported toxicity across a wide range of CD4 counts in women exposed to NVP for the first time during pregnancy⁵⁷; these toxicities have not been reported in women or infants receiving single-dose NVP for prevention of vertical transmission. Emergence of NVP resistance following single-dose NVP has been shown; administration of postpartum antiretrovirals to the mother (and infant) may reduce the frequency of detection of drug resistant strains.

<p>Efavirenz (EFV)</p> <ul style="list-style-type: none"> FDA pregnancy category D Moderate placenta transfer (cord blood concentrations similar to maternal plasma concentration in rats, rabbits, primates)⁴ <p>Animal data⁴</p> <ul style="list-style-type: none"> Hepatocellular carcinoma and adenoma and pulmonary alveolar/bronchiolar adenomas reported in female mice; however no indication of this effect in male mice or rats Significant central nervous system malformations (anencephaly, anophthalmia, cleft palate) reported in monkeys receiving EFV in first trimester at doses comparable to human therapeutic exposure <p>Human data</p> <ul style="list-style-type: none"> Limited well-controlled studies in pregnant women; meta-analysis of observational cohorts of birth defects in infants with first trimester exposure (1,437 live births) found no increased risk of overall birth defects compared to non EFV-based regimens (RR 0.85, 95% CI, 0.61-1.20) with one neural tube defect observed.⁴²; large prospective cohort in antiretroviral exposed infants (13,124 live births) found significant association between EFV exposure in first trimester and neurological defects (adjusted OR 3.15, 95% CI 1.09-9.09).⁴³ APR 2.7% (18 of 679 births, 95% CI 1.6-4.2%); 6 retrospective case reports of CNS defects (including 3 cases of meningocele), 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 trimester.⁴¹ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Contraindicated in first trimester of pregnancy Women receiving EFV should be instructed to avoid pregnancy; recommend barrier contraception in combination with other hormonal contraceptives <p>Dosing</p> <ul style="list-style-type: none"> <i>Sustiva</i>[®] 600 mg once daily at bedtime <i>Atripla</i>[®] (TDF 300 mg/FTC 200 mg/EFV 600 mg) 1 tab once daily at bedtime May take on empty stomach to reduce side effects Limited pharmacokinetic data available; one pharmacokinetic study has shown that EFV AUC is lower in third trimester compared to postpartum however majority of third trimester levels were above target exposure¹⁹¹; no dose alteration required. <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> Avoid in first trimester of pregnancy as described above.
<p>Etravirine (ETR)</p> <ul style="list-style-type: none"> FDA pregnancy category B Placental transfer unknown (cord-to-maternal blood ratio from case report data 0.33)¹⁹² <p>Animal data⁴</p> <ul style="list-style-type: none"> Hepatocellular carcinoma and adenoma reported in mice; however no indication of this effect in rats No evidence of embryotoxicity or teratogenicity in rabbits or rats at doses comparable to human therapeutic exposure <p>Human data</p> <ul style="list-style-type: none"> No adequate or well-controlled studies and few case report data in pregnant women. 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Insufficient safety and pharmacokinetic data to recommend use during pregnancy <p>Dosing</p> <ul style="list-style-type: none"> <i>Intelence</i>[®] 200mg twice daily Take with food to increase total AUC drug concentration Single pharmacokinetic study in 4 pregnant women reported that drug levels and AUC were similar to those in non-pregnant adults¹⁹² dose adjustment required in pregnancy is not currently required.
<p>Rilpivirine (RPV)</p> <ul style="list-style-type: none"> FDA pregnancy category B Placental transfer unknown <p>Animal data⁴</p> <ul style="list-style-type: none"> Hepatocellular carcinoma reported in mice; however no indication of this effect in rats No evidence of embryotoxicity or teratogenicity in rats or rabbits at doses 15 times and 70 times usual human dose respectively <p>Human data</p> <ul style="list-style-type: none"> No published experience in human pregnancy 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Insufficient safety and pharmacokinetic data to recommend use during pregnancy <p>Dosing</p> <ul style="list-style-type: none"> <i>Edurani</i>[®] 25mg once daily <i>Complera</i>[®] (TDF 300 mg/FTC 200 mg/RPV 25 mg) 1 tab once daily Take with food (avoid protein rich nutritional drinks) to increase total AUC and C_{max} drug concentration No pharmacokinetic studies in pregnancy; not known if dose adjustment is required.
<p>Protease inhibitors (PIs)</p> <ul style="list-style-type: none"> PIs are recommended for use in combination regimens with two NRTI drugs (alternative to using an NNRT) PI class concerns: hyperglycemia and new onset or exacerbation of existing diabetes reported with PIs; unclear if pregnancy further increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see text for details). 	
<p>Lopinavir-ritonavir (LPV/r)</p> <ul style="list-style-type: none"> FDA pregnancy category C Low placental transfer (cord-to-maternal blood ratio LPV 0.20, RTV minimal) <p>Animal data⁴</p>	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Preferred PI for use in combination with dual NRTI backbone <p>Dosing</p>

<ul style="list-style-type: none"> Hepatocellular carcinoma and adenoma reported in mice at doses 2 times (LPV) and 5 times (RTV) usual human dose. Embryotoxic in rats; no evidence of teratogenicity in rats or rabbits <p>Human data</p> <ul style="list-style-type: none"> 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%)⁴¹ 	<ul style="list-style-type: none"> <i>Kaletra</i>[®] (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 <p>Pharmacokinetic studies show AUC is decreased in third trimester^{193, 194}</p> <ul style="list-style-type: none"> 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 nonpregnant adults taking standard dose¹⁹⁵; may consider increased dose to LPV/r 600 mg/150 mg twice daily in third trimester, particularly in women who are PI experienced No data exists evaluating LPV/r drug levels using once daily dosing in pregnancy; once daily dosing not recommended <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> Well-tolerated, short term safety data in Phase I/II clinical studies
<p>Atazanavir (ATV)</p> <ul style="list-style-type: none"> Approved by FDA for use in pregnancy FDA pregnancy category B Low placental transfer (cord-to-maternal blood ratio 0.10-0.20) <p>Animal data⁴</p> <ul style="list-style-type: none"> 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 <p>Human data</p> <ul style="list-style-type: none"> No adequate or well-controlled studies in pregnant women No evidence of human teratogenicity; APR 1.9% (13 of 669 births; 95% CI 1.0-3.3%)⁴¹ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Alternative PI for use in combination with dual NRTI backbone <p>Dosing</p> <ul style="list-style-type: none"> Must be combined with low dose RTV (ATV/r) in pregnancy <i>Reyataz</i>[®] ATV/r 300/100mg once daily Take with food to increase absorption and minimize stomach upset Three pharmacokinetic studies^{49, 51, 52} evaluating ATV/r 300 mg /100 mg (without any interacting medications) have shown decreased plasma concentrations in third trimester compared with non pregnant adults, however most women achieved HIV viral load < 50 copies/mL and did not require dose adjustment; Two pharmacokinetic studies^{51, 52} evaluating ATV/r 400 mg/100 mg (without any interacting medications) in the third trimester have shown similar drug ATV AUC as compared to nonpregnant controls; TDF reduces ATV exposure 25% in pregnant women; increasing the dose to ATV/r 400 mg/100 mg in women receiving TDF has shown similar ATV AUC as compared to nonpregnant controls⁵²; Standard dose ATV/r 300 mg/100 mg can be used in pregnancy; consider increase dose in third trimester to ATV/r 400 mg/100 mg if combined therapy with either H2-receptor antagonist or tenofovir; Insufficient data to support combined use of ATV + TDF + H2-Receptor antagonist. <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> ATV increases indirect (unconjugated) bilirubin; theoretical concern regarding increased bilirubin exacerbating physiologic hyperbilirubinemia in infants has not been observed in clinical trials to date.¹⁹⁶
<p>Ritonavir (RTV)</p> <ul style="list-style-type: none"> FDA pregnancy category B Minimal placental transfer <p>Animal data⁴</p> <ul style="list-style-type: none"> Hepatocellular carcinoma and adenomas observed in male mice at high doses; developmental toxicity (decreased body weight, ossification delays) observed at high doses <p>Human data</p> <ul style="list-style-type: none"> Limited experience at full dose in human pregnancy; when used as a low-dose RTV boosting there is no evidence of human teratogenicity; APR 2.2% (39 of 1,741 births, 95% CI 1.6-3.0%)⁴¹ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Only used at low-dose in combination with second PI to increase serum drug levels of second PI <p>Dosing</p> <ul style="list-style-type: none"> <i>Norvir</i>[®] 100-400 mg PO per day in 1-2 divided doses (depending on combination with specific PI) Take with food to minimize stomach upset 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 compared to postpartum^{52, 197}; no dose adjustments are recommended in pregnancy

<p>Darunavir (DRV)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category C ▪ Placental transfer unknown (cord-to-maternal blood ratio based on case reports 0.24) ¹⁹⁸ <p>Animal data ⁴</p> <ul style="list-style-type: none"> ▪ 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; <p>Human data</p> <ul style="list-style-type: none"> ▪ No adequate or well-controlled studies in pregnancy ▪ Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ Insufficient safety and pharmacokinetic data to recommend use during pregnancy <p>Dosing</p> <ul style="list-style-type: none"> ▪ Must be combined with low dose RTV (DRV/r) ▪ <i>Prezista</i>® antiretroviral naive patients or antiretroviral experienced patients without DRV resistance mutations: DRV/r 800 mg/100 mg once daily; antiretroviral experience patients with resistance mutations: DRV/r 600 mg/100 mg twice daily. ▪ Take with food to minimize stomach upset. ▪ 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. ¹⁹⁸⁻²⁰⁰ ▪ 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.
<p>Saquinavir (SQV)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category B ▪ Minimal placental transfer <p>Animal data ⁴</p> <ul style="list-style-type: none"> ▪ No evidence of carcinogenicity, embryotoxicity, or teratogenicity in mice, rats, or rabbits at doses 21-26% of usual human doses <p>Human data</p> <ul style="list-style-type: none"> ▪ No adequate or well-conducted clinical studies in pregnant women ▪ Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects ▪ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ Alternative PI for use in combination with dual NRTI backbone <p>Dosing</p> <ul style="list-style-type: none"> ▪ Must be combined with low dose RTV (SQV/r) ▪ <i>Invirase</i>®/SQV/r 1000 mg/100 mg twice daily ▪ Take with meals or within 2 hours after a meal ▪ 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 compared to postpartum ²⁰¹; a second study using the same dosing has shown 50% decrease in third trimester levels without loss of virologic control ²⁰²; data is insufficient to recommend a dosage adjustment in pregnancy and data is too limited to recommend once daily dosing. <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> ▪ Well tolerated, short term safety demonstrated for mothers and infants; baseline EKG recommended before starting because PR and/or QT interval prolongation have been observed; no evidence pregnancy increases risk
<p>Nelfinavir (NFV)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category B ▪ Minimal placental transfer <p>Animal data ⁴</p> <ul style="list-style-type: none"> ▪ Thyroid follicular cell adenoma and carcinoma observed in rates receiving similar to 3 times usual human dose; no evidence of embryonic or teratogenicity in rats or rabbits <p>Human data</p> <ul style="list-style-type: none"> ▪ No evidence of human teratogenicity; APR 3.9% (47 of 1,204 births, 95% CI 2.9-5.2%). ⁴¹ ▪ Well-tolerated, short term safety demonstrated for mothers and infants 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ Use in special circumstances when alternative agents are not tolerated in combination with dual NRTI backbone <p>Dosing</p> <ul style="list-style-type: none"> ▪ <i>Viracept</i>® 1250 mg twice daily (750 mg three times daily not recommended in pregnancy) ▪ Pharmacokinetic study data is conflicting; one phase I/II pharmacokinetic study has shown that adequate drug levels are achieved throughout pregnancy using 1250 mg twice daily ²⁰³; two other studies have shown lower NFV concentrations in the third trimester compared to the second trimester and postpartum however viral load was adequately suppressed ^{204, 205}; data is insufficient to recommend a dosage adjustment in pregnancy. <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> ▪ Extensive experience in pregnancy however clinical trials in non-pregnant NFV based regimens had lower rate of viral response compared to LPV/r or EFV based regimens, with similar viral response rates compared to ATV/r and NVP. ▪ The concern regarding the presence of the impurity ethyl methanesulfonate (EMS), a potential carcinogen and teratogen in animals, in NFV manufactured before 2008 has

	<p>been mitigated by establishment of maximum allowed EMS limits established by the FDA</p>
<p>Indinavir (IDV)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category C ▪ Minimal placental transfer <p>Animal data⁴</p> <ul style="list-style-type: none"> ▪ Thyroid adenomas observed in rats at dose 1.3 times usual human dose, however no indication of any tumor types in mice. ▪ No evidence of embryotoxicity or teratogenicity in rabbits or dogs at 3% and 50% of maternal levels; increase incidence in 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 <p>Human data</p> <ul style="list-style-type: none"> ▪ 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%)⁴¹ 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ For use in special circumstances when alternative agents cannot be used in combination with dual NRTI backbone <p>Dosing</p> <ul style="list-style-type: none"> ▪ Must be combined with low dose RTV (IDV/r) in pregnancy ▪ <i>Crixivan</i>® 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 compared to postpartum and nonpregnant patients and two pharmacokinetic studies evaluating IDV 400mg twice daily combined with low-dose RTV have shown decreases in IDV levels during pregnancy without loss of virologic control.⁴ <p>Optimal dose in pregnancy is not established; HIV levels and trough IDV concentrations should be monitored; must be combined with low dose RTV</p> <p>Adverse events/concerns in pregnancy</p> <ul style="list-style-type: none"> ▪ IDV increases indirect (unconjugated) bilirubin; theoretical concern regarding increased bilirubin exacerbating physiologic hyperbilirubinemia in infants has not been reported; potential for renal stones; unclear if pregnancy increases risk.
<p>Fosamprenavir (FPV)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category C ▪ Placental transfer unknown <p>Animal data⁴</p> <ul style="list-style-type: none"> ▪ Hepatocellular carcinoma and adenoma observed in rats and mice at doses ranging from 0.3-1.4 times usual human dose ▪ Embryotoxic in rabbits; no evidence of gross structural abnormalities in rats or rabbits however minor skeletal variations (decreased ossification of femur, humerus, trochlea) and decreased body weights observed <p>Human data</p> <ul style="list-style-type: none"> ▪ No adequate or well-conducted studies in pregnant women ▪ Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ Insufficient safety and pharmacokinetic data to recommend use during pregnancy <p>Dosing</p> <ul style="list-style-type: none"> ▪ Recommended to be combined with low dose RTV (FPV/r) in pregnancy ▪ <i>Lexiva</i> vs. <i>Telzir</i>® antiretroviral naïve patients: FPV 1400 mg twice daily or FPV/r 1400 mg/100-200 mg once daily or FPV/r 700 mg/100 mg twice daily; PI experienced patients: FPV 700 mg/100 mg twice daily. ▪ Limited pharmacokinetic data available; one study evaluating FPV/r 700 mg/100 mg twice daily has shown lower amprenavir (active moiety) concentrations during pregnancy compared to postpartum and nonpregnant patients, however levels were considered adequate for patients without PI resistance mutations²⁰⁶; no data available in pregnancy using FPV without low-dose RTV; preliminary evidence suggest no dose adjustment is required in pregnancy and data is too limited to recommend once daily or unboosted FPV.
<p>Tipranavir (TPV)</p> <ul style="list-style-type: none"> ▪ FDA pregnancy category C ▪ Placental transfer unknown; moderate transfer reported in one case report (cord-to-maternal blood ratio 0.41)²⁰⁷ <p>Animal data⁴</p> <ul style="list-style-type: none"> ▪ Hepatocellular carcinoma and adenoma observed in mice; this effect was not observed in rats ▪ No evidence of embryotoxicity or gross structural abnormalities in rats or rabbits at doses 0.2-1.1 times usual human dose; however growth inhibition observed in rats at 0.8 times human doses <p>Human data</p> <ul style="list-style-type: none"> ▪ No adequate or well-controlled studies in pregnant women ▪ Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> ▪ Insufficient safety and pharmacokinetic data to recommend use during pregnancy <p>Dosing</p> <ul style="list-style-type: none"> ▪ Must be combined with low dose ritonavir (TPV/r) ▪ <i>Aptivus</i>® TPV/r 500 mg/200 mg twice daily ▪ No pharmacokinetic studies in pregnancy; not known if dose adjustment is required. <p>Adverse events/concern in pregnancy</p> <ul style="list-style-type: none"> ▪ Severe potentially fatal clinical hepatitis and intracranial hemorrhage have been reported in nonpregnant population; no evidence pregnancy increases risk.

Entry Inhibitors	
<p>Enfuvirtide (T20)</p> <ul style="list-style-type: none"> FDA pregnancy category B No placental transfer based on single case report²⁰⁷ No evidence of teratogenicity in rats or rabbits at 27 and 3 times usual human dose respectively⁴ No adequate or well-documented studies in pregnant women 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Insufficient safety and pharmacokinetic data to recommend use in pregnancy <p>Dosing</p> <ul style="list-style-type: none"> Fuzeon® 90 mg (1mL) subcutaneously twice daily No pharmacokinetics studies in pregnancy; not known if dose adjustment is required.
<p>Maraviroc (MVC)</p> <ul style="list-style-type: none"> FDA pregnancy category B Placental transfer unknown <p>Animal Data⁴</p> <ul style="list-style-type: none"> No evidence of embryotoxicity, carcinogenicity or teratogenicity in rats or rabbits at 20 times and 5 times usual human dose <p>Human Data</p> <ul style="list-style-type: none"> No adequate or well-documented studies in pregnant women Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Insufficient safety and pharmacokinetic data to recommend use during pregnancy <p>Dosing</p> <ul style="list-style-type: none"> Celsentri® 150 mg twice daily when given with strong CYP3A inhibitors; 300 mg twice daily when given with drugs that are not strong CYP3A inducers or inhibitors; 600 mg twice daily when given with CYP3A inducers. No pharmacokinetic studies in pregnancy; not known if dose adjustment is required.
Integrase Inhibitors	
<p>Raltegravir (RAL)</p> <ul style="list-style-type: none"> FDA pregnancy category C Placental transfer unknown (cord-to-maternal blood ratio from case reports 1.0)¹⁶⁸ <p>Animal Data⁴</p> <ul style="list-style-type: none"> No evidence of embryotoxicity, carcinogenicity or teratogenicity in rats or rabbits at 3-4 times usual human dose; increase in incidence of supernumerary ribs reported in rats at 3 times usual human dose. <p>Human Data</p> <ul style="list-style-type: none"> No adequate or well-documented studies in pregnant women Few pregnancy exposures have been reported to the APR; no conclusion can be made about risk of birth defects 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Insufficient safety and pharmacokinetic data to recommend use during pregnancy <p>Dosing</p> <ul style="list-style-type: none"> Isentress® 400mg twice daily Pharmacokinetic study published in abstract form reports no differences in third trimester compared with postpartum and nonpregnant patients¹⁶⁸; preliminary evidence suggests no dose alteration required in pregnancy.
<p>Elvitegravir (EVG)-Cobicistat (COBI)</p> <ul style="list-style-type: none"> FDA pregnancy category B Placental transfer unknown <p>Animal Data^{4, 172}</p> <ul style="list-style-type: none"> EVG: No evidence of teratogenicity or an effect on reproductive function in rats or rabbits at 23 and 0.2 times higher respectively than usual human dose COBI: No evidence of teratogenicity or an effect on reproductive function in rats or rabbits at 1.8 and 4.3 times higher respectively than usual human dose <p>Human Data</p> <ul style="list-style-type: none"> No adequate or well-documented studies in pregnant women 	<p>Recommendations for use in pregnancy</p> <ul style="list-style-type: none"> Insufficient safety and pharmacokinetic data to recommend use during pregnancy <p>Dosing</p> <ul style="list-style-type: none"> Stribild® (TDF 300 mg/FTC 200 mg/EVG 150 mg/ COBI 150 mg) 1 tab once daily with food No pharmacokinetics studies in pregnancy; not known if dose adjustment is required

NRTI = nucleotide reverse transcriptase inhibitor, NNRTI = nonnucleotide reverse transcriptase inhibitor, PI = protease inhibitor, FDA = Food and Drug Administration, HPB = Health Protection Branch, ZDV = zidovudine, APR = Antiretroviral Pregnancy Registry, 3TC = lamivudine, ABC = abacavir, TDF = tenofovir, DDI = didanosine, d4T = stavudine, IV = intravenous, HLA = human leukocyte antigen, FTC = emtricitabine, EVF = efavirenz, RR = relative risk, OR = odds ratio, AUC = area under the curve, NVP = nevirapine, ETR = etravirine, RPV = rilpivirine, Cmax = maximum concentration, LPV/r = lopinavir/ritonavir, H₂RA = histamine type 2 receptor antagonist, SQV = saquinavir, EKG = electrocardiogram, NFV = nelfinavir, EMS = ethyl methanesulfonate, IDV = indinavir, FPV = fosamprenavir, TPV = tipranavir, T20 = enfuvirtide, MVC = maraviroc, CYP = cytochrome P450, RAL = raltegravir, EVG = elvitegravir, COBI = cobicistat

Table 6: United States Food and Drug Administration Pharmaceutical Pregnancy Categories²⁰⁸

A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk during later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and adequate and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant woman despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

APPENDIX B:

Summary of intra and post partum recommendations and management algorithm for women with known HIV infection or women in whom HIV infection has not been ruled out

This applies to: a) women with known HIV infection and b) women with potential HIV infection based on rapid HIV antibody test result and c) women considered at high risk of HIV infection but with unknown HIV status (when rapid HIV antibody test is not available)

Oak Tree Clinic personnel (604-875-221) are available to provide telephone advice regarding any HIV infected pregnant woman and her infant in British Columbia. After 1630 hours and on weekends, contact Children's and Women's Hospital (604-875-2161) and ask for the Level 1 Obstetrician on call.

1. Ensure that maximal confidentiality of the woman's HIV status is maintained.
2. Universal Precautions: Ensure that standard universal precautions are undertaken for blood and body fluid protection (utilize gown, mask, eye protection and gloves for delivery). Consult your infection control manual for details. No additional precautions are required.
3. Labs on admission:
 - CBC, differential, creatinine, urea, AST, ALT, bilirubin, glucose
 - HIV viral load
 - CD4-cell count
 - Ensure all prenatal blood work has been done, including: Hepatitis B and C virus serology, RPR, Rubella, Varicella IgG
 - Send placenta to pathology for examination after delivery
 - Ensure appropriate study bloodwork is obtained (as per pre-obtained consent).
4. General Management of Labour and Delivery:
 - Epidurals are not contraindicated.
 - Avoid artificial rupture of membranes unless necessary for obstetrical management.
 - Prolonged rupture of membranes should be avoided if possible.
 - Administer oxytocin as per protocol if there is rupture of membranes and woman is not in labour.
 - Avoid use of scalp electrodes, fetal scalp sampling or intrauterine pressure catheters unless absolutely necessary.
 - Group B Streptococcus prophylaxis as per standard guidelines.
 - Avoid use of ergonovine maleate for management of postpartum hemorrhage if possible (risk of exaggerated vasoconstriction in women receiving protease inhibitors).
5. Mode of Delivery
 - Should be discussed in detail with women known to be HIV infected.
 - See Antenatal Record for patient specific recommendations from the Oak Tree Clinic.

-
- A. Women on optimal antenatal antiretroviral therapy with a recent HIV viral load (within last 4 weeks) less than 1,000 copies/mL are recommended to have a *vaginal delivery* if obstetrically appropriate and woman was adherent to antenatal antiretroviral therapy.
- B. Women not on optimal antiretroviral therapy (e.g., no antenatal antiretroviral therapy or with a recent HIV viral load [within last 4 weeks] or projected viral load greater than 1,000 copies/mL) should be offered a *pre-labour cesarean section* at approximately 38 to 39 weeks of completed gestation. If the woman is in labour or there has been rupture of membranes, caesarian section has not shown benefit in reducing transmission.
6. Continue antenatally prescribed antiretroviral therapy for as long as possible during labour.
- Exception: discontinue oral stavudine (d4T or Zerit[®]) due to antagonistic interaction with intravenous zidovudine.
7. Initiate intrapartum antiretroviral therapy
- With rupture of membranes at any time
 - With onset of labour, spontaneous or induced (even if preterm)
 - At time of induction of labour if rapid progression anticipated
 - At least 2 hours prior to planned cesarean section
 - In any situation where delivery is anticipated
- A. **All women: give intravenous zidovudine throughout labour and delivery regardless of antepartum antiretroviral regimen and mode of delivery**
- Zidovudine (AZT, Retrovir[®]) dosage:*
- 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 six hours, re-administer the loading dose and resume continuous infusion when labour recommences.
- B. **Women who did not receive any antenatal antiretroviral therapy during pregnancy: also give single-dose Nevirapine 200 mg orally x 1 dose** as soon as possible at onset of labour or presentation to labour/delivery suite.
8. Post-partum antiretroviral therapy
- A. Women who were 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 were not receiving antenatal antiretroviral therapy but 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. A consult should be made to the Oak Tree clinic to determine need for continuation of therapy or institution of alternate antiretroviral regimen.

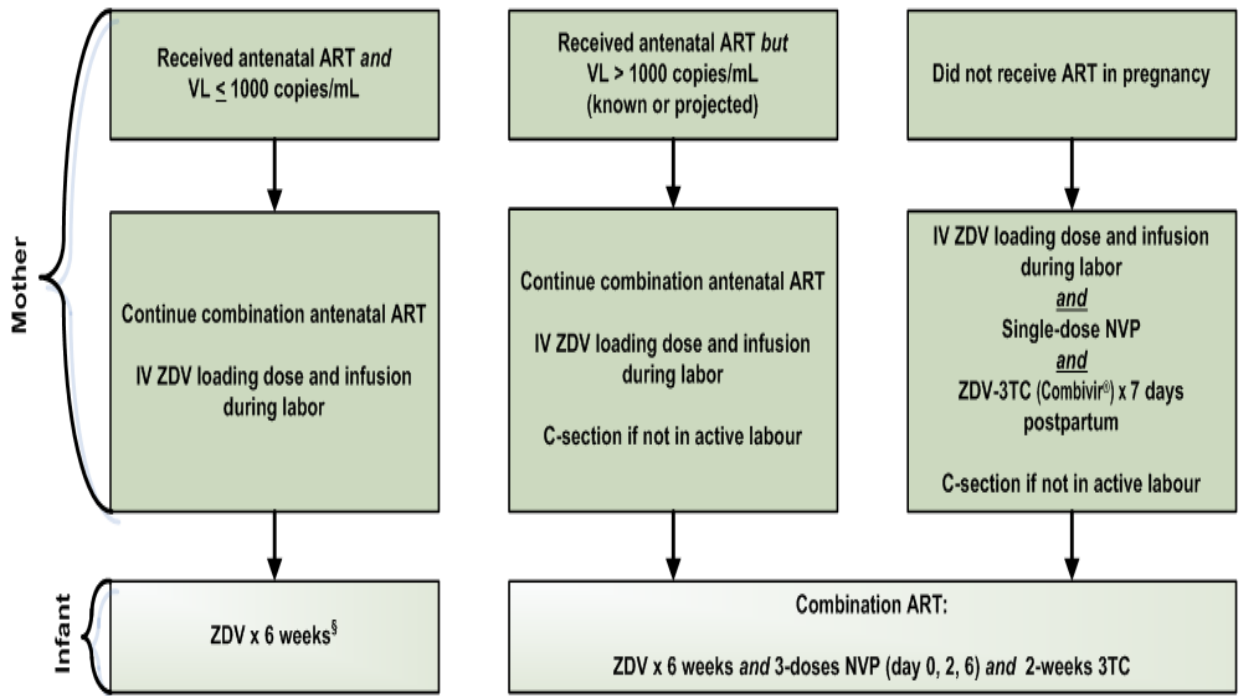
9. Prophylaxis against opportunistic infections should be offered to women who are immunocompromised.
10. Assessment and discussion of contraception, mental health, the need for social services or treatment of substance use should occur as indicated prior to discharge.
11. **Breastfeeding is contraindicated**
 - Women with known HIV infection: breastfeeding contraindicated irrespective of maternal antiretroviral therapy and viral load.
 - Women in whom HIV infection has not been ruled out: breast milk pumping and avoidance of breast milk infant feeding recommended until HIV negative status confirmation

Women should be referred to the Oak Tree Clinic (604-875-2212) for post-partum assessment and offered ongoing appropriate HIV care, combination antiretroviral therapy as per non-pregnant adult guidelines.

Complete Guidelines at: <http://www.oaktreeclinic.bc.ca>

MANAGEMENT ALGORITHM FOR HIV INFECTED WOMAN AND HER INFANT

(VL = Viral Load, ART = Antiretroviral Therapy, ZDV = zidovudine, C-section = cesarean section, 3TC = lamivudine, NVP = nevirapine)
 > greater than, ≤ less than or equal to



§ 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.

APPENDIX C:

Summary of recommendations and management algorithm for women with unknown HIV status or ongoing risk of HIV infection

Oak Tree Clinic personnel (604-875-2212) are available to provide telephone advice regarding any HIV infected pregnant woman and her infant in British Columbia. After 1630 hours and on weekends, contact Children's and Women's Hospital (604-875-2161) and ask for the Level 1 Obstetrician on call.

High Risk Categories for HIV Infection

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

Institutions where Rapid HIV Antibody Testing is NOT available:

1. Contact the PHSA laboratory result line at 1-877-747-2522 to access BC Centre for Disease Control (CDC) prenatal HIV serology results (weekdays 0800-1700). If outside of these hours and/or laboratory results are not available proceed to #2 below.
2. Offer HIV testing if HIV status is not available or if woman has ongoing risk of HIV infection since last serology test result as follows:
 - Draw STAT HIV EIA (antibody) – send blood (4 mL) in gold top tube to BC CDC Lab using PHSA Laboratories Serology screening requisition
 - Draw STAT Diagnostic HIV PCR test – send blood (4 mL) in EDTA tube to BC CDC Lab using PHSA Laboratories Serology screening requisition
 - *If woman is unavailable for testing, draw HIV EIA (antibody) and HIV PCR from the infant within 48 hours of age*
 - HIV EIA (antibody) is priority test - send blood (minimum 2 mL) in gold top tube to BC CDC Lab using PHSA Laboratories HIV Serology screening requisition.
 - Diagnostic HIV PCR - send blood (minimum 2 mL) in EDTA tube to BC CDC Lab using PHSA Laboratories HIV Serology screening requisition. Request “Infant Diagnostic HIV PCR” under Other tests.
3. Recommended intervention until HIV test results are known
 - Initiate maternal and infant treatment for prevention of MTCT-HIV.

- *If any HIV test (HIV EIA or HIV PCR) drawn is **positive** in mother or infant: immediately refer to Oak Tree Clinic (604-875-2212).*
- *If all HIV EIA and HIV PCR tests drawn are **negative** in the mother and infant: discontinue all antiretroviral drug therapy*

Institutions where Rapid HIV Antibody Testing is available:

1. Contact the PHSA laboratory result line at 1-877-747-2522 to access BC Centre for Disease Control (CDC) prenatal HIV serology results (weekdays 0800-1700). If outside of these hours and/or laboratory results are not available proceed to #2 below.
2. Offer HIV testing if HIV status is not available or if woman has ongoing risk of HIV infection since last serology test result as follows:
 - All women should be offered Rapid HIV Antibody Testing.
 - For women considered at high risk of HIV with undocumented prenatal HIV serology or who have ongoing risk of HIV since most recent HIV serology result, also draw a confirmatory Prenatal Diagnostic HIV PCR test.
 - See below for Rapid HIV Test pre- and post-test discussion points.

Rapid HIV test

- *A protocol should be established at each institution*
- *At Children’s and Women’s Hospital use C&W Hematology and Chemistry requisition. Request ‘Rapid HIV Test’ under “Miscellaneous” on requisition.*
- *Send blood (one 4 mL EDTA tube *and* one 4 mL gold-top tube) and requisition to C&W laboratory as a STAT order.*

Prenatal Diagnostic HIV PCR

- *Use PHSA Laboratories Serology Screening requisition. Request Prenatal Diagnostic HIV PCR under “Other Tests” on requisition.*
- *Send blood (4 mL in EDTA tube) and requisition to C&W laboratory for transport to PHSA laboratories at BC CDC.*

3. Recommended intervention based on rapid HIV test result

<i>HIGH risk of HIV and undocumented prenatal HIV serology (or ongoing risk of HIV risk since most recent HIV test)</i>	
<i>Preliminary reactive or Indeterminate or Invalid:</i>	<i>Initiate treatment for prevention of MTCT-HIV</i>
<i>Non-reactive but involved in high risk HIV transmission activity in previous 4-weeks (within possible ‘window’ period of infection):</i>	<i>Initiate treatment for prevention of MTCT-HIV</i>

Non-reactive <i>and</i> no identifiable risk within the past 4 weeks	No further intervention.
<i>LOW risk of HIV and undocumented prenatal HIV serology</i>	
Preliminary reactive <i>or</i> Indeterminate	Initiate treatment for prevention of MTCT-HIV
Non-reactive <i>or</i> Invalid	No further intervention

Rapid HIV Test Counseling - Pre- and Post-test Discussion Points

Pre-test Discussion:

- Information about HIV and nature of test
- Reason why HIV testing recommended (risk of transmission, long term health of woman)
- Expected benefits of testing (treatment of woman and infant, decreased transmission)
- Voluntary nature of testing
- Answer any questions

Post-test Discussion: Inform woman of test result.

Non-reactive (negative test): no antibodies to HIV were detected

- Discuss any further needs of harm reduction, further testing
- If high risk behavior in *last four weeks* (i.e., within ‘window period’ of infection where antibodies have not yet been produced) there is a possibility of acute infection
 - Discuss implications of the window period with the woman.
 - Inform that confirmatory testing results will be available in approximately one week
 - Inform woman of treatment recommendations to prevent MTCT-HIV

Invalid: test will not work with blood sample provided

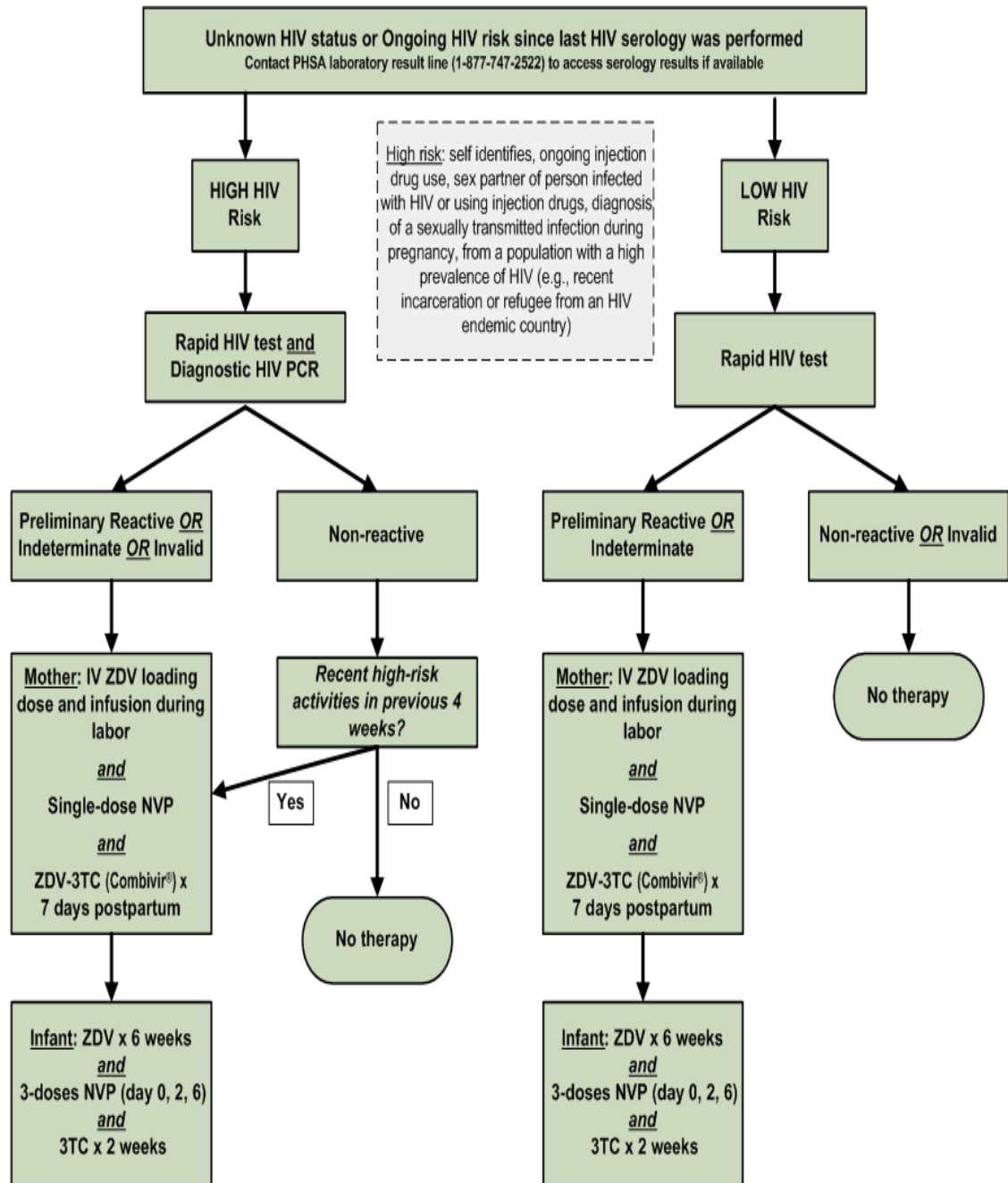
- If high risk behavior *at any time* during pregnancy inform woman there may be a possibility of infection
 - Inform that confirmatory testing results will be available in approximately one week
 - Inform woman of treatment recommendations to prevent MTCT-HIV

Preliminary reactive (preliminary positive): antibodies to HIV were detected

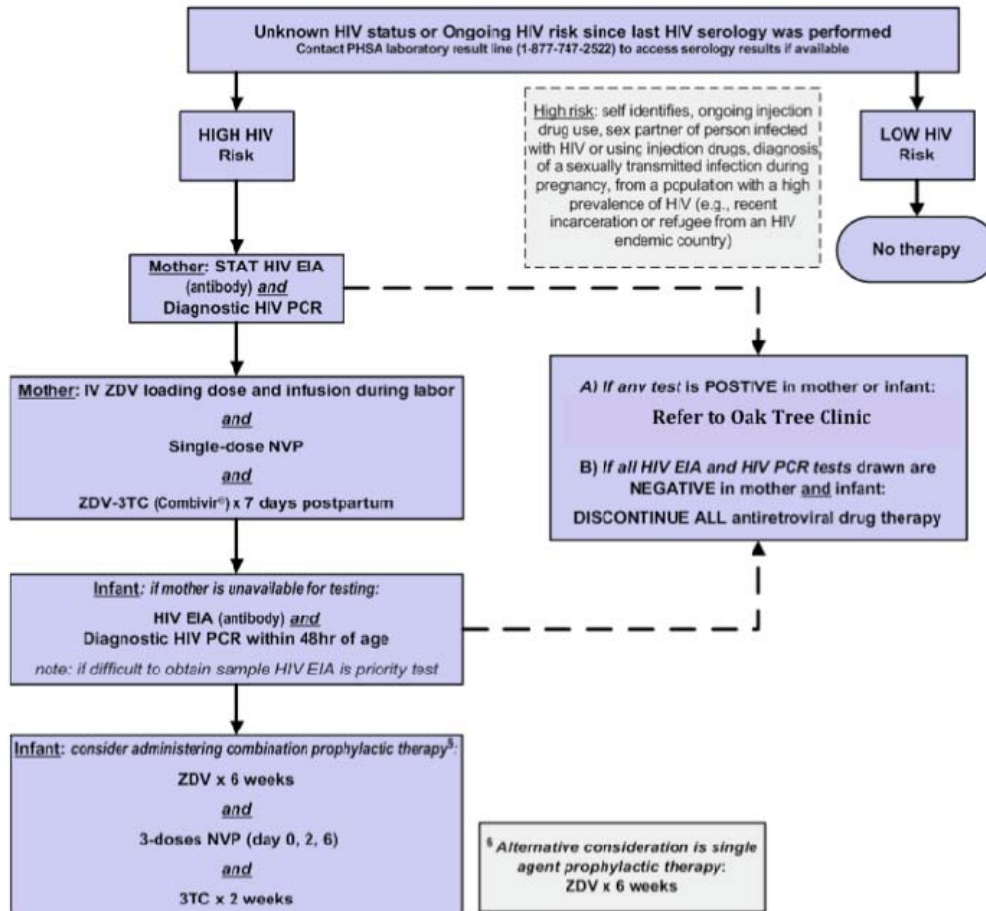
OR *Indeterminate: unable to interpret result*

- Discuss with woman that infection with HIV is possible and a confirmatory blood test is required (diagnostic HIV PCR results available in approximately one week).
- Inform woman of immediate treatment recommendations to prevent MTCT-HIV.
- Discuss transmission prevention.
- Discuss the follow-up care and support available to the woman.
- Notify the Oak Tree Clinic (604-875-2212). Leave message if after hours.
- Notify local health authority of preliminary positive result.
- Document discussion in woman’s Health Record.
- Ensure contact information for woman is available in the Health Record.

MANAGEMENT ALGORITHM FOR WOMAN OF UNKNOWN HIV STATUS OR ONGOING HIV RISK
 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)



MANAGEMENT ALGORITHM FOR WOMAN OF UNKNOWN HIV STATUS OR ONGOING HIV RISK
Management Algorithm for Woman of Unknown HIV Status or Ongoing HIV Risk in Institutions where Rapid HIV Antibody Test is NOT AVAILABLE
 (ZDV = zidovudine, 3TC = lamivudine, NVP = nevirapine)



APPENDIX D:

Summary of recommendations for infants born to mothers with known HIV infection or mothers in whom HIV infection has not been ruled out

This applies to infants born to: a) mothers with known HIV infection and b) mothers with potential HIV infection based on rapid HIV antibody test result and c) mothers considered at high risk of HIV infection but with unknown HIV status (when rapid HIV antibody test is not available)

Oak Tree Clinic personnel (604-875-2212) are available to provide telephone advice regarding any HIV infected pregnant woman and her infant in British Columbia. After 1630 hours and on weekends, contact Children's and Women's Hospital (604-875-2161) and ask for the Pediatric Infectious Disease consultant on call.

1. Ensure that maximal confidentiality of the woman's HIV status is maintained.
2. Universal precautions: Ensure that standard universal precautions are undertaken for blood and body fluid protection. Consult your infection control manual for details. No additional precautions are required.
3. Wash injection site prior to intramuscular injections or blood sampling.
4. **Breastfeeding is contraindicated.**
 - Mother with known HIV infection: breastfeeding contraindicated irrespective of maternal antiretroviral therapy and viral load.
 - Mother in whom HIV infection has not been ruled out: breast milk pumping and avoidance of breast milk infant feeding recommended until HIV negative status confirmation.
5. Offer prevention of MTCT-HIV treatment to the infant, whether or not the mother received antiretroviral therapy at delivery.

a) All Infants: give oral (PO) or intravenous (IV) zidovudine beginning immediately after birth

- Oral therapy is preferred but IV route may be used if infant is unable to tolerate oral feeds.

Zidovudine (ZDV, AZT, Retrovir[®]) dosage:

Gestational age	Recommended (Twice Daily Dosing for all infants)	Alternate (Three times Daily Dosing for pre-term infants)
Term (≥ 35 weeks gestation)	ZDV 4 mg/kg/dose PO every 12 hours for 6 weeks <i>or</i>	

	ZDV 3 mg/kg/dose IV* every 12 hours	
30 – 34 weeks gestation	ZDV 2 mg/kg/dose PO every 12 hours for 2 weeks then 3 mg/kg/dose PO every 12 hours until 6 weeks <i>or</i> 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	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.
≤ 29 weeks gestation	ZDV 2 mg/kg/dose PO every 12 hours for 4 weeks then 3 mg/kg/dose PO every 12 hours until 6 weeks <i>or</i> 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	ZDV 2 mg/kg/dose PO (1.5 mg/kg/dose IV*) every 12 hours for 4 weeks then every 8 hours until 6 weeks.

* Use IV formulation only as long as 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 and when the rapid HIV antibody test is not available: may still consider prophylaxis with only single agent zidovudine.

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 (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.

- 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):
 - *If any HIV test (HIV EIA or HIV PCR) drawn is **positive** in mother *or* infant: immediately refer to Oak Tree Clinic (604-875-2212).*

-
- *If all HIV tests (HIV EIA and HIV PCR) drawn are **negative** in mother and infant:* may discontinue all antiretroviral drug therapy
6. Labs to be ordered within 48 hours after birth:
 - CBC, differential, creatinine, urea, AST, ALT, bilirubin
 - Infants born to mothers with known HIV infection or potential HIV infection based on rapid HIV antibody testing:
 - Infant diagnostic HIV PCR
 - Use PHSA Lab Serology Screening Requisition. Request ‘Infant Diagnostic HIV PCR’ under Other Tests
 - Send blood (minimum 2 mL in EDTA tube) and requisition to PHSA laboratories at the BC CDC
 - Infants born to mothers with unknown HIV status (where rapid HIV antibody testing is not available):
 - HIV EIA (antibody) - This is priority test over HIV PCR if the mother is not available for testing and if difficult to obtain blood sample from infant
 - Use PHSA Lab Serology Screening requisition.
 - Send blood (minimum 2 mL in gold top tube) and requisition to PHSA laboratories at the BC CDC
 - Infant diagnostic HIV PCR within 48 hours
 - Use PHSA Lab Serology Screening Requisition. Request ‘Infant Diagnostic HIV PCR’ under Other Tests
 - Send blood (minimum 2 mL in EDTA tube) and requisition to PHSA laboratories at the BC CDC
 7. Check maternal HBV status. If mother is HBV surface antigen positive (HBSAg+) or has unknown status, administer first dose of HBV vaccine and HBV Immune Globulin to infant within 12 hours after birth.
 8. Ensure that the remainder of the zidovudine bottle is 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, ensure that adequate medication supply is provided to the parent/guardian on discharge from hospital to complete the treatment course.
 9. All infants born to HIV positive women should be referred for follow-up assessment and care to the Oak Tree Clinic 604-875-2212, with initial visits at 2, 4, and 6 weeks post delivery. If there are any questions or concerns after 16:30 hours on weekdays or on weekends, call the BC Children’s Hospital Pediatric Infectious Disease consultant on call (604-875-2161).

Complete guidelines available at <http://www.oaktreeclinic.bc.ca>.

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